THE AMERICAN PSYCHIATRIC ASSOCIATION PRACTICE GUIDELINES FOR PHARMACOLOGICAL TREATMENT OF PATIENTS WITH ALCOHOL USE DISORDER

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Introduction

Overview of the Development Process

Since the publication of the Institute of Medicine report, *Clinical Practice Guidelines We Can Trust*, (2011), there has been an increasing focus on using clearly defined, transparent processes for rating the quality of evidence and the strength of the overall body of evidence in systematic reviews of the scientific literature. This guideline was developed using a process intended to be consistent with the recommendations of the National Academy of Medicine (formerly Institute of Medicine) (2011), the Principles for the Development of Specialty Society Clinical Guidelines of the Council of Medical Specialty Societies (2012) and the requirements of the Agency for Healthcare Research and Quality (AHRQ) for inclusion of a guideline in the National Guidelines Clearinghouse. Parameters used for the guideline's systematic review are included with the full text of the guidelines; the development process is fully described in the following document available on the American Psychiatric Association (APA) website:
http://www.psychiatry.org/File%20Library/Psychiatrists/Practice/Clinical%20Practice%20Guidelines/Guideline-Development-Process.pdf.

Rating the Strength of Research Evidence and Recommendations

The guideline recommendations are rated using GRADE (Grading of Recommendations Assessment, Development and Evaluation), which is used by multiple professional organizations around the world to develop practice guideline recommendations (Guyatt et al., 2013). With the GRADE approach, the strength of a guideline statement reflects the level of confidence that potential benefits of an intervention outweigh the potential harms (Andrews et al., 2013). This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. Evidence for the benefit of a particular intervention within a specific clinical context is identified through systematic review and is then balanced against the evidence for harms. In this regard, harms are broadly defined and might include direct and indirect costs of the intervention (including opportunity costs) as well as potential for adverse events from the intervention. Whenever possible, we have followed the admonition to current guideline development groups to avoid using words such as "might" or "consider" in drafting these recommendations as they can be difficult for clinicians to interpret (Shiffman et al., 2005).

As described under Guideline Development Process, each final rating is a consensus judgment of the authors of the guidelines and is endorsed by the APA Board of Trustees. A "recommendation" (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. A "suggestion" (denoted by the numeral 2 after the guideline statement) indicates uncertainty, i.e., the balance of benefits and harms is difficult to judge, or either the benefits or the harms are unclear. Each guideline statement also has an associated rating for the "strength of supporting research evidence". Three ratings are used: high, moderate, or low (denoted by the letters A, B and C, respectively) and reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect

on a specific health outcome, precision of the estimate of effect, and risk of bias in available studies (AHRQ 2014; Guyatt et al., 2006; Balshem et al., 2011).

It is well recognized that there are guideline topics and clinical circumstances for which high quality evidence from clinical trials is not possible or unethical to obtain (CMSS, 2012). For example, many questions need to be asked as part of an assessment and inquiring about a particular symptom or element of the history cannot be separated out for study as a discrete intervention. It would also be impossible to separate changes in outcomes due to assessment from changes in outcomes due to ensuing treatment. Research on psychiatric assessments and some psychiatric interventions can also be complicated by multiple confounding factors such as the interaction between the clinician and the patient or the patient's unique circumstances and experiences. For these and other reasons, many topics covered in this guideline have relied on forms of evidence such as consensus opinions of experienced clinicians or indirect findings from observational studies rather than being based upon research from randomized trials. The GRADE working group and guidelines developed by other professional organizations have noted that a strong recommendation may be appropriate even in the absence of research evidence when sensible alternatives do not exist (Andrews et al., 2013; Brito et al, 2013; Djulbegovic et al., 2009; Hazlehurst et al., 2013).

Proper Use of Guidelines

The APA Practice Guidelines are assessments of current scientific and clinical information provided as an educational service. The guidelines: 1) should not be considered as a statement of the standard of care or inclusive of all proper treatments or methods of care; 2) are not continually updated and may not reflect the most recent evidence, as new evidence may emerge between the time information is developed and when the Guidelines are published or read; 3) address only the question(s) or issue(s) specifically identified; 4) do not mandate any particular course of medical care; 5) are not intended to substitute for the independent professional judgment of the treating provider; and 6) do not account for individual variation among patients. As such, it is not possible to draw conclusions about the effects of omitting a particular recommendation, either in general or for a specific patient. Furthermore, adherence to these guidelines will not ensure a successful outcome for every individual, nor should these guidelines be interpreted as including all proper methods of evaluation and care or excluding other acceptable methods of evaluation and care aimed at the same results. The ultimate recommendation regarding a particular assessment, clinical procedure, or treatment plan must be made by the clinician in light of the psychiatric evaluation, other clinical data, and the diagnostic and treatment options available. Such recommendations should be made in collaboration with the patient, whenever possible, and incorporate the patient’s personal and sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes. For all of these reasons, the APA cautions against the use of guidelines in litigation. Use of these guidelines is voluntary. APA provides the guidelines on an “as is” basis, and makes no warranty, expressed or implied, regarding them. APA assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the guidelines or for any errors or omissions.

Guideline Statement Summary

Assessment and Determination of Treatment Goals

1. APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include assessment of current and past use of tobacco and alcohol as well as any misuse of other substances including prescribed or over-the-counter medications or supplements.
2. APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include a quantitative behavioral measure to detect the presence of alcohol misuse and assess its severity.
3. APA suggests (2C) that physiological biomarkers (e.g., blood phosphatidylethanol [PEth], blood carbohydrate deficient transferrin [CDT] alone and in combination with gamma-glutamyl transferase [GGT]) be used to identify persistently elevated levels of alcohol consumption as part of the initial evaluation of patients with alcohol use disorder or in the treatment of individuals who have an indication for ongoing monitoring of their alcohol use.
4. APA recommends (1C) that patients be assessed for co-occurring conditions (including substance use disorders, other psychiatric disorders, and other medical disorders) that may influence the selection of pharmacotherapy for alcohol use disorder.
5. APA suggests (2C) that the initial goals of treatment of alcohol use disorder (e.g., abstinence from alcohol use, reduction or moderation of alcohol use, other elements of harm reduction) be agreed upon between the patient and clinician and that this be documented in the medical record.
6. APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of the patient's legal obligations (e.g., abstinence from alcohol use, monitoring of abstinence) and that this be documented in the medical record.
7. APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of risks to self (e.g., physical health, occupational functioning, legal involvement) and others (e.g., impaired driving) from continued use of alcohol and that this discussion be documented in the medical record.

Nonpharmacotherapy Treatments

8. APA recommends (1C) that patients with alcohol use disorder have a documented comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Selection of a Pharmacotherapy

9. APA recommends (1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who:
   - have a goal of reducing alcohol consumption or achieving abstinence;
   - prefer pharmacotherapy or have not responded to nonpharmacological treatments alone; and

- have no contraindications to the use of these medications.

10. APA suggests (2C) that disulfiram be offered to patients with moderate to severe alcohol use disorder who:
    - have a goal of achieving abstinence;
    - prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate;
    - are capable of understanding the risks of alcohol consumption while taking disulfiram; and
    - have no contraindications to the use of this medication.
11. APA suggests (2C) that topiramate, gabapentin, or ondansetron be offered to patients with moderate to severe alcohol use disorder who:
    - have a goal of reducing alcohol consumption or achieving abstinence;
    - prefer topiramate, gabapentin, or ondansetron or are intolerant to or have not responded to naltrexone and acamprosate; and
    - have no contraindications to the use of these medications.

Recommendations Against Use of Specific Medications

12. APA recommends (1B) that antidepressant medications not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment.
13. APA recommends (1C) that, in individuals with alcohol use disorder, benzodiazepines not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment.
14. APA recommends (1C) that, for pregnant or breastfeeding women with alcohol use disorder, pharmacologic treatments not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacologic treatment.
15. APA recommends (1B) that acamprosate not be used by patients who have severe renal impairment.
16. APA recommends (1B) that, for individuals with mild-to-moderate renal impairment, acamprosate not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function.
17. APA recommends (1C) that naltrexone not be used by patients who have acute hepatitis or hepatic failure.
18. APA recommends (1C) that naltrexone not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids.

Treatment of Alcohol Use Disorder and Co-occurring Conditions

19. APA recommends (1C) that, in patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone be prescribed to individuals who:
    - wish to abstain from opioid use and either abstain from or reduce alcohol use

and

- who are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.

Rationale

The goal of this guideline is to improve the quality of care and treatment outcomes for patients with alcohol use disorder (AUD), as defined by DSM-5 (American Psychiatric Association, 2013). The guideline focuses specifically on evidence-based pharmacologic treatments for AUD, a topic of increasing interest given the burden of AUD in the population and the availability of several U.S. Food and Drug Administration (FDA)-approved medications for this disorder. Evidence-based psychotherapeutic treatments for AUD, including cognitive behavioral therapy and motivational enhancement therapy (Anton et al., 2006; Martin and Rehm, 2012), also play a major role in the treatment of AUD, but specific recommendations related to these modalities are outside the scope of this guideline. Instead, the recommendations in this guideline focus on the use of medications for treatment of AUD. The guideline does not apply to the use of these same medications for indications other than AUD.

Worldwide, the estimated 12-month adult prevalence of AUD is 8.5%, with an estimated lifetime prevalence of 20% (Slade et al., 2016a). In the United States (U.S.), AUD has estimated values for 12-month and lifetime prevalence of 13.9% and 29.1% respectively, with approximately half of individuals with lifetime AUD having a severe disorder (Grant et al., 2015). Rates of AUD in U.S. adults vary by race/ethnicity (Grant et al., 2015; Delker et al., 2016) with 12-month prevalence rates being highest among Native Americans and Alaska Natives (19.2%) as compared to Whites (14.0%), Hispanics (13.6%), African Americans (14.4%), and Asian Americans and Pacific Islanders (10.6%). Onset of AUD is most commonly between ages 18-29 and men are more likely to be diagnosed with the disorder as compared to women (12-month prevalence in the U.S. 17.6% vs. 10.4%; Grant et al., 2015). However, in recent decades, differences between men and women in patterns of alcohol use have become less pronounced (White et al., 2015; Slade et al., 2016b) and overall rates of AUD appear to be increasing (Grant et al., 2015).

AUD places a significant strain on both the personal and public health of the U.S. population. According to a 2006 Centers for Disease Control and Prevention (CDC)-sponsored study (Bouchery et al., 2011), AUD and its sequelae cost the U.S. $223.5 billion annually and account for significant excess mortality (Kendler et al., 2016). Globally, AUD is associated with a substantial burden of disease in terms of years of life lost to premature mortality, disability-adjusted life years, and years lived with disability (Whiteford et al., 2013). Additionally, problematic alcohol use has been linked to motor vehicle accidents (Kelly et al., 2004), poor academic performance (Williams et al., 2003; Wolaver, 2002), increased risk of suicide (American Psychiatric Association, 2015; Darvishi et al., 2015), increased criminal activity including intimate partner violence perpetration (Okuda et al., 2015), and increased transmission risks for human immunodeficiency virus (HIV) and other sexually transmitted infections (Monroe et al., 2016; Rashad & Kaestner, 2004; Williams et al., 2016). Additionally, many symptoms of AUD relate to the inability to regulate alcohol use and associated impairments in insight often lead to

delays in accessing care (Chapman et al., 2015). Access to care can also be challenging because AUD often co-occurs with other psychiatric disorders (Grant et al., 2015) and each disorder will need to be treated. Furthermore, the co-occurrence of AUD and other psychiatric disorders reduces treatment outcomes for both types of disorders (Drake et al., 2013) and can be an unrecognized source of treatment resistance.

Despite its high prevalence and numerous negative consequences, AUD remains undertreated. Effective and evidence-based interventions are available but fewer than 1 in 10 individuals in the U.S. with a 12-month diagnosis of AUD receive any treatment (Substance Abuse and Mental Health Services Administration, 2014; Grant et al., 2015). Because psychosocial interventions alone yield variable treatment outcomes (Anton et al., 2006), pharmacotherapy offers an important augmenting or alternative form of treatment. Nevertheless, one study found that of the 11 million people in the U.S. with AUD, only 674,000 received psychopharmacologic treatment (Mark et al., 2009). Receipt of evidence-based care is even less common. Furthermore, treatment availability and the type of treatment provided can vary based on geography and, in the U.S., insurance coverage (Hagedorn et al., 2016; Mark et al., 2015) including formulary restrictions (Harris et al., 2013). In a systematic literature review focused on this disparity, Hagedorn et al. (2016) identified contributing factors at the level of patients (e.g., lack of awareness of treatment options) and clinicians (e.g., perceived low demand and low confidence in the efficacy of pharmacotherapy). Other clinician barriers to prescribing medications for AUD include an inability to provide suitable psychosocial co-interventions and lack of familiarity with medications (O'Malley and O'Connor, 2011; Harris et al., 2013).

Accordingly, this practice guideline provides evidence-based recommendations aimed at increasing knowledge and appropriate use of medications for AUD. The overall goal of this guideline is to enhance the treatment of AUD for millions of affected individuals, thereby reducing the significant psychosocial and public health consequences of this important psychiatric condition.

Guideline Statements and Implementation

Assessment and Determination of Treatment Goals

Statement 1

APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include assessment of current and past use of tobacco and alcohol as well as any misuse of other substances including prescribed or over-the-counter medications or supplements.

Implementation

For any patient who is undergoing an initial psychiatric evaluation, it is important to assess the patient's use of tobacco, alcohol, and other substances, as well as any misuse of prescribed or over-the-counter medications or supplements (Guideline II. Substance Use Assessment in American Psychiatric Association, The American Psychiatric Association Practice Guidelines for the Psychiatric Evaluation of Adults, Third Edition, 2016). In individuals with AUD, both the 12 month and lifetime odds ratio of nicotine use and other substance use disorders are increased (Grant et al., 2015), which supports the

need to inquire about past as well as current use. In addition, knowledge of past and current use can influence treatment planning. Information can be obtained through face-to-face interviews, standardized assessment tools, laboratory testing, and input from collateral sources such as family members, other health professionals, or medical records.

In face-to-face interviews with the patient, a nonjudgmental and open-ended approach to questions is typically most informative. Questioning and terminology should be adapted to the individual patient based on factors such as age or culture. The specific substances that are asked about will vary with the clinical context and may include but are not limited to alcohol; caffeine; cannabis; hallucinogens; inhalants; opioids; sedatives, hypnotics, and anxiolytics; stimulants, including amphetamine-type substances, cocaine, and other stimulants; tobacco; and other substances. Questions about misuse of prescribed or over-the-counter medications or supplements can often be introduced while the clinician is taking a history of the patient's prescribed medications. Depending on the substance(s) being used, additional follow-up questions will generally be needed to delineate the route, quantity, frequency, pattern, typical setting, and circumstances of use as well as self-perceived benefits and psychiatric and other consequences of use. Observations made during the interview can provide additional clues to possible use (e.g., an odor of cigarettes or alcohol on the patient's breath; physical signs of injection drug use; slurred speech, tremulousness or other evidence of alcohol or substance intoxication or withdrawal).

Information from self-report rating scales can complement information from the face-to-face interview (Guideline II. Substance Use Assessment in American Psychiatric Association, The American Psychiatric Association Practice Guidelines for the Psychiatric Evaluation of Adults, Third Edition, 2016). The Self-Rated Level 1 Cross-Cutting Symptom Measure of DSM-5 (available online at http://www.psychiatry.org/practice/dsm/dsm5/online-assessment-measures) permits initial screening; patients can be asked for additional details on substance use items through administration of the DSM-5 Level 2—Substance Use Measure (American Psychiatric Association 2013).

Benefits and Harms

Benefits: Assessment of the current and past use of alcohol is beneficial in verifying that AUD is present and in identifying its severity and longitudinal course. Knowledge of the patient's current pattern of alcohol use provides important baseline data for assessing the effects of subsequent interventions. Individuals with AUD often use tobacco and misuse of other substances. Identifying these conditions, if present, is important to developing a treatment plan that can reduce associated symptoms, morbidity, and mortality. Information about past use is also beneficial in identifying potential health risks from prior use and monitoring for relapse of other substance use disorders.

Harms:[1] Some individuals may become anxious or annoyed if asked multiple questions during the evaluation including questions about use of substances. This could interfere with the therapeutic

[1] Harms may include serious adverse events, less serious adverse events that affect tolerability, minor adverse events, negative effects of the intervention on quality of life, barriers and inconveniences associated with treatment and other negative aspects of the treatment that may influence decision making by the patient, the clinician or both.

relationship between the patient and the clinician. Another potential consequence is that time used to focus on assessment of tobacco, alcohol and other substance use could reduce time available to address other issues of importance to the patient or of relevance to diagnosis and treatment planning.

Patient Preferences: Although there is no specific evidence on patient preferences related to assessment in individuals with AUD, clinical experience suggests that the majority of patients are cooperative with and accepting of these types of questions as part of an initial assessment.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. This recommendation is also consistent with Guideline II on Substance Use Assessment as part of the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015). The level of research evidence is rated as low because there is minimal research on the benefits and harms of assessing tobacco, alcohol, and other substance use as part of the psychiatric evaluation. However, screening for use of tobacco, alcohol, and other substances has been studied in other settings such as primary care. In addition, expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves the identification and diagnosis of substance use disorders. (See APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015) for additional details.)

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

As described in APA's Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015), individuals who were identified by peers as experts in psychiatric evaluation assessed patients for use of alcohol or other substances at consistently high rates whereas assessment of past and current tobacco use were also high but showed opportunity for improvement. The typical practices of other psychiatrists and mental health professionals are unknown but rates of tobacco use screening have been declining among psychiatrists practicing in ambulatory settings (Rogers and Sherman 2014). Data from ambulatory settings (Glass et al., 2016) suggest that many individuals receive screening for alcohol use but approximately one-third of individuals do not. Rates of screening for use of other substances, including misuse of prescribed or over-the-counter (OTC) medications, are likely to be less than rates of screening for either tobacco or alcohol use.

Several existing measures are of relevance to this recommendation. National Quality Forum (NQF) Measure 110, “Bipolar Disorder and Major Depression: Appraisal for Alcohol or Chemical Substance Use,” assesses the percentage of patients with depression or bipolar disorder with evidence of an initial assessment that includes an appraisal for alcohol or substance use (http://www.qualityforum.org/QPS/0110). In terms of tobacco use, the NQF endorsed Measure 028, “Preventive Care & Screening: Tobacco Use: Screening & Cessation Intervention,” assesses the percentage of adult patients who are screened every 2 years for tobacco use and who receive cessation counseling intervention if identified as a tobacco user (http://www.qualityforum.org/QPS/0028). Several

other NQF endorsed treatment performance measures are related to screening for tobacco use in inpatient settings. Before adopting any measures, it is important to determine whether the measure has been validated in the population and setting of interest. Thus, it is recommended at this time that only measures specified or endorsed for outpatients be used in that treatment setting.

The most effective manner to assess and report on measures related to substance use is unclear. Several options for reporting are in practice, and have been proposed.

As described in APA's Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015), a comprehensive measure could be derived that assesses the percentage of patients seen in an initial evaluation who are screened for the use of tobacco, alcohol, or other substances as well as for the misuse of prescribed or OTC medications.

Because existing measures already include a tobacco use screening measure, it may be preferable to focus new measure development on assessment of current and past alcohol use. Such a measure could be paired with a distinct measure on assessment of substance use. Alternatively, a measure on the assessment of alcohol use could be paired with a measure that determines whether treatment for AUD was initiated.

In practices that use an electronic health record, a measure on the assessment of past and current alcohol use could be implemented by measuring for the presence or absence of text in corresponding fields labeled “past alcohol use” and “current alcohol use.” This approach would aim to ensure that assessment has occurred and is documented in a patient’s record but would allow for maximum flexibility in how clinicians document findings of their assessments without endorsing use of a specific scale or method of assessment. Regardless of the approach that is chosen, quality improvement activities derived from this recommendation, including performance measures, should not oversimplify the process of assessing alcohol use, as alcohol use is commonly underreported by patients and often requires use of clinical interviewing skills to elicit accurate information. Exceptions to the denominator of the measure should be specified and might include individuals who are unable to participate in the evaluation because of their current mental status. Other exceptions might also be appropriate.

Statement 2

APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include a quantitative behavioral measure to detect the presence of alcohol misuse and assess its severity.

Implementation

Quantitative behavioral measures should be used during the initial psychiatric evaluation of a patient with AUD to detect the presence of alcohol misuse and determine its severity. A number of validated scales and screening tools have been developed (e.g., AUDIT-C, AUDIT, CRAFFT, CAGE) Although recommending a particular scale is outside the scope of this practice guideline, considerations in choosing a scale include the age of the patient, clinical setting, time available for administration, and therapeutic objective (i.e., screening vs. diagnosis vs. on-going monitoring). For example, the CAGE questionnaire (Ewing, 1984) has been studied as a screening tool for AUD but does not provide enough

information to suggest a diagnosis of AUD or to be used in monitoring alcohol use in patients with known AUD (do Amaral and Malbergier, 2008). The CRAFFT is intended to be developmentally appropriate for adolescents (Knight et al. 1999) whereas the AUDIT (Saunders et al. 1993) and its shortened form, the AUDIT-C (Bush et al. 1998), are more appropriate for use with adult patients. Additionally, co-occurring psychiatric conditions or cognitive impairment may limit some patients' ability to complete self-report instruments. In these circumstances, it may be necessary to place greater reliance on collateral sources of information such as family members or staff members of sober houses or community residence programs, if applicable.

Benefits and Harms

Benefits: Use of a quantitative behavioral measure as part of the initial evaluation can establish baseline information on the patient's reported use of alcohol and on symptoms and impairment associated with alcohol use. As compared to a clinical interview, use of a quantitative behavioral measure may improve the consistency with which this information is obtained. When administered through paper-based or electronic self-report, use of quantitative behavioral measures may allow routine questions to be asked more efficiently.

Harms: The harms of using a quantitative behavioral measure include the time required for administration and review. Overreliance on quantitative measures may lead other aspects of the patient's symptoms and clinical presentation to be overlooked. In addition, some patients may have difficulty completing self-report scales or may interpret questions incorrectly. Patients may also view quantitative measures as impersonal or may feel annoyed by having to complete detailed questionnaires. Changes in the workflow of clinical practices may be needed to incorporate quantitative behavioral measures into routine care.

Patient Preferences: Clinical experience suggests that the majority of patients are cooperative with and accepting of quantitative behavioral measures as part of an initial assessment.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. This recommendation is also consistent with Guideline VII on Quantitative Assessment as part of the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015). The level of research evidence for this recommendation is rated as low. Evidence suggests that quantitative behavioral measures have good sensitivity and specificity in identifying risky drinking behaviors and AUD but data come predominantly from hospital-based, emergency department, and primary care settings rather than from psychiatric settings. There is minimal research on the harms of using quantitative behavioral measures as part of the psychiatric evaluation as compared to assessment as usual. However, expert opinion suggests that harms of assessment are minimal compared to the benefits of such assessments in improving identification and assessment of AUD. (See APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015) for additional details.)

Differences of opinion among writing group members: Eight writing group members voted to recommend this statement and one writing group member voted to suggest this statement.

Quality Measurement Considerations

It is not known how frequently psychiatrists and other health professionals use a quantitative behavioral measure to detect the presence of alcohol misuse and assess its severity in ambulatory settings. However, anecdotal observations suggest variability in the routine use of such measures.

Use of quantitative behavioral measure to assess individuals with AUD could be one approach to meeting a measure on assessing past and current use of alcohol. As described in Statement 1, a measure could consider the presence or absence of scoring from a relevant measurement tool but should avoid endorsing use of a specific scale.

One example measure is the NQF endorsed measure number 2152: Preventive care and screening: percentage of patients aged 18 years and older who were screened for unhealthy alcohol use using a systematic screening method at least once within the last 24 months AND who received brief counseling if identified as an unhealthy alcohol user. The measure specifies the use of the Alcohol Use Disorders Identification Test (AUDIT), the AUDIT-C screening instruments, or single question screening on the number of times in the past year the individual consumed 5 or more drinks in a day for men or 4 or more drinks in a day for women and those over age 65. Brief counseling is described as at least one session of "a minimum of 5-15 minutes, which may include: feedback on alcohol use and harms; identification of high risk situations for drinking and coping strategies; increased motivation and the development of a personal plan to reduce drinking." A process-focused internal quality improvement measure could also determine rates of quantitative behavioral measure use and implement quality improvement initiatives to increase the frequency at which such measures are used in individuals with AUD.

Statement 3

APA suggests (2C) that physiological biomarkers (e.g., blood phosphatidylethanol [PEth], blood carbohydrate deficient transferrin [CDT] alone and in combination with gamma-glutamyl transferase [GGT]) be used to identify persistently elevated levels of alcohol consumption as part of the initial evaluation of patients with alcohol use disorder or in the treatment of individuals who have an indication for ongoing monitoring of their alcohol use.

Implementation

Alcohol consumption can also be evaluated and monitored using alcohol biomarkers (see reviews by the Substance Abuse and Mental Health Services Administration (2012) and Dasgupta (2015)).

Biomarkers for alcohol consumption are not intended to replace the clinical interview and quantitative behavioral measures but may augment these assessments (do Amaral and Malbergier, 2008) along with input from collateral informants. Alcohol consumption biomarkers may be useful in certain patient populations such as those with co-occurring psychiatric illness or cognitive impairment that limits the ability to self-report alcohol use. Biomarker testing may also be of use when a clinician suspects a patient to be minimizing reported use of alcohol or when verification of abstinence is needed (e.g., in court-mandated alcohol treatment). In addition, some biomarkers can help to evaluate for alcohol-related organ damage, which may prompt treatment referral for medical complications of alcohol use.

When biomarkers are used, results should be discussed with patients in ways that encourage open and honest communication about alcohol consumption.

Biomarkers may be obtained from a variety of sources (e.g., blood, urine, hair). Direct biomarkers measure alcohol or alcohol metabolites over a time course of hours (blood ethanol level) to days (urine/hair ethyl glucuronide). In contrast, indirect biomarkers typically reflect organ damage or physiologic dysfunction resulting from more chronic, heavy alcohol consumption.

There are several other factors to consider when choosing a biomarker. It is important to evaluate for co-occurring medical conditions or medications that may interfere with biomarker testing. Interpreting biomarker levels is further complicated by variations in assay techniques and threshold values for a positive test (Weykamp et al., 2013). Different thresholds may also be necessary depending on the patient's therapeutic goal (e.g., abstinence vs. moderation) (Balldin et al., 2010). Insurance coverage for specific biomarkers can also influence test selection.

Serum ethanol level

Serum ethanol level is a direct biomarker commonly used in the acute intoxication phase. Depending upon the amount of alcohol ingested, it normalizes within hours of cessation of drinking and typically follows zero-order kinetics (Jones, 2011). Regulatory alcohol limits (e.g., for driving) are commonly based on the serum ethanol level.

Ethyl glucuronide

Ethyl glucuronide is a metabolite of alcohol and therefore a direct biomarker. In contrast to serum ethanol, ethyl glucuronide can be detected in urine or hair up to 2-3 days after the last drink, with longer periods of detection with hair samples (Kelly and Mozayani, 2012). In fact, Pirro et al (2011) and Morini et al (2009) found that hair ethyl glucuronide had better sensitivity and specificity for active heavy drinking compared to “traditional” biomarkers including %CDT and GGT. Ethyl glucuronide in meconium can also be used to detect fetal alcohol exposure (Bager et al., 2017). A false-positive ethyl gluconide result can occur with incidental exposure to products that contain alcohol (Kelly and Mozayani, 2012). Co-occurring urinary tract infection can result in a false-negative test due to accelerated elimination of urine ethyl glucuronide (Helander and Dahl, 2005).

Phosphatidylethanol (PEth)

Ethanol interacts with phosphatidylcholine on erythrocyte cell membranes to form phosphatidylethanol (PEth). As a result, PEth serves as a whole blood biomarker of recent consumption of alcohol. As a direct biomarker, PEth differs from serum ethanol level in two ways. First, PEth requires a longer duration of heavier alcohol use to become elevated (at least 50 g for several weeks) and remains elevated for 2-3 weeks after cessation of drinking (Isaksson et al., 2011). It also has nearly 100% sensitivity for alcohol consumption making it more sensitive than many other biomarkers (Isaksson et al., 2011; Walther et al., 2015; Wurst et al., 2015).

AST, ALT, and GGT

Over time, heavy alcohol consumption damages hepatocytes. Such damage can be measured with indirect serum biomarkers such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) but elevations in these enzymes are not specific for alcohol-induced liver injury and may reflect hepatic damage due to other conditions (Conigrave et al., 2003).

GGT is among the most commonly used alcohol biomarkers (Whitfield, 2001). Elevations in GGT reflect both altered hepatic metabolism and hepatocyte damage in the setting of sustained heavy alcohol consumption (60 g or more for 3 to 6 weeks). However, the relationship between alcohol consumption and GGT elevation can vary among individuals (sensitivity 64% and specificity 72%). Therefore, a normal GGT level does not rule out heavy alcohol consumption (Conigrave et al., 2003). Additionally, adolescents and young adults who drink alcohol heavily do not usually have elevations in GGT. Obesity, smoking, diabetes mellitus, and viral hepatitis C can also lead to elevated levels of GGT (Puukka et al., 2007). False positive elevations of GGT have also been associated with certain medications (e.g., barbiturates, phenytoin, monoamine oxidase inhibitors, tricyclic antidepressants, warfarin, thiazide diuretics, and anabolic steroids; Dasgupta, 2015). False negative results can occur with excessive caffeine consumption (>4 cups per day), which may lower GGT levels (Dasgupta, 2015).

Mean Corpuscular Volume (MCV)

Mean corpuscular volume (MCV) is increased with heavy alcohol use, even in the presence of normal folate and vitamin B12 levels, and can remain increased for 3-4 months after abstaining from alcohol. MCV, however, has a low sensitivity as an indirect biomarker of alcohol consumption (<50%) (Conigrave et al., 2003) and other causes of macrocytosis are possible (e.g., vitamin B12 or folate deficiency).

Carbohydrate Deficient Transferrin (CDT)

Carbohydrate-deficient transferrin (CDT) was the first FDA-approved alcohol biomarker and refers collectively to isoforms of transferrin, an iron-transporting protein synthesized by the liver. However, with sustained heavy alcohol consumption, the serum concentration of CDT increases through a mechanism that is not fully understood (Niemelä 2016). CDT increases after just one week of heavy alcohol consumption and slowly returns to normal with abstinence (half-life=14 days). CDT is typically the minor isoform found in humans and is sensitive to levels of total transferrin. Thus, in clinical practice, CDT is expressed as %CDT (the ratio of CDT to total transferrin), which has the advantage of using a single threshold value for men and women. Arndt et al (1999) found that a threshold value of 2.4 %CDT achieved 84% sensitivity and 92% specificity. False-positive findings with CDT levels can result from end-stage liver disease, genetic variants of CDT, or conditions that increase total transferrin levels (e.g., iron deficiency, chronic illness, or menopause) (Fleming et al., 2004). False-negative results have been associated with female sex (obviated by using %CDT), cirrhosis (Fagan et al., 2014), binge alcohol use, or acute blood loss. Additionally, some anti-epileptic medications and ACE inhibitors can elevate %CDT whereas loop diuretics may lower %CDT levels.

When used in combination with GGT, %CDT can be used to derive an even more accurate assessment of alcohol consumption using the formula: GGT - %CDT = [0.8 x ln(GGT)] + [1.3 x ln(%CDT)]

This combined GGT-%CDT parameter, has a sensitivity and specificity that are estimated at 94% and 100% respectively with a threshold value for a positive result of 4.0 (Anttila et al., 2003).

Trait markers

Trait biomarkers (e.g., genetic polymorphisms) are under investigation to help clinicians assess a patient's risk of developing AUD or likelihood of responding to a particular treatment. This research has yielded promising results but requires further confirmation before recommending trait biomarkers for routine clinical use (Jonas et al., 2014).

Benefits and Harms

Benefits: Physiological biomarkers can complement the findings of self-report with an objective measure of alcohol use. Evidence suggests that some physiological biomarkers have adequate sensitivity, specificity, and positive predictive values; however, the interpretation of the results will depend upon the specific physiological biomarker being tested and the threshold values used to define a positive test result. Biomarker results can be helpful in determining the initial severity of AUD and in identifying relapses into drinking or heavy drinking that require adjustments to the plan of treatment. Some indirect biomarkers (e.g., AST, ALT, GGT, CDT, MCV) can also reflect physiological damage related to alcohol consumption and may signal a need for further medical monitoring or intervention.

Harms: False positive results can occur with physiological biomarkers although the rate varies with the test, the testing method, and the threshold values for a positive test result. Co-occurring medical conditions and use of specific medications can generate false positive test results and may require more expensive confirmatory testing. A false positive biomarker result can be particularly problematic if a patient is having abstinence monitored as part of employment, legal obligations, or other treatment requirements. Discussions with patients about false positive results can also affect the therapeutic relationship if a patient feels that he or she is not trusted by the clinician. Similarly, false negative results can be problematic by conveying an incorrect picture of the patient's actual use of alcohol, which may lead to inappropriate clinical decisions. Costs of physiological biomarkers can be a barrier for some patients, depending on insurance status and the frequency of biomarker use. Patients may also experience anxiety about having blood drawn or while awaiting test results. Pain, bruising, or other side effects can occur with phlebotomy for blood-based biomarkers. If phlebotomy occurs at a separate laboratory testing center, practical barriers may include time spent in going for testing, time off from work, or issues with transportation.

Patient Preferences: Patients may not wish to undergo phlebotomy for assessment of blood biomarkers. Patient preferences may be affected by testing costs, anxiety related to laboratory testing, or practical barriers. Patients who are ambivalent about abstinence from alcohol use may also prefer to avoid physiological biomarker testing.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the harms of the statement although patient preferences may differ and additional research evidence may influence the strength of the guideline statement. Although there are demonstrated benefits to the use of physiological biomarkers,

some patients may experience harms related to false positive or false negative test results. Patient preferences about testing may vary, and there are costs and practical barriers that may be associated with physiological biomarker use.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure.

Statement 4

APA recommends (1C) that patients be assessed for co-occurring conditions (including substance use disorders, other psychiatric disorders, and other medical disorders) that may influence the selection of pharmacotherapy for alcohol use disorder.

Implementation

AUD frequently co-occurs with other psychiatric disorders, particularly mood or anxiety disorders (Hasin et al., 2005). The relationship between alcohol use and psychiatric symptoms is complex and likely bidirectional (Grant et al., 2004; Kenneson et al., 2013; Martins and Gorelick, 2011). Alcohol may reduce some symptoms (e.g., anxiety) while exacerbating others (e.g., depressed mood), either during periods of use or withdrawal. Problematic alcohol use may also occur in the context of certain disorders that result in impaired impulse control (e.g., bipolar disorder or borderline personality disorder) or may itself lead to worsening behavioral disinhibition. Therefore, it is important to screen for other co-occurring psychiatric disorders. It is particularly important to assess a patient's risk for suicide and aggressive behaviors because heavy alcohol use is a known risk factor for both suicide (Norstrom and Rossow, 2016) and violence (Abramsky et al., 2011; Branas et al., 2016). Such assessments can be accomplished through clinical interview, mental status examination, and use of quantitative measures. Additionally, as described above, screening for other substance use disorders is important for treatment planning because co-occurring substance use disorders may influence medication considerations. For example, an individual with co-morbid AUD and opioid use disorder might benefit from naltrexone to treat both disorders after an informed consent discussion that includes the risk of precipitated opioid withdrawal. More detailed recommendations about screening for co-occurring conditions can be found in the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015).

It is also important to screen for non-psychiatric medical conditions that may have arisen as sequelae of or independent from heavy alcohol use. Such assessments include, but are not limited to. measuring serum creatinine and hepatic transaminase levels. One should also evaluate for other causes of hepatic (e.g., viral hepatitis) or renal (e.g., diabetes mellitus, hypertension, HIV) impairment because this may influence choice of AUD pharmacotherapy. For example, acamprosate is contraindicated in severe renal disease (CrCl<30) and naltrexone must be used cautiously in individuals with hepatic impairment.

Benefits and Harms

Benefits: Individuals with AUD often have other co-occurring disorders. When such conditions are present, they are important to identify. Pharmacotherapies for AUD may interact with treatments for

other disorders, and specific medical conditions may be contraindications for the use of specific pharmacotherapies for AUD. In addition, some medications are indicated for more than one condition and knowledge of all relevant diagnoses can aid in treatment choice.

Harms: Some individuals may have difficulty concentrating or may become annoyed if asked multiple questions during the evaluation. This could interfere with the therapeutic relationship between the patient and the clinician. Another potential consequence is that time used to focus on assessment of co-occurring disorders could reduce time available to address other issues of importance to the patient or of relevance to diagnosis and treatment planning.

Patient Preferences: Clinical experience suggests that the majority of patients are cooperative with and accepting of assessments for other conditions that may influence treatment options.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. This recommendation is also consistent with Guideline I on Review of Psychiatric Symptoms, Trauma History, and Psychiatric Treatment History and with Guideline VI on Assessment of Medical Health as part of the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015). The level of research evidence is rated as low because there is minimal research on the benefits and harms of assessing for co-occurring conditions as part of the psychiatric evaluation as compared to not conducting such assessments. However, expert opinion suggests that such assessments improve the identification and diagnosis of other psychiatric disorders and other medical disorders that can influence treatment planning. (See APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015) for additional details.)

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

As described in APA's Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015), individuals who were identified by peers as experts in psychiatric evaluation reported high rates of inquiring about co-occurring conditions. The typical practices of other psychiatrists and mental health professionals are unknown. There are many challenges in developing a quality measure from assessment-related recommendations (American Psychiatric Association, 2015). There are no NQF-endorsed recommendations on this topic. However, some unendorsed measures exist related to co-occurring conditions in individuals with psychiatric illness. These would be useful to review before considering development of a new measure. In addition, with the increasing use of electronic medical record systems and associated recording of problems and diagnoses using structured terminology, it may be possible to develop electronic measures from this recommendation that could be used for process focused internal quality improvement initiatives.

Statement 5

APA suggests (2C) that the initial goals of treatment of alcohol use disorder (e.g., abstinence from alcohol use, reduction or moderation of alcohol use, other elements of harm reduction) be agreed upon between the patient and clinician and that this be documented in the medical record.

Implementation

Clinicians should collaborate with patients to identify specific treatment goals regarding their alcohol use. Options might include abstinence, reduction in alcohol use, or eliminating drinking in particular high-risk situations (e.g., at work, before driving, when responsible for caring for children). Data have shown that having explicit drinking goals at baseline may be associated with improved AUD treatment outcomes (Dunn and Strain, 2013). Abstinence as a pre-treatment goal has been associated with greater rates of abstinence or moderation, but all groups with an explicit pre-treatment goal showed some reduction in alcohol use. Below are some examples of abstinent and non-abstinent drinking goals as described by Dunn and Strain ,2013):

Abstinent Drinking Goals	1. I want to be totally abstinent from all alcohol for a period of time, after which I will make a new decision about whether or not I will use alcohol again anyway. 2. I want to quit using alcohol once and for all, even though I realize I may slip up and use alcohol again once in a while. 3. I want to quit using alcohol once and for all, to be totally abstinent, and never use alcohol ever again for the rest of my life.
Non-abstinent Drinking Goals	1. I want to use alcohol in a controlled manner to be in control of how often I use and how much I use. 2. I don't want using alcohol to be a habit for me anymore, but would occasionally like to use alcohol when I really have an urge.

Motivational interviewing (MI) is one model for having such discussions with patients (Miller and Rollnick, 2013; Levounis et al., 2017). In MI, the clinician first asks permission to discuss alcohol use. After the patient consents, the goal is to help the patient articulate his/her ambivalence about drinking by asking about positive and negative aspects of alcohol use along with assessments of readiness to reduce drinking and confidence in their ability to do so. Such discussions are facilitated by a clinician stance that is curious and nonjudgmental, while also expressing concern for the patient's wellbeing.

Clinicians should clearly document the agreed upon treatment goals in the medical record. Additional documentation may be needed when the goal a patient is willing to accept does not align with what the clinician believes is safest. For example, a patient may only agree to a reduction in drinking but continue to drink in situations that place them at risk of legal involvement (e.g., DUIs, DWIs) or of significant medical sequelae from alcohol use (e.g., hepatic injury). Documentation should reflect that both the clinician and patient understand these risks and have engaged in a discussion about them.

Benefits and Harms

Benefits: Discussing and agreeing upon the initial goals of treatment facilitates treatment planning in several respects by eliciting patient preferences and motivations, permitting education on the value of

harm reduction and abstinence, setting expectations for treatment, and establishing a framework for shared decision-making. It may also assist in forming a therapeutic relationship between the patient and clinician. For some pharmacotherapies, particularly disulfiram, the patient's treatment goal may influence the choice of a pharmacotherapy. Documentation of treatment goals promotes accurate communication among all those caring for the patient and can serve as a reminder of initial discussions about treatment goals.

Harms: The only identifiable harm from this recommendation relates to the time spent in discussion and documentation that may reduce the opportunity to focus on other aspects of the evaluation.

Patient Preferences: Clinical experience suggests that patients are cooperative with and accepting of efforts to establish initial goals of treatment.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the potential harms. The advantages of specifically setting and documenting goals as compared to assessment as usual are less clear (low strength of research evidence), which influenced the strength of the guideline statement (suggestion). No information is available on the harms of such an approach.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure. A process-focused internal quality improvement measure could determine rates of documenting initial treatment goals and quality improvement initiatives could be implemented to increase the frequency at which such discussions and documentation occur in individuals with AUD.

Statement 6

APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of the patient's legal obligations (e.g., abstinence from alcohol use, monitoring of abstinence) and that this be documented in the medical record.

Implementation

Some patients come to treatment as a consequence of legal involvement and their engagement in treatment may be court-mandated. The initial assessment of AUD should include inquiry about legal involvement and any legal obligations the patient may have in relation to alcohol use. For individuals in mandated treatment, reporting requirements will vary with the local jurisdiction but should be discussed with the patient. Mandated treatment situations may also influence the treatment goals (e.g., abstinence) and the monitoring of abstinence such as with serum ethanol levels, ethanol breath tests or other alcohol-related biomarkers. It is important to document any such legal obligations in the medical record along with a discussion of the treatment plan and therapeutic goals.

Benefits and Harms

Benefits: Identifying and discussing the patient's legal obligations as part of the initial goals of treatment facilitates treatment planning and setting of expectations for treatment. Documentation of any legal obligations promotes accurate communication among all those caring for the patient and can serve as a reminder of initial discussions about treatment goals.

Harms: A potential harm of this recommendation relates to the time spent in discussion and documentation that may reduce the opportunity to focus on other aspects of the evaluation. If legal obligations and related details of legal history are documented in a patient's chart, other health care team members who read those details may treat the patient differently and the patient's privacy could also be compromised.

Patient Preferences: Clinical experience suggests that patients recognize the importance of meeting their legal obligations for treatment and wish to have these addressed by the treating clinician. Some patients may be anxious or uncomfortable about discussing legal issues. They may also have concerns about the privacy of information about their legal history in the medical record.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the harms. The level of research evidence is rated as low because there is minimal research on whether discussing and documenting patients' legal obligations improves outcomes. No information is available on the harms of such an approach. The strength of the statement (suggestion) was influenced by the potential variations in patient preferences as well as the uncertainty that benefits of the statement would outweigh harms for the majority of patients.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure. A process-focused internal quality improvement measure could determine rates of documenting initial treatment goals and implement quality improvement initiatives to increase the frequency at which such discussions and documentation occur in individuals with AUD.

Statement 7

APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of risks to self (e.g., physical health, occupational functioning, legal involvement) and others (e.g., impaired driving) from continued use of alcohol and that this discussion be documented in the medical record.

Implementation

Discussion of risks to self and others from continued alcohol use will be a natural outgrowth of the assessment. Most individuals who are seeking treatment will already have experienced some negative consequences of alcohol use in terms of occupational, academic, social, or interpersonal functioning; legal involvement; use of alcohol in physically hazardous situations; or physical or psychological

problems related to alcohol use or alcohol withdrawal. Patients will typically mention some negative experiences with alcohol in the context of describing current motivations for treatment. Additional risks can be explored with the patient and documented, with the aim of reducing harms associated with drinking. Screening instruments such as the Drinker Inventory of Consequences (Miller et al., 1995) or the shortened version, the Short Index of Problems (SIP; Forcehimes et al., 2007; Feinn et al., 2003) may aide clinicians in identifying and supporting discussions of negative consequences of alcohol use.

Benefits and Harms

Benefits: Discussing potential risks to self and to others from continued use of alcohol can have a number of benefits. Such risks will often contribute to the patient's motivation for treatment, and knowledge of the patient's concerns, preferences, and motivations can facilitate treatment planning. Discussion of such risks permits education on the value of harm reduction and abstinence and helps set expectations for treatment. Documentation of such discussions promotes accurate communication among all those caring for the patient and can serve as a reminder of initial treatment goals.

Harms: A possible harm of this statement relates to the time spent in discussion and documentation that may reduce the opportunity to focus on other aspects of the evaluation. Some patients may be reluctant to discuss risks to self or others or become anxious while discussing such risks.

Patient Preferences: Clinical experience suggests that patients are cooperative with and accepting of discussions about harms of alcohol use although some individuals may minimize the possibility of harms, particularly if they are ambivalent about reducing or abstaining from alcohol use.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the harms. The strength of the statement (suggestion) was influenced by the uncertainty of whether such a discussion and documentation improves outcomes relative to a more general discussion of goals with the patient. Studies of motivational interviewing offer some support for this suggestion, but the level of research evidence is rated as low because there is minimal research on the benefits or harms of specifically discussing and documenting the risks to self and others of continued alcohol use.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure. A process-focused internal quality improvement measure could determine rates of documenting initial treatment goals and quality improvement initiatives could be implemented to increase the frequency at which such discussions and documentation occur in individuals with AUD.

Nonpharmacotherapy Treatments

Statement 8

APA recommends (1C) that patients with alcohol use disorder have a documented comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Implementation

In treating individuals with AUD, it is important to consider both non-pharmacological and pharmacological treatment approaches and develop a plan of treatment that is person-centered. Although recommending a particular non-pharmacological approach is outside the scope of this practice guideline, there are several evidence-based options for the treatment of AUD. These include motivational enhancement therapy (MET) (Lenz et al., 2016) and cognitive behavioral therapy (CBT) for AUD (Epstein and McCrady, 2009). MET is a manualized psychotherapy based on the principles of motivational interviewing that has been shown in multiple studies to have a small-to-medium effect size on achieving abstinence (Dieperink et al., 2014; Lenz et al., 2016). This treatment is designed to help patients develop intrinsic motivation to reduce or abstain from alcohol use by helping them explore their own ambivalence of alcohol use and its sequelae. CBT focuses on the relationships between thoughts, feelings, and behaviors (Epstein and McCrady, 2009). Particular attention is paid to strategies that help the patient manage urges and triggers (i.e., cues) to drink. Medical Management (MM) is also a manualized treatment (Pettinati et al. 2004) that was developed for use in the COMBINE study. It provides education and strategies to support abstinence and promote medication adherence. Self-help groups such as Alcoholics Anonymous and other 12-Step programs may be helpful for some patients. However, there is a paucity of research into these modalities and variability between groups in terms of their focus and structure (Ferri et al., 2006). For these reasons, self-help groups can augment evidence-based psychotherapeutic and pharmacological interventions in the initial treatment of AUD, but there is insufficient evidence for usage as a first-line, stand-alone treatment. They may also have some utility for patients during a maintenance phase of treatment.

A person-centered treatment plan should be documented in the medical record and updated at appropriate intervals. Such a plan does not need to adhere to a defined development process (e.g., face-to-face multidisciplinary team meeting) or format (e.g., time-specified goals and objectives), but it should give an overview of the identified clinical and psychosocial issues along with a specific plan for further evaluation, ongoing monitoring, and nonpharmacological and pharmacological interventions, as indicated. Depending on the urgency of the initial clinical presentation, the availability of laboratory results, or collateral informants, the initial treatment plan may need to be augmented over several visits and as more details of history and treatment response are obtained. Collateral informants such as family members, friends, or other treating health professionals may express specific concerns about the individual's alcohol use or related behaviors. If present, such concerns should be documented and addressed as part of the treatment plan. Additionally, the patient’s goals and readiness to change their alcohol consumption may evolve over time and necessitate changes to the treatment plan. Such person-centered treatment plans may require tailoring based on sociocultural factors such as gender and age (Kerr-Correa et al., 2007; Sudhinaraset et al., 2016).

Benefits and Harms

Benefits: Development and documentation of a comprehensive treatment plan assures that the clinician has considered the available non-pharmacological and pharmacological options for treatment, and identified those treatments that are best suited to the needs of the individual patient with a goal of improving overall outcome. It may also assist in forming a therapeutic relationship, eliciting patient preferences, permitting education about possible treatments, setting expectations for treatment, and establishing a framework for shared decision-making. Documentation of a treatment plan promotes accurate communication among all those caring for the patient and can serve as a reminder of prior discussions about treatment.

Harms: The only identifiable harm from this recommendation relates to the time spent in discussion and documentation that may reduce the opportunity to focus on other aspects of the evaluation.

Patient Preferences: Clinical experience suggests that patients are cooperative with and accepting of efforts to establish initial goals and plans of treatment.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. The level of research evidence is rated as low because no information is available on the harms of such an approach. There is also minimal research on whether developing and documenting a specific treatment plan improves outcomes as compared to assessment and documentation as usual. However, the majority of studies of pharmacotherapy for AUD included non-pharmacological treatments aimed at providing supportive counseling, enhancing coping strategies, and promoting adherence. This indirect evidence supports the benefits of comprehensive treatment planning.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

It is not known whether psychiatrists and other mental health professionals typically develop and document a comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments. However, there is likely to be variability. Among individuals who were identified with AUD with screening in general ambulatory settings, only a small fraction received any information about treatment (Glass et al., 2016). Nevertheless, a performance measure derived from this recommendation is not recommended because of the associated burdens and practical challenges. Clinical judgment would be needed to determine whether a documented treatment plan was comprehensive and person-centered, even if listed treatments were evidence-based. If a performance measure assessed for the presence or absence of specific text in the medical record, increased documentation burden could result and overuse of standardized language that would not accurately reflect what has occurred in practice.

Selection of a Pharmacotherapy

Statement 9

APA recommends (1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of reducing alcohol consumption or achieving abstinence;**
- **prefer pharmacotherapy or have not responded to nonpharmacological treatments alone; and**
- **have no contraindications to the use of these medications.**

Implementation

Naltrexone and acamprosate have the best available evidence as pharmacotherapy for patients with AUD. In most studies, participants were included on the basis of a DSM-IV diagnosis of alcohol dependence, which roughly corresponds to moderate-to-severe AUD in DSM-5 (Hasin et al., 2013; Peer et al., 2013; Compton et al., 2013). Use of these medications may also be appropriate to consider on an individualized basis for patients with mild AUD, particularly if the patient prefers this treatment modality.

In the AHRQ review (Jonas et al., 2012), there was no evidence that either of these medications was superior to the other. Thus, other factors will likely guide medication selection including ease of administration, side effect profile, and the presence of co-occurring conditions that would affect treatment with a specific medication. There is no evidence regarding the specific duration of treatment with these medications. Decisions about the duration of treatment with these medications will also be based on individual factors such as patient preference, disorder severity, history of relapses, potential consequences of relapse, clinical response, and tolerability.

Acamprosate is a glutamate receptor antagonist that is efficacious in the treatment of AUD. In a systematic review of the literature by AHRQ (Jonas et al., 2012), acamprosate was efficacious when administered at a mean dose of 1998 mg per day (typically, 666 mg three times per day). Individuals who were randomly assigned to acamprosate were significantly less likely to return to drinking after attaining abstinence and had a significant reduction in the number of drinking days, although data on the number of heavy drinking days were mixed. Most experts recommend starting treatment as soon as abstinence is attained and continuing even if the patient relapses. Serum creatinine should be measured before initiating treatment. Acamprosate is contraindicated if estimated creatinine clearance (CrCl) is less than 30 mL/min, and dose reduction may be necessary for values between 30 and 50 mL/min. Common side effects include diarrhea (17% compared to 10% in placebo; Micromedex, 2017a). Therefore, screening for other psychiatric conditions is an important part of the initial evaluation of AUD.

Naltrexone is a mu-opioid receptor antagonist that has efficacy in the treatment of both AUD and opioid use disorder. This medication has been associated with a reduced likelihood of return to drinking and with fewer drinking days overall. Naltrexone is also thought to decrease the subjective experience of "craving." Naltrexone is available in both a daily oral and monthly depot intramuscular (IM) injection.

Although long-acting IM naltrexone may improve adherence, there have been no head-to-head comparisons of oral vs. IM naltrexone for AUD and both formulations appear to be effective. The recommended dose of oral naltrexone is 50 mg daily; however, some patients may require doses up to 100 mg daily to achieve efficacy (Garbutt et al., 2005; McCaul et al., 2000a; McCaul et al., 2000b). For long-acting naltrexone, the typical starting dose is 380 mg IM every four weeks. Potential side effects of naltrexone include abdominal pain (11% vs. 8% in placebo), diarrhea (13% vs. 10% in placebo), nausea (29% vs. 11% in placebo), vomiting (12% vs. 6% in placebo), and dizziness (13% vs. 4% in placebo; Micromedex, 2017c). Gastrointestinal side effects may occur more often among women than men (Herbeck et al., 2016). Hepatic functioning can also be affected by naltrexone, and the labelling includes a warning about use of this medication in patients with acute hepatitis or liver failure. Because naltrexone is an opioid receptor antagonist, naltrexone may lead to reduce effectiveness of opioids taken for analgesia. It is advisable for patients to carry a wallet card noting that they are taking naltrexone so this information will be available to emergency personnel. Additionally, patients must be abstinent from opioids for 7-10 days prior to starting naltrexone and should be informed of the risk for precipitating opioid withdrawal if used in conjunction with an opioid.

Benefits and Harms

Benefits: Acamprosate is associated with a small benefit on the outcomes of returning to any drinking and on the number of drinking days (moderate strength of research evidence). Naltrexone is associated with a small benefit on the outcomes of returning to any drinking, returning to heavy drinking, frequency of drinking days, and frequency of heavy drinking days (moderate strength of research evidence). In head-to-head comparisons, neither acamprosate nor naltrexone showed superiority to the other medication in terms of return to heavy drinking (moderate strength of research evidence), return to any drinking (moderate strength of research evidence), or percentage of drinking days (low strength of research evidence).

Harms: The harms of acamprosate are small in magnitude with slight overall increases in anxiety, diarrhea, and vomiting as compared to placebo (moderate strength of research evidence). The harms of naltrexone are small in magnitude with slight overall increases in dizziness, nausea, and vomiting relative to placebo (moderate strength of research evidence). For many potential harms, including mortality, evidence was not available or was rated by the AHRQ review as insufficient. However, withdrawals from the studies due to adverse events did not differ from placebo for acamprosate (low strength of research evidence) and were only slightly greater than placebo for naltrexone (moderate strength of research evidence).

Patient Preferences: Some patients prefer to avoid use of medication whereas others prefer to take a medication than to use non-pharmacological treatment approaches. Some patients may also prefer one medication over another medication, based on prior treatment experiences, available medication formulations, or other factors. However, clinical experience suggests that the majority of patients would want to be offered the option of these pharmacotherapies for AUD.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. For both

acamprosate and naltrexone, the harms of treatment were considered minimal as long as there was no contraindication to the use of the medication. Although the positive effects of acamprosate and naltrexone were small, the benefit of each medication was viewed as far outweighing the harms when non-pharmacological approaches had not produced an effect or when patients preferred to use one of these medications as an initial treatment option. In addition, it was noted that even small effect sizes may be clinically meaningful because of the significant morbidity associated with AUD. There was no evidence to suggest that either medication should be used in preference to the other for patients with moderate to severe AUD. Patients with mild AUD rarely participated in clinical trials of naltrexone and acamprosate pharmacotherapy. Although they might respond to these medications, patients with mild AUD are not included in this recommendation due to the lack of research evidence.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

Information from the Veterans Health Administration suggests low rates of pharmacotherapy for AUD. Approximately 3% of patients with AUD received a prescription for naltrexone with less than 10% of those treated with naltrexone receiving long-acting injectable naltrexone (Iheanacho et al., 2013; Marienfeld et al., 2014).

Given the clinical considerations associated with the selection of a pharmacotherapy for a patient with AUD, a performance measure derived from this recommendation is not recommended. Clinical judgment would be needed to assess whether contraindications to treatment are present and to determine if there was a lack of response to nonpharmacological treatments alone. Increased documentation burden could result if each element of the recommendation needed to be recorded as standardized or structured text. Alternatively, if information was recorded as free text, additional time would be needed in reviewing documentation and determining if measure criteria were met. However, this recommendation could be used as a process-focused internal quality improvement measure by tracking rates of prescribing for naltrexone and acamprosate in individuals with AUD. Changes in prescribing rates could be determined after initiatives to educate clinicians or reduce barriers to pharmacotherapy use (Harris et al., 2016; Abraham et al., 2011). Electronic decision support could identify individuals with a new diagnosis of moderate-to-severe AUD (as documented as a problem or diagnosis) and provide information on acamprosate and naltrexone for consideration by the clinician through a passive alert or "infobutton." (Del Fiol et al., 2012)

Statement 10

APA suggests (2C) that disulfiram be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of achieving abstinence;**
- **prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate;**
- **are capable of understanding the risks of alcohol consumption while taking disulfiram; and**

- **have no contraindications to the use of this medication.**

Implementation

Disulfiram is an inhibitor of the enzyme aldehyde dehydrogenase, which breaks down the ethanol byproduct acetaldehyde. When a patient consumes alcohol within 12-24 hours of taking disulfiram, the accumulation of acetaldehyde produces a response that includes tachycardia, flushing, headache, nausea, and vomiting. In this way, disulfiram serves to negatively reinforce abstinence from alcohol. Because of this, disulfiram is only appropriate for individuals seeking abstinence and contraindicated in patients who are actively using alcohol. Many clinicians also recommend involving a family member or roommate as a direct observer of daily medication adherence.

Before prescribing disulfiram, patients should consent to taking the medication and be fully informed of the physiologic consequences of consuming alcohol on disulfiram. They should be instructed to abstain from drinking alcohol for at least 12 hours after taking the medication and be advised that reactions with alcohol can occur up to 14 days after taking disulfiram. It is important to caution patients that certain medications (e.g., metronidazole, ritonavir) and any product containing alcohol (e.g., certain mouth washes and cold remedies) may provoke a reaction. For example, the oral concentrate formulation of sertraline contains 12% alcohol, which can precipitate a reaction with disulfiram. Before starting disulfiram, baseline cardiac and hepatic function may be appropriate to assess. Disulfiram may also not be appropriate for individuals with a recent myocardial infarction or coronary artery disease given the risk of tachycardia if they were to consume alcohol. Disulfiram is not generally recommended in patients with a seizure disorder due to the possibility of accidental disulfiram-alcohol reactions. It is important to advise patients to carry a wallet card noting that they are taking disulfiram so this information will be available to emergency personnel.

Given the physiological consequences of drinking in combination with disulfiram and the evidence for efficacy of naltrexone and acamprosate, disulfiram is not generally chosen as an initial therapy. However, there may be circumstances in which an individual patient prefers disulfiram or has a clear goal of abstinence for which disulfiram would be indicated. Regarding the duration of treatment with disulfiram, there is no evidence available; such decisions are likely to be based on individual factors such as patient preference, disorder severity, history of relapses, potential consequences of relapse, clinical response, and tolerability.

Benefits and Harms

Benefits: Benefits for disulfiram on alcohol related outcomes were not reported in the AHRQ review (low strength of research evidence). However, a subsequent meta-analysis (Skinner et al., 2014) that included open-label studies (low strength of research evidence) showed a moderate effect of disulfiram as compared to no disulfiram as well as compared to acamprosate, naltrexone, and topiramate. In studies where medication adherence was assured through supervised administration, the effect of disulfiram was large (Skinner et al., 2014).

Harms: There were insufficient data on harms of disulfiram to conduct meta-analysis in the AHRQ report. When open-label studies were included (low strength of research evidence; Skinner et al., 2014),

there was a significantly greater number of adverse events with disulfiram than with control conditions. The package insert for disulfiram lists multiple significant harms that can occur if alcohol-containing products are ingested concomitantly with disulfiram use.

Patient Preferences: Because of its aversive events, some patients may prefer to take disulfiram as compared to other AUD pharmacotherapies or non-pharmacological treatments to help strengthen their motivation to abstain from alcohol. Other patients may prefer not to take disulfiram due to the potential for significant adverse events if ingested concomitantly with alcohol.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the harms. The strength of research evidence is rated as low as there were insufficient data from randomized controlled trials (RCT) and the bulk of the research evidence for benefits and for harms was from open-label studies. With carefully selected patients in clinical trials, adverse events were somewhat greater with disulfiram. However, serious adverse events were few and comparable in numbers to serious adverse events in comparison groups. Consequently, the potential benefits of disulfiram were viewed as outweighing the harms for most patients given the medium to large effect size for the benefit of disulfiram when open-label studies are considered and the clinical consensus of a benefit of disulfiram during its long history of use. In addition, it was noted that even small effect sizes may be clinically meaningful because of the significant morbidity associated with AUD. The strength of the guideline statement (suggestion) was influenced both by the strength of research evidence and by patient preferences related to disulfiram as compared to other interventions.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure.

Statement 11

APA suggests (2C) that topiramate, gabapentin, or ondansetron be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of reducing alcohol consumption or achieving abstinence;**
- **prefer topiramate, gabapentin, or ondansetron or are intolerant to or have not responded to naltrexone and acamprosate;**
  and
- **have no contraindications to the use of these medications.**

Implementation

Several additional medications may be efficacious in the treatment of moderate-to-severe AUD. These include topiramate, gabapentin, and ondansetron. Although these medications will typically be used after trials of naltrexone and acamprosate, patient preference may lead to earlier use. Other factors that can guide medication selection include ease of administration, side effect profile, and the presence of

co-occurring conditions that would affect treatment with a specific medication. Efficacy data, however, come from a limited number of smaller studies. For this reason, they are considered second-line to naltrexone and acamprosate. There is no specific evidence on the optimal duration of treatment with these medications; such decisions are likely to be based on individual factors such as patient preference, disorder severity, history of relapses, potential consequences of relapse, clinical response, and tolerability.

In clinical trials, topiramate was associated with significant reductions in heavy drinking days and in the subjective experience of "craving" (Guglielmo et al., 2015; Martinotti et al., 2014), typically at doses of 200- 300 mg daily. Because of its association with weight loss in 4-21% of patients (Micromedex, 2017e), topiramate may be a medication to consider in patients with obesity. Other common side effects of topiramate include sedation, cognitive dysfunction (e.g., effects on short-term memory) (3-12%), dizziness (4-25%), paresthesias (1-51%), and gastrointestinal side effects (2-11% vs. 6% in placebo) (Micromedex, 2017e). Less common but notable side effects include metabolic acidosis, nephrolithiasis, and precipitation of acute angle-closure glaucoma. When initiating treatment with topiramate, it may be appropriate to assess renal function and cognitive status at baseline. Caution is also warranted in patients at risk for falls including the elderly.

Gabapentin, at doses between 900-1800 mg per day, was associated with an increased rate of abstinence and a reduction in heavy drinking days in a single

RCT (Anton et al., 2011; Mason et al., 2014). Dose-dependent sedation is the most common side effect of gabapentin occurring in approximately 21% of patients (Micromedex, 2017b). Gabapentin is contraindicated in severe renal impairment.

Ondansetron may be efficacious for reducing heavy drinking days at a dose of 16mg per day. Response to ondansetron may be greater in individuals with early onset as compared to later onset AUD. Side effects like diarrhea and constipation can occur (Micromedex, 2017d). In addition, some research suggests that ondansetron may be particularly helpful in individuals with a specific polymorphism in the serotonin transporter gene; however, this data is preliminary and further research is necessary before incorporating this genetic marker into clinical practice.

Other medications including valproic acid, baclofen, and buspirone are being investigated for use in the treatment of AUD; however, currently the evidence for their use is limited.

Benefits and Harms

Benefits: Topiramate is associated with moderate benefit on drinks per drinking day, percentage of heavy drinking days, and percentage of drinking days (moderate strength of research evidence) and gabapentin is associated with moderate benefit on rates of abstinence and abstinence from heavy drinking (low to moderate strength of research evidence). Ondansetron is associated with small to moderate benefit on drinks per day, drinks per drinking day and rate of abstinence (low strength of research evidence) in selected subgroups of patients (based on genetic polymorphism subtype or age of onset of AUD).

Harms: Topiramate is associated with an increased likelihood of cognitive dysfunction and numbness, tingling, or paresthesias relative to placebo (moderate strength of research evidence). Metabolic acidosis has been reported when topiramate is used to treat other conditions, and reductions in dose are needed in patients with co-occurring renal impairment. Less often, topiramate has been associated with development of nephrolithiasis or acute angle closure glaucoma. Gabapentin was not associated with an increased likelihood of adverse events relative to placebo (low strength of research evidence). In studies that examine side effects of gabapentin in other conditions reported, side effects have included dizziness and somnolence but are typically mild. Ondansetron is associated with minimal harms with an increased likelihood of constipation relative to placebo (low strength of research evidence). A potential for QTc prolongation has also been reported with ondansetron.

Patient Preferences: Clinical experience suggests that many patients would want to be offered the option of these pharmacotherapies for AUD, particularly if therapies such as naltrexone or acamprosate were not helpful or had contraindications. Some patients may also prefer one medication over another medication based on factors such as prior treatment experiences, available medication formulations, or side effect profiles.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as likely to outweigh the harms. Gabapentin and ondansetron had small positive effects, but the harms of treatment were seen as being minimal as long as there was no contraindication to the use of the medication. In addition, it was noted that even small effect sizes may be clinically meaningful because of the significant morbidity associated with AUD. With topiramate, benefits were moderate but patients often expressed concern about associated cognitive dysfunction. The role of patient preference in being offered potentially helpful medications was also taken into consideration in rating the strength of the guideline statement (suggestion). There was no evidence comparing these medications to each other, which also supports a role for patient preference based on factors such as medication availability or side effect profiles.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this suggestion.

Quality Measurement Considerations

As a suggestion, this statement is inappropriate for use as a quality measure.

Recommendations Against Use of Specific Medications

Statement 12

APA recommends (1B) that antidepressant medications not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment.

Implementation

Antidepressant medications are not recommended to treat AUD because of their lack of efficacy for alcohol-related outcomes. Nevertheless, AUD often co-occurs with other psychiatric disorders, which

can affect access to care and reduces treatment outcomes for both types of disorders (Drake et al., 2013). Consequently, individuals with AUD may require antidepressants for the treatment of co-occurring psychiatric disorders (e.g., depressive disorders, anxiety disorders, OCD). Recommendations regarding the treatment of such conditions is beyond the scope of this document, but the initial evaluation of a patient with AUD should include assessment for co-occurring psychiatric disorders.

Benefits and Harms

Benefits: The benefits of this statement are that patients would not be exposed to antidepressant medications (with the associated possibility of side effects) when a therapeutic response to those medications would be unlikely in terms of alcohol-related outcomes (moderate strength of research evidence).

Harms: The harms of this statement are that some individuals may not be offered a medication that could be useful to them in reducing drinking behaviors.

Patient Preferences: Clinical experience suggests that few patients would want to receive a medication that may have side effects and that is unlikely to improve alcohol related outcomes.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of avoiding side effects from a treatment that is likely to be ineffective for AUD was viewed as far outweighing the potential harms of restricting access to antidepressants to a small number of patients whose AUD may show some response. Individuals with other indications for treatment with an antidepressant agent for co-occurring depressive disorders, anxiety disorders, or posttraumatic stress disorder would still be able to receive an antidepressant for those conditions. The strength of the guideline statement (recommendation) was influenced both by the strength of research evidence and by patient preferences for avoiding medication side effects and avoiding ineffective therapies.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure because the recommendation would not pertain to the majority of individuals with AUD. However, this recommendation may be appropriate for use in the Choosing Wisely initiative. It could also be used as an internal quality improvement measure if prescribing of antidepressant medications appears to be frequent among patients with AUD. Furthermore, this recommendation could be integrated into electronic clinical decision support. If an order for an antidepressant is entered for an individual with AUD, the clinicians could be alerted to consider whether antidepressant therapy is indicated or not. The alert could be configured so that it would not be presented to the clinician for patients with a documented problem or diagnosis of major depressive disorder, obsessive-compulsive disorder, post-traumatic stress disorder, or panic disorder with or without agoraphobia.

Statement 13

APA recommends (1C) that, in individuals with alcohol use disorder, benzodiazepines not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment.

Implementation

There is no evidence for the use of benzodiazepines in the primary treatment of AUD, except for the treatment of alcohol withdrawal and alcohol detoxification. However, there may still be situations in which prescribing a benzodiazepine is appropriate to treat a co-occurring psychiatric condition such as an anxiety disorder. Clinicians should exercise caution because benzodiazepine use in the setting of alcohol intoxication carries with it an increased risk for sedation, behavioral impairment, respiratory depression, and death in severe cases. Clinicians should discuss this risk with patients who are actively drinking alcohol and consider alternative medications when possible. If a benzodiazepine is prescribed, one might consider prescribing only a limited quantity at the lowest possible dose in order to mitigate these risks.

Benefits and Harms

Harms: The harms of this statement are that some individuals may not be offered a medication that could be useful to them as an individual in reducing drinking behaviors.

Patient Preferences: Some patients may request treatment with a benzodiazepine based on short-term anxiolytic effects or beliefs that it may serve as a substitute for alcohol. However, generally patients do not want to receive a medication that may have side effects and that is unlikely to improve outcomes for one's condition.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of avoiding side effects from a treatment that is likely to be ineffective for AUD was viewed as far outweighing the potential harms of restricting access to benzodiazepines to a small number of patients whose AUD may show some response. The potential for developing tolerance to or misuse of benzodiazepines was given additional weight in the recommendation to avoid using this class of medications in a patient with AUD except for the acute treatment of alcohol withdrawal. Individuals with other indications for treatment with a benzodiazepine would still be able to receive the medication after consideration of the advantages and disadvantages for the individual. In determining the strength of the guideline statement (recommendation), the fact that some patients may desire treatment with a benzodiazepine was given less weight than the potential for side effects, misuse or developing tolerance to benzodiazepines particularly because no studies have examined whether benzodiazepines have any efficacy in reducing drinking behaviors.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure. Most clinicians are already aware of the potential difficulties in using benzodiazepines to treat an individual with AUD, unless acute

alcohol withdrawal or another appropriate indication is present. However, this recommendation may be appropriate for use in the Choosing Wisely initiative. In addition, this recommendation may be appropriate for integration into electronic clinical decision support. Clinicians could be alerted to consider whether an appropriate indication exists for benzodiazepine treatment if a benzodiazepine order is entered for an individual with a documented problem or diagnosis of AUD.

Statement 14

APA recommends (1C) that, for pregnant or breastfeeding women with alcohol use disorder, pharmacologic treatments not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacologic treatment.

Implementation

There is limited evidence regarding the potential risks posed to a fetus or infant exposed to pharmacotherapies for AUD (Briggs et al., 2015). There does appear to be an increased risk of malformation associated with use of topiramate (Briggs et al., 2015; Weston et al., 2016; Alsaad et al., 2015; Tennis et al., 2015) and inconsistent findings on possible cardiac septal defects with ondansetron, although the overall risk of malformation is low (Carstairs, 2016). Data in pregnant animals are not available for disulfiram, but suggest a low risk for use of ondansetron, moderate risk for use of naltrexone, high risk for use of acamprosate, and possible risks for use of gabapentin and topiramate (Briggs et al., 2015). For these reasons, it is recommended that non-pharmacologic interventions be used preferentially for treating AUD during pregnancy. For individuals who become pregnant while taking a medication to treat AUD, the risk to continue or stop pharmacologic treatment should be individualized to the patient. Potential risk to the fetus from medication should be balanced against the risk of relapse to alcohol use, which itself carries teratogenic risk. Decisions about breastfeeding and use of these medications in breastfeeding women also require individualized discussion with the patient and the infant's pediatrician. Again, data are limited but there may be potential for toxicity with disulfiram, naltrexone, and topiramate (Briggs et al., 2015), whereas acamprosate, gabapentin, and ondansetron are noted to be "probably compatible" with breastfeeding (Briggs et al., 2015).

Benefits and Harms

Benefits: The benefits of this statement are that a fetus or infant would not be exposed to medication used to treat AUD and the potential for adverse events (including malformations) from such an exposure would be minimized.

Harms: The potential harms of this statement are that a woman might not receive treatment with medication for AUD and would not experience any associated reductions in drinking behavior from AUD pharmacotherapy. This could also contribute to harms for the fetus or infant due to the effects of ongoing alcohol use.

Patient Preferences: Clinical experience suggests that most women who are pregnant or breastfeeding prefer to use non-pharmacological treatment approaches as compared to pharmacotherapy to minimize the risk of possible malformations or side effects in their child.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of avoiding medications for AUD treatment while pregnant or breastfeeding were viewed as far outweighing the potential harms of restricting access to these medications. In determining the strength of the guideline statement (recommendation), the relatively small magnitude of clinical benefit with naltrexone and acamprosate was considered (moderate strength of research evidence) as well as the uncertainty of knowledge about teratogenic effects of these medications. The balance of benefits and harms was less clear for topiramate, gabapentin and ondansetron. The guideline statement also considers the preference of most women and their partners to avoid medications if pregnant or breastfeeding as far as possible.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this is recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure. The recommendation would not pertain to the majority of individuals with AUD and adherence with this recommendation is already likely to be high as a result of the patient and clinician concern about use of medication while pregnant or breastfeeding. However, this recommendation may be appropriate for integration into electronic clinical decision support. In women who are pregnant or breastfeeding, clinicians could be alerted to avoid pharmacotherapy for AUD except under the circumstances noted in the recommendation.

Statement 15

APA recommends (1B) that acamprosate not be used by patients who have severe renal impairment.

Implementation

Baseline renal function should be assessed before starting acamprosate. A creatinine clearance less than 30 mL/min is a contraindication to the use of acamprosate and an alternative medication such as naltrexone should be used.

Benefits and Harms

Benefits: Avoiding use of acamprosate in patients with severe renal impairment is beneficial because the patient would also avoid experiencing toxicity from excessive drug levels as a result of reduced clearance of acamprosate.

Harms: The potential harm of this recommendation is that it could restrict access to acamprosate for a patient who might otherwise benefit from it.

Patient Preferences: Clinical experience suggests that few patients would want to receive a medication that may have significant increases in potential toxicity in the presence of severe co-occurring renal impairment.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. This recommendation is rated as having a moderate strength of evidence because the single

pharmacokinetic study in individuals with renal impairment showed linear increases in acamprosate levels with reductions in creatinine clearance (Sennesael J, 1992).

The strength of the guideline statement (recommendation) was influenced by the value placed on the FDA recommendation, the availability of other effective medications, and the desire of clinicians and patients to avoid known toxicities of medication.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure. Adherence with this recommendation is already likely to be high as a result of the FDA warning about use of acamprosate in individuals with severe renal impairment. However, this recommendation may be appropriate for integration into electronic clinical decision support. Clinicians could be alerted to use a different pharmacotherapy for AUD in individuals with a documented problem or diagnosis of severe renal impairment.

Statement 16

APA recommends (1B) that, for individuals with mild-to-moderate renal impairment, acamprosate not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function.

Implementation

Baseline renal function should be assessed before starting acamprosate. For a creatinine clearance between 30 and 50 mL/min, a reduced dose of 333 mg three times per day is suggested. Alternatively, a different medication such as naltrexone could be used.

Benefits and Harms

Benefits: Avoiding first-line use of acamprosate in patients with mild to moderate renal impairment is beneficial because the patient would avoid experiencing toxicity from excessive drug levels as a result of reduced clearance of acamprosate. Similarly, if acamprosate were used in patients with mild to moderate renal impairment, reducing the administered dose would also reduce the likelihood of experiencing toxicity.

Harms: The potential harm of this statement is that it could restrict access to acamprosate for a patient who might otherwise benefit from it.

Patient Preferences: Clinical experience suggests that most patients would prefer to begin treatment with a medication that is less likely to be associated with side effects, when efficacy is otherwise comparable. In addition, virtually all patients would want to have doses of medication adjusted to reduce the possibility of medication related toxicity.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as far outweighing the potential harms. The benefits of this

statement were expected to be greatest for individuals with moderate renal impairment but the statement was also viewed as applicable to those with mild renal impairment. This recommendation is rated as having a moderate strength of evidence because the single pharmacokinetic study in individuals with renal impairment showed linear increases in acamprosate levels with reductions in creatinine clearance (Sennesael J, 1992).

This finding was sufficient for the Food and Drug Administration to include information in the package insert about reducing acamprosate doses in the presence of moderate renal impairment. The strength of the guideline statement (recommendation) was influenced both by the value placed on the FDA recommendation as well as the desire of clinicians and patients to avoid known toxicities of medication.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure. Although clinicians may be less aware of the need to adjust the dosing of acamprosate in mild-to-moderate renal impairment, the recommendation would not pertain to the majority of individuals with AUD. However, this recommendation may be appropriate for integration into electronic clinical decision support. Clinicians could be alerted to consider a different pharmacotherapy for AUD in individuals with a documented problem or diagnosis of renal impairment. If an order for acamprosate is placed after review of the preceding alert, clinical decision support could advise adjusting the dose of the medication in proportion to the degree of renal impairment.

Statement 17

APA recommends (1C) that naltrexone not be used by patients who have acute hepatitis or hepatic failure.

Implementation

Based upon some data from clinical trials, individuals treated with naltrexone may exhibit increases in hepatic enzyme levels or other signs of hepatocellular injury. Therefore, it would be appropriate to obtain baseline and one-month follow-up liver-function tests with continued monitoring as clinically appropriate.

Benefits and Harms

Benefits: Because of initial reports that naltrexone may be associated with hepatic changes, it is beneficial to avoid use of naltrexone in patients with acute hepatitis or hepatic failure to minimize the risk of additional hepatic damage.

Harms: The potential harm of this recommendation is that it could restrict access to naltrexone for a patient who might otherwise benefit from it.

Patient Preferences: Clinical experience suggests that few patients would want to receive a medication that may have significant increases in potential toxicity in the presence of acute hepatitis or hepatic failure.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this recommendation were viewed as far outweighing the potential harms. The evidence for naltrexone associated hepatoxicity is relatively weak (low strength of research evidence). It is based primarily on early studies of other conditions (e.g., obesity, dementia) in which some patients had several fold elevations in hepatic transaminase levels (Mitchell et al., 1987; Knopman and Hartman , 1986; Verebey and Mulé , 1986; Pfohl et al., 1986; Malcolm et al., 1985). However, the finding was sufficient for the Food and Drug Administration to include a warning that naltrexone should not be used in individuals with acute hepatitis or hepatic failure. The strength of the guideline statement (recommendation) was influenced both by the value placed on the FDA recommendation as well as the desire of clinicians and patients to avoid toxicities of medication.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure. Adherence with this recommendation is already likely to be high as a result of the FDA warning about use of naltrexone in individuals with acute hepatitis or hepatic failure. However, this recommendation may be appropriate for integration into electronic clinical decision support. Clinicians could be alerted to consider a different pharmacotherapy for AUD in individuals with a documented problem or diagnosis of acute hepatitis or hepatic failure.

Statement 18

APA recommends (1C) that naltrexone not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids.

Implementation

Because naltrexone is a mu-opioid receptor antagonist, it is efficacious in treating both AUD and opioid use disorder. However, before starting naltrexone, patients must be abstinent from opioids for five to seven days (depending on the duration of action of the opioid) due to the risk for precipitating opioid withdrawal. It is also important that patients understand the risk of precipitated withdrawal if they continue to use opioids during treatment initiation with naltrexone. Strategies for minimizing the risk of opioid withdrawal might include starting with a small test dose of oral naltrexone (e.g., 25 mg) and/or obtaining a urine drug screen for opioids before initiating treatment.

Benefits and Harms

Benefits: It is beneficial to avoid use of naltrexone in individuals who are currently using opioids because the addition of naltrexone to an opioid will produce a withdrawal syndrome. It is also beneficial to avoid using naltrexone in an individual who may need opioid medications in the near future, because those medications would not have their usual efficacy if naltrexone had been previously administered.

Harms: The potential harm of this statement is that it could restrict access to naltrexone for a patient who might otherwise benefit from it. However, an individual with co-occurring AUD and opioid use

disorder could receive naltrexone to treat both disorders if able to maintain abstinence for a clinically appropriate period of time before starting on naltrexone.

Patient Preferences: Clinical experience suggests that patients do not wish to experience the significant opioid withdrawal syndrome that is precipitated by giving an opioid antagonist in the presence of an opioid. Patients also would not wish to forego adequate pain control due to a prior use of naltrexone if their anticipated pain needs could not be adequately controlled using non-opioid medications.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as far outweighing the potential harms. Although there is no research evidence that addresses the precise clinical circumstances described in the statement, clinical use of opioid antagonists to reverse effects of opioid intoxication produces a predictable syndrome of opioid withdrawal that is consistent with the neurobiological mechanisms of opioid antagonists such as naltrexone. Product labeling for naltrexone warns that abruptly precipitating opioid withdrawal by administering an opioid antagonist to an opioid-dependent patient can result in severe withdrawal that in some individuals may require hospital admission and intensive care unit management. The strength of the guideline statement (recommendation) was influenced by these clinical observations as well as by patient preferences.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure because, among individuals who present for treatment of AUD, the fraction of patients who use or have an anticipated need for opioids is likely to be small. However, this recommendation may be appropriate for integration into electronic clinical decision support. At the time of placing an initial order for naltrexone, clinicians could be alerted to consider whether the individual is currently using opioids or has an anticipated need for opioids.

Treatment of Alcohol Use Disorder and Co-Occurring Conditions

Statement 19

APA recommends (1C) that, in patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone be prescribed to individuals who:

- **wish to abstain from opioid use and either abstain from or reduce alcohol use and**
- **who are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.**

Implementation

Because naltrexone is a mu-opioid receptor antagonist, it is efficacious in treating both AUD and opioid use disorder. Protocols have been developed for transitioning patients from opioid agonist (i.e.,

methadone or buprenorphine) to antagonist therapy with naltrexone (Mannelli et al., 2012). Note that, before starting naltrexone, patients must be abstinent from opioids for five to seven days (depending on the duration of action of the opioid) due to the risk for precipitating opioid withdrawal. Strategies for minimizing the risk of opioid withdrawal might include starting with a small test dose of oral naltrexone (e.g., 25 mg) and/or obtaining a urine drug screen for opioids before initiating treatment.

Benefits and Harms

Benefits: Naltrexone has benefits in treating AUD (see Statement 9) and evidence from some studies supports the efficacy of naltrexone in individuals with opioid use disorder (Timko et al., 2016; Larney et al., 2014; Minozzi et al., 2011). It is also beneficial to treat both disorders with a single medication in order to reduce the potential for some side effects and for medication interactions. Adherence with treatment may also be improved by less complicated medication regimens.

Harms: The harms of treating AUD and co-occurring opioid use disorder with naltrexone are that a patient may not experience therapeutic benefits from naltrexone for both disorders.

Patient Preferences: Most patients prefer to take the smallest number of medications that will address all their symptoms and diagnoses, with the goals of minimizing side effects, cost, and inconvenience in taking multiple medications or doses.

Balancing of Benefits and Harms in Rating the Strength of the Guideline Statement: The potential benefits of this statement were viewed as far outweighing the potential harms. Clinical experience supports the value of prescribing the smallest number of medications and medication doses that will address the patient's clinical condition. Although there is no research evidence that addresses the precise clinical circumstances described in the recommendation, the strength of the guideline statement (recommendation) was influenced by the evidence for naltrexone efficacy in both AUD and opioid use disorder as well as by clinical experience and patient preferences.

Differences of opinion among writing group members: None. The writing group voted unanimously in favor of this recommendation.

Quality Measurement Considerations

This statement is not likely to be appropriate for use as a quality measure because the fraction of patients who have AUD and a co-occurring opioid use disorder is likely to be small. However, this recommendation may be appropriate for integration into electronic clinical decision support. Clinicians could be alerted to consider whether naltrexone would be an appropriate pharmacotherapy for individuals with documented AUD and opioid use disorder as a problem or diagnosis.

Areas for Further Research

This practice guideline incorporates available evidence on the treatment of AUD; however, additional research is essential (Jonas et al., 2014; Litten et al., 2014). More knowledge is needed about the basic neurobiology and genetics of AUD if we are to understand the etiology of this disorder and develop novel treatments. In terms of clinical practice, most knowledge of assessment and documentation is

based on clinical consensus. For ethical and practical reasons, well-designed studies are difficult to conduct on topics such as:

- Developing and documenting a comprehensive, person-centered, evidence-based plan of treatment
- Discussing, gaining patient agreement and documenting initial goals of treatment, including legal obligations and risks to self or others
- Assessing current and past tobacco, alcohol and other substance use
- Assessing for co-occurring conditions that are common in individuals with AUD or that would influence treatment choices

In terms of other means of assessing individuals with AUD, additional research is needed on topics such as:

- Optimizing selection and use of quantitative measures for initial evaluation and for longitudinal monitoring
- Individualizing selection of a physiological biomarker for initial evaluation and for longitudinal monitoring, based upon the goals of treatment, goals of monitoring, and test performance (including predictive value)
- Determining the appropriate frequency of longitudinal monitoring with quantitative measures and with physiological biomarkers

Although naltrexone and acamprosate have been well-studied in placebo-controlled and some head-to-head trials, other pharmacotherapies for AUD require additional study with adequately powered sample sizes and appropriate methods for analysis of missing data. We also need more knowledge on the efficacy, effectiveness, and adverse events of available and novel pharmacotherapies for AUD in individuals with:

- Other co-occurring psychiatric conditions (including other substance use disorders) and co-occurring medical conditions
- Differing severities of AUD, including mild AUD
- Different settings for treatment including primary care, general ambulatory psychiatry, and specialized alcohol treatment programs

Measured outcomes should focus on quality of life, including physical and mental health, as well as outcomes related to alcohol consumption. In addition, studies need to identify the magnitude of reduction in alcohol consumption that is associated with a clinical meaningful effect on outcomes.

In terms of specific subgroups of patients, additional information is needed on the:

- Comparative effectiveness of naltrexone versus combination therapy (e.g., acamprosate plus opioid agonist) for individuals with AUD and opioid use disorder
- Effects of alcohol pharmacotherapy in women who have become pregnant while taking one of these medications, as measured through registry studies

- Differential treatment responses that would allow personalized medication selection and dose based on factors such as:
    - Patient sex/gender
    - Patient age
    - Patient preferences for treatment goals or approaches
    - Pattern and amount of alcohol consumption
    - Age of onset of AUD
    - Duration of AUD
    - Family history of AUD
    - Pharmacogenetic alleles
    - Prior response (or lack of response) to treatment
    - Concomitant treatments
    - Presence or absence of specific co-occurring disorders or symptoms (e.g., suicidal ideas, aggressive behaviors, anxiety)

Other aspects of clinical pharmacotherapy for AUD that require additional research include the:

- Optimal period of abstinence (if any) before initiating treatment with a specific pharmacotherapy
- Duration of treatment needed once the patient has achieved abstinence or a reduction in alcohol consumption
- Duration of treatment needed before changing to a different medication in a patient with a lack of response or a partial response to treatment
- Sequence with which treatment options (including pharmacological and non-pharmacological approaches) should be used
- Impact of different medication formulations (e.g. oral, long-acting injectable, implantable) on treatment outcomes, including adverse events

Finally, we need more studies on ways to improve the quality of care that is received by individuals with AUD, including:

- Developing educational initiatives or health care delivery system changes to enhance guideline adherence
- Identifying approaches to address underuse of guideline concordant pharmacotherapy of AUD
- Addressing disparities in access to and receipt of guideline concordant treatment for AUD
- Developing improved approaches to reduce treatment dropouts and maintain adherence to pharmacotherapy

Together with the already sizable evidence base on AUD and its treatment, additional research on these and other topics could lead to significant improvements in outcomes for patients with AUD.

Guideline Development Process

This guideline was developed using a process intended to meet standards of the National Academy of Medicine (formerly Institute of Medicine) (2011). The process is fully described in a document available on the APA website: http://www.psychiatry.org/File%20Library/Practice/APA-Guideline-Development-Process--updated-2011-.pdf. The development process included the following key elements.

Management of Potential Conflicts of Interest

Members of the Guideline Writing Group (GWG) are required to disclose all potential conflicts of interest before appointment, before and during guideline development, and on publication. If any potential conflicts are found or disclosed during the guideline development process, the member would recuse themselves from a related discussion and voting of a related recommendation. The members of both the GWG and the Systematic Review Group (SRG) as well as the two consultants reported no conflicts of interest. The Disclosures section includes more detailed disclosure information for each GWG and SRG member and for the consultants involved in the guideline's development.

Guideline Writing Group Composition

The GWG was initially composed of seven psychiatrists and one registered nurse with general research and clinical expertise. This non-topic specific group was intended to provide diverse and balanced views on the guideline topic to minimize potential bias. For subject matter expertise, two experts on AUD were added, one of whom is board-certified in both internal medicine and addiction medicine and the other of whom is board-certified in psychiatry with subspecialty certification in child and adolescent psychiatry. One consultant (J.M.) was also added to the GWG to provide input on quality measure considerations. An additional consultant (J.K.) assisted with drafting of guideline text. The vice-chair of the GWG (L.J.F.) provided methodological expertise on topics such as appraising the strength of research evidence. The GWG was also diverse and balanced with respect to other characteristics, such as geographical location and demographic background.

XXX was involved in reviewing the draft and provided perspective from patients, families, and other care partners <<N.B. add the name(s) of the group(s) after public comment>>.

Systematic Review Methodology

The AHRQ's systematic review on *Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings* (Jonas et al., 2014) served as the predominant source of information for this guideline. Both the AHRQ review and the guideline are based upon a systematic search of available research evidence using MEDLINE (PubMed), the Cochrane Library, PsycINFO, CINAHL, and EMBASE databases. The search terms and limits used are available in the appendix. Results were limited to English-language, adult (18 and older), and human-only studies. The search that informed the AHRQ review (Jonas et al., 2014) was from January 1, 1970 to October 11, 2013, and the subsequent search of the literature by the APA staff was from September 1, 2013 through April 24, 2016. Literature from the updated search was screened by two reviewers (L.J.F. and S-H.H.) according to APA's general screening criteria (i.e., RCT, systematic review or meta-analysis, or observational study with a sample of at least 50 individuals; human; study of the effects of a specific intervention or psychiatric disorder or symptoms). Abstracts were then reviewed

by one individual (L.J.F.), with verification by a second reviewer (S-H.H.) to determine whether they met eligibility criteria.

Studies were included if subjects were adults (age 18 years or older) with AUD, including alcohol abuse or alcohol dependence as defined in DSM-IV-TR (American Psychiatric Association, 2000), who received treatment with medications approved by FDA for treating alcohol dependence (acamprosate, disulfiram, naltrexone) or with medications that have been used off-label or are under investigation to treat AUD (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, gabapentin, imipramine, nalmefene, olanzapine, ondansetron, paroxetine, prazosin, quetiapine, sertraline, topiramate, valproate, varenicline, viloxazine). Outcomes could include consumption related outcomes (e.g., return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day, time to lapse or relapse), health outcomes (e.g., accidents, injuries, quality of life, function, mortality), and adverse events including study withdrawal. Studies also needed to be published in English and included at least 12 weeks of outpatient follow-up from the time of treatment initiation.

Exclusion criteria were studies of children and adolescents under 18 years of age, trials in which the purpose of pharmacotherapy was to treat alcohol withdrawal, trials with craving or cue reactivity as primary outcomes, studies that were conducted predominantly in inpatient settings or with follow-up of less than 12 weeks, and those that were published in non-English languages.

Literature Search Results <<N.B. may include a PRISMA diagram before publication>>

		AHRQ Search	APA Search	Total
Articles identified		5844	2927	8771
	PubMed	1226	124	1350
	EMBASE	1730	545	2275
	Cochrane	958	1838	2796
	CINAHL	467	239	706
	PsycInfo	1010	181	1191
	Other sources	453	------	453
Duplicates removed		2423	2007	4430
Records screened		3460	920	4380
Records excluded		2924	772	3696
Articles assessed for eligibility		536	148	684
Articles excluded		369	94	463
	Non-English	11	0	11
	Wrong publication type	23	34	57
	Wrong population	38	5	43
	Wrong intervention	20	23[a]	43
	Wrong comparator	52	1	53
	Wrong outcome	64	4	68
	Wrong setting	18	0	18

	Wrong study design	90	4	94
	Duration < 12 weeks	46	23[b]	69
	Outdated systematic review	2	0	2
Studies in qualitative synthesis		135	42[c]	177
Articles in qualitative synthesis		167	54 [c]	221
Studies in quantitative synthesis		96	0	96

[a] Includes 19 articles on nalmefene, which is not marketed in the US or Canada

[b] Includes meta-analyses in which the majority of studies had a duration of less than 12 weeks

[C] <<NB: Need to verify the number of included studies prior to publication>>

Additional targeted searches were conducted in MEDLINE (PubMed) on alcohol biomarkers, patient preferences in AUD pharmacotherapy, and use of pharmacotherapy for AUD during pregnancy and while breastfeeding. The search terms, limits used and dates of these searches are available in the appendix. Results were limited to English-language, adult (18 and older), and human-only studies. These titles and abstracts were reviewed for relevance by one individual (L.J.F.).

Rating the Strength of Supporting Research Evidence

"Strength of supporting research evidence" describes the level of confidence that findings from scientific observation and testing of an effect of an intervention reflect the true effect. Confidence is enhanced by factors such as rigorous study design and minimal potential for study bias.

Ratings are determined, in accordance with the AHRQ's *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (Agency for Healthcare Research and Quality 2014), by the methodologist (L.J.F.) and reviewed by members of the SRG and GWG. Available clinical trials are assessed across four primary domains: risk of bias, consistency of findings across studies, directness of the effect on a specific health outcome, and precision of the estimate of effect.

The ratings are defined as follows:

- **High** (denoted by the letter A) = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate** (denoted by the letter B) = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- **Low** (denoted by the letter C) = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.

The AHRQ has an additional category of “insufficient” for evidence that is unavailable or does not permit estimation of an effect. The APA uses the “low” rating when evidence is insufficient because there is low confidence in the conclusion and further research, if conducted, would likely change the estimated effect or confidence in the estimated effect.

Some of the statements in this guideline are based upon accepted principles of assessment and clinical care, which the GRADE Working Group has termed "good practice statements" (Guyatt et al., 2016). Direct evidence for these statements was typically unavailable and a detailed systematic review to support these statements was outside the scope of this guideline. Nevertheless, these statements were viewed as essential to the care of individuals with AUD and, thus, have been included in the guideline. They have been given a strength of supporting research evidence for purposes of transparency.

Rating the Strength of Recommendations

Each guideline statement is separately rated to indicate strength of recommendation and strength of supporting research evidence.

“Strength of recommendation” describes the level of confidence that potential benefits of an intervention outweigh potential harms. This level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. As described in “Rating the Strength of Supporting Research Evidence”, the rating is a consensus judgment of the authors of the guideline and is endorsed by the APA Board of Trustees.

There are two possible ratings: recommendation or suggestion. These correspond to ratings of “strong” or “weak” (also termed “conditional”) as defined under the GRADE method for rating recommendations in clinical practice guidelines (described in publications such as Guyatt et al. 2008 and others available on the website of the GRADE Working Group at http://gradeworkinggroup.org/index.htm). “Recommendation” (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. “Suggestion” (denoted by the numeral 2 after the guideline statement) indicates uncertainty (i.e., the balance of benefits and harms is difficult to judge or either the benefits or the harms are unclear).

When a negative statement is made, ratings of strength of recommendation should be understood as meaning the inverse of the above (e.g., “recommendation” indicates confidence that harms clearly outweigh benefits).

The GWG determined ratings of strength of recommendation by a modified Delphi method using blind, iterative voting and discussion. In order for the GWG members to be able to ask for clarifications about the evidence, the wording of statements, or the process, the vice-chair of the GWG served as a resource and did not vote on statements. All other formally appointed GWG members including the chair voted.

In weighing potential benefits and harms, the GWG considered the strength of supporting research evidence, their own clinical experiences and opinions, and patient preferences. For recommendations, at least 8 out of 9 members must have voted to “recommend” the intervention or assessment after two rounds of voting, and at most 1 member was allowed to vote other than “recommend” the intervention

or assessment. One the basis of the discussion among the GWG members, adjustments to the wording of recommendations could be made between the voting rounds. If this level of consensus was not achieved, the GWG could have agreed to make a "suggestion" rather than a "recommendation." No suggestion or statement could have been made if three or more members voted "no statement." Differences of opinion within the group about ratings of strength of recommendation, if any, are described under "Potential Benefits and Harms."

Use of Guidelines to Enhance Quality of Care

Clinical practice guidelines can help enhance quality by synthesizing available research evidence and delineating recommendations for care based on the available evidence. In some circumstances, practice guideline recommendations will be appropriate to use in developing quality measures. Guideline statements can also be used in other ways, such as educational activities or electronic clinical decision support, to enhance the quality of care that patients receive.

Typically, guideline recommendations that are chosen for development into quality measures will advance one or more aims of the Institute of Medicine's report on Crossing the Quality Chasm (2001) and the ongoing work guided by the multi-stakeholder-integrated AHRQ-led National Quality Strategy by facilitating care that is safe, effective, patient-centered, timely, efficient, and equitable. Quality measures will often focus on gaps in care or on care processes and outcomes that have significant variability across specialties, healthcare settings, geographic areas, or patients' demographic characteristics. For many guideline statements, evidence of practice gaps or variability will be based on anecdotal observations since the typical practices of psychiatrists and other health professionals will be unknown. Variability in the use of guideline recommended approaches may reflect appropriate differences that are tailored to the patient's needs and preferences. Variability may also indicate a need to strengthen clinician knowledge, to address regional or socioeconomic barriers to care, or to increase the time available to assess patients and document decision making. When performance is compared among organizations, variability may reflect a need for quality improvement initiatives to improve overall outcomes, but could also reflect differences in case-mix or co-occurring illnesses.

When a guideline recommendation is considered for development into a quality measure, it must be possible to define the applicable patient group (i.e., the denominator) and the clinical action or outcome of interest that is measured (i.e., the numerator) in validated, clear, and quantifiable terms. Furthermore, the clinician's performance on the measure must be readily ascertained from chart review, patient-reported outcome measures, or administrative data, including registry data. Documentation of quality measures can be challenging and, depending on the practice setting, can pose practical barriers to meaningful interpretation of quality measures based on guideline recommendations. For example, when recommendations relate to patient assessment or treatment selection, clinical judgment may need to be used to determine whether the clinician has addressed the factors that merit emphasis for an individual patient. In other circumstances, standardized instruments can facilitate quality measurement reporting, but it is difficult to assess the appropriateness of clinical judgment in a validated, standardized manner. Furthermore, utilization of standardized assessments remains low (Fortney et al., 2017) and clinical findings are not routinely documented in a standardized format. Many clinicians appropriately use free text prose to describe symptoms, response to treatment,

discussions with family, plans of treatment, and other aspects of care and clinical decision making. Reviewing these free text records for measurement purposes would be impractical, and it would be inappropriate to hold clinicians accountable to such measures, without significant increases in electronic medical record use and advances in natural language processing technology.

Conceptually, quality measures can be developed for purposes of accountability, for internal quality improvement (QI) or both. Accountability measures require clinicians to report their rate of performance of a specified process, intermediate outcome, or outcome in a specified group of patients. Because these data are used to determine financial incentives or penalties based on performance, accountability measures must be scientifically validated, have a strong evidence-base, and fill gaps in care. In contrast, internal quality improvement measures are typically designed by and for individual providers, health systems, or payers. They typically focus on measurements that can suggest ways for clinicians or administrators to improve efficiency and delivery of services within a particular setting. Internal QI programs may or may not link performance with payment and, in general, these measures are not subject to strict testing and validation requirements. Quality improvement activities including performance measures derived from these guidelines should yield improvements in quality of care to justify any clinician burden (e.g., documentation burden) or related administrative costs (e.g., for manual extraction of data from charts, for modifications of electronic medical record systems to capture required data elements). Possible unintended consequences of any derived measures would also need to be addressed in testing of a fully specified measure in a variety of practice settings. For example, highly specified measures may lead to overuse of standardized language that does not accurately reflect what has occurred in practice. If multiple discrete fields are used to capture information on a paper or electronic record form, data will be easily retrievable and reportable but oversimplification is a possible unintended consequence of measurement. Just as guideline developers must balance the benefits and harms of a particular guideline recommendation, developers of performance measures must weigh the potential benefits, burdens and unintended consequences in optimizing quality measure design and testing.

External Review

This guideline was made available for review in XX 2017 by stakeholders, including the APA membership, scientific and clinical experts, allied organizations, and the public. In addition, a number of patient advocacy organizations were invited for input. XXX individuals and XX organizations submitted comments on the guideline (see the Individuals Submitted Comments section for the list of the names) << N.B. include and update the list after public comment>>. The Chair and Co-chair of the GWG reviewed and addressed all comments received; substantive issues were reviewed by the GWG. <<N.B. update the numbers after public comment.>>

Funding and Approval

This guideline development project was funded and supported by the APA without any involvement of industry or external funding. The guideline was submitted to the APA Assembly and APA Board of Trustees for approval on XXX and XXX, respectively. <<N.B. Add the dates>>

Disclosures

Dr. Reus is employed as a professor of psychiatry at the University of California, San Francisco School of Medicine. He is past Chairman of the Board of the Accreditation Council for Continuing Medical Education (ACCME). He receives travel funds from the ACCME and the American Board of Psychiatry and Neurology (ABPN) for board meetings and test development. He receives research grant support from the National Institute of Mental Health (NIMH) and National Institute on Drug Abuse and honoraria for NIMH grant review service. He reports no conflicts of interest with his work on this guideline.

Dr. Fochtmann is employed as a professor of psychiatry, pharmacological sciences, and biomedical informatics at Stony Brook University. She consults for the American Psychiatric Association on the development of practice guidelines and has received travel funds to attend meetings related to these duties. She reports no conflicts of interest with her work on this guideline.

Dr. Bukstein is employed by Boston Children's Hospital where he is Vice Chair for the Department of psychiatry. He is also Professor of Psychiatry at Harvard Medical School. He has received royalties from Taylor Francis Press and Wolters Kluwer. He is co-chair of the Committee on Quality issues of the American Academy of Child and Adolescent Psychiatry. He reports no conflicts of interest with his work on this guideline.

Dr. Eyler is employed as a professor of psychiatry and family medicine at the Robert Larner, MD, College of Medicine at the University of Vermont in Burlington, Vermont, and as an attending psychiatrist at the University of Vermont Medical Center and its affiliated hospitals. During the period of preparation of this guideline, honoraria have been received from non-industry sponsored academic and community presentations. He has provided clinical consultation on gender dysphoria to the department of corrections of the state of New Hampshire, and general psychiatric consultation at The Health Center, a federally qualified health center in Plainfield, Vermont. He is a member of the advisory committee of the Samara Fund, a philanthropic group serving the LGBT communities in Vermont. He has received fees or royalties from Johns Hopkins University Press, Taylor & Francis, and Healthwise, Inc. Travel funds have been provided by the American Psychiatric Association, related to service on the Assembly Executive Committee. He reports no conflicts of interest with his work on this guideline.

Dr. Hilty is employed as a professor of psychiatry at the University of Southern California. He reports no conflicts of interest with his work on this guideline.

Dr. Horvitz-Lennon is employed as a physician scientist at the RAND Corporation, as a professor at the Pardee RAND Graduate School, and as an attending psychiatrist with Cambridge Health Alliance. She reports no conflicts of interest with her work on this guideline.

Dr. Mahoney is employed as a researcher and clinical nurse specialist at The Menninger Clinic in Houston, Texas. She is also an associate professor in the Department of Psychiatry and Behavioral Sciences at Baylor College of Medicine. She reports no conflicts of interest with her work on this guideline.

Dr. Pasic is employed as a professor of psychiatry at the University of Washington. She is a member of the board of the American Association of Emergency Psychiatry. She reports no conflicts of interest with her work on this guideline.

Dr. Weaver is employed as a professor of psychiatry and medical director of the Center for Neurobehavioral Research on Addiction at The University of Texas Health Science Center at Houston. He receives research grant support from the National Institute on Drug Abuse. He is Chair of the Addiction Medicine Sub-board for the American Board of Preventive Medicine. He is a member of the Publications Council and the Annual Conference Committee for the American Society of Addiction Medicine. He is a member of the Behavioral Health Advisory Committee for the Texas Childrens Health Plan. He receives travel funds from The Addiction Medicine Foundation for presentations and exam development, and from The Joint Commission as a member of a technical advisory panel. He receives royalties from UpToDate as a content author. He occasionally provides medical expert witness consultation for legal cases. During the period of preparation of this guideline, honoraria have been received from the U.S. Drug Enforcement Administration. He reports no conflict of interest with his work on this guideline.

Dr. Wills is employed as an assistant professor of psychiatry at University Hospitals, Case Medical Center. She also has a private practice in forensic psychiatry. She receives no royalties from any entity. She receives travel funds but no honoraria from the American Academy of Psychiatry and the Law. She provides medicolegal consultation and expert testimony to courts. She reports no conflicts of interest with her work on this guideline.

Dr. Kidd is employed as a fourth-year resident in psychiatry at New York Presbyterian (Columbia University), Columbia University Medical Center, and the New York State Psychiatric Institute. He is a member of the APA Council on Quality Care, the Area 2 Resident-Fellow Member Representative to the APA Assembly, and the Chair of the APA/APAF Leadership fellowship; for which he receives travel funds.

Dr. McIntyre is a clinical professor of psychiatry at the University of Rochester. His is in full time private practice and is Medical Director of HCR, a home health care agency. Dr. McIntyre is the Chair of the Board of PCPI and Chair of the Quality Collaborative of Monroe County Medical Society. He serves on the Boards of several other not-for-profit organizations. He reports no conflicts of interest with his work on this guideline.

Dr. Yager is employed as a professor of psychiatry at the University of Colorado. He reports no conflicts of interest with his work on this guideline.

Ms. Hong is employed as a research manager for the practice guidelines program at American Psychiatric Association. She reports no conflicts of interest with her work on this guideline.

Individuals and Organizations That Submitted Comments

<<N.B. This section will be updated after public comment.>>

References

Abraham AJ, Knudsen HK, Roman PM: A longitudinal examination of alcohol pharmacotherapy adoption in substance use disorder treatment programs: patterns of sustainability and discontinuation. J Stud Alcohol Drugs 72(4):669-677, 2011

Abramsky T, Watts CH, Garcia-Moreno C, et al: What factors are associated with recent intimate partner violence? findings from the WHO multi-country study on women's health and domestic violence. BMC Public Health 11:109, 2011

Adamson SJ, Heather N, Morton V, Raistrick D: UKATT Research Team. Initial preference for drinking goal in the treatment of alcohol problems: II. Treatment outcomes. Alcohol Alcohol 45(2):136-142, 2010

Adamson SJ, Sellman JD, Foulds JA, et al: A randomized trial of combined citalopram and naltrexone for nonabstinent outpatients with co-occurring alcohol dependence and major depression. J Clin Psychopharmacol 35(2):143-149, 2015

Agency for Healthcare Research and Quality: Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD, Agency for Healthcare Research and Quality. January 2014. Available at: http://www.effectivehealthcare.ahrq.gov/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=318. Accessed on February 15, 2017

Ahmadi J, Ahmadi N: A double blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence. German Journal of Psychiatry 5(4):85-89, 2002

Ahmadi J, Babaeebeigi M, Maany I, et al: Naltrexone for alcohol-dependent patients. Ir J Med Sci 173(1):34-37, 2004 PMID: 15732235

Alatalo P, Koivisto H, Puukka K, et al: Biomarkers of liver status in heavy drinkers, moderate drinkers and abstainers. Alcohol 44(2):199-203, 2009

Al-Otaiba Z, Worden BL, McCrady BS, Epstein EE: Accounting for self-selected drinking goals in the assessment of treatment outcome. Psychol Addict Behav 22(3):439-443, 2008

Alsaad AM, Chaudhry SA, Koren G: First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis. Reprod Toxicol 53:45-50, 2015 Review. 25797654

ALK21-014: Efficacy and Safety of Medisorb® Naltrexone (VIVITROL®) After Enforced Abstinence, 2011

American College of Obstetricians and Gynecologists: Committee on Health Care for Underserved Women. Committee opinion no. 496: At-risk drinking and alcohol dependence: obstetric and gynecologic implications. Obstet Gynecol 118(2 Pt 1):383-388, 2011

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision. Washington, DC, American Psychiatric Association, 2000

American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Arlington, VA, American Psychiatric Publishing, 2013

American Psychiatric Association: Practice Guidelines for the Psychiatric Evaluation of Adults, 3rd Edition. Arlington, VA, American Psychiatric Association Publishing, 2015

Andréasson S, Danielsson AK, Wallhed-Finn S: Preferences regarding treatment for alcohol problems. Alcohol Alcohol 48(6):694-699, 2013

Andrews JC, Schünemann HJ, Oxman AD, et al: GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 66(7):726–735, 2013 23570745

Anton RF: Testing combined pharmacotherapies and behavioral interventions for alcohol dependence (the COMBINE study): A pilot feasibility study. Alcohol 27(7):1123-1131, 2003

Anton RF, Moak DH, Latham PK, et al: Posttreatment results of combining naltrexone with cognitive-behavior therapy for the treatment of alcoholism. J Clin Psychopharmacol 21(1):72-77, 2001 PMID: 11199951

Anton RF, Moak DH, Latham P, et al: Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. J Clin Psychopharmacol 25(4):349-357, 2005 PMID: 16012278

Anton RF, Moak DH, Waid LR, et al: Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial. Am J Psychiatry 156(11):1758-1764, 1999 PMID: 10553740

Anton RF, Myrick H, Wright TM, et al: Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry 168(7):709-717, 2011 PMID: 21454917

Anton RF, O'Malley SS, Ciraulo DA, et al: COMBINE Study Research Group: Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA 295(17):2003-2017, 2006 PMID: 16670409

Anton RF, Oroszi G, O'Malley S, et al: An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry 65(2):135-144, 2008 PMID: 18250251

Anttila P, Jarvi K, Latvala J, et al: A new modified gamma-%CDT method improves the detection of problem drinking: studies in alcoholics with or without liver disease. Clin Chim Acta 338(1-2):45-51, 2003

Arias AJ, Gelernter J, Gueorguieva R, et al: Pharmacogenetics of naltrexone and disulfiram in alcohol dependent, dually diagnosed veterans. Am J Addict 23(3):288-293, 2014

Arndt T, Behnken L, Martens B, Hackler R: Evaluation of the cut-off for serum carbohydrate deficient transferrin as a marker of chronic alcohol abuse determination by ChronAlco ID assay. J Lab Med 23: 507-510, 1999

Bager H, Christensen LP, Husby S, Bjerregaard L: Biomarkers for the Detection of Prenatal Alcohol Exposure: A Review. Alcohol Clin Exp Res 41(2):251-261, 2017

Balldin J, Berggren U, Berglund K, et al: Gamma-glutamyltransferase in alcohol use disorders: Modification of decision limits in relation to treatment goals? Scand J Clin Lab Invest 70(2):71-74, 2010

Balldin J, Berglund M, Borg S, et al: A 6-month controlled naltrexone study: combined effect with cognitive behavioral therapy in outpatient treatment of alcohol dependence. Alcohol Clin Exp Res 27(7):1142-1149, 2003 PMID: 12878920

Balshem H, Helfand M, Schünemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64(4):401–406, 2011 21208779

Baltieri DA, Daro FR, Ribeiro PL, et al: Comparing topiramate with naltrexone in the treatment of alcohol dependence. Addiction 103(12):2035-2044, 2008 PMID: 18855810

Baltieri DA, Daro FR, Ribeiro PL, et al: Effects of topiramate or naltrexone on tobacco use among male alcohol-dependent outpatients. Drug Alcohol Depend 105(1-2):33-41, 2009 PMID: 19595518

Baltieri DA, De Andrade AG: Acamprosate in alcohol dependence: a randomized controlled efficacy study in a standard clinical setting. J Stud Alcohol 65(1):136-139, 2004 PMID: 15000513

Barrio P, Gual A: Patient-centered care interventions for the management of alcohol use disorders: a systematic review of randomized controlled trials. Patient Prefer Adherence 10:1823-1845, 2016

Batki SL, Pennington DL, Lasher B, et al: Topiramate treatment of alcohol use disorder in veterans with posttraumatic stress disorder: a randomized controlled pilot trial. Alcohol Clin Exp Res 38(8):2169-2177, 2014

Berger L, Brondino M, Fisher M, et al: Alcohol use disorder treatment: the association of pretreatment use and the role of drinking goal. J Am Board Fam Med 29(1):37-49, 2016 26769876

Berger L, Fisher M, Brondino M, et al: Efficacy of acamprosate for alcohol dependence in a family medicine setting in the United States: a randomized, double-blind, placebo-controlled study. Alcohol Clin Exp Res 37(4):668-674, 2013

Bergstrom JP, Helander A: Clinical characteristics of carbohydrate-deficient transferrin (%disialotransferrin) measured by hplc: Sensitivity, specificity, gender effects, and relationship with other alcohol biomarkers. Alcohol Alcohol 43(4):436-441, 2008

Bertholet N, Winter MR, Cheng DM, et al: How accurate are blood (or breath) tests for identifying self-reported heavy drinking among people with alcohol dependence? Alcohol Alcohol 49(4):423-429, 2014

1835 Besson J, Aeby F, Kasas A, et al: Combined efficacy of acamprosate and disulfiram in the treatment of
1836 alcoholism: a controlled study. Alcohol Clin Exp Res 22(3):573-579, 1998 PMID: 9622434

1837 Bogenschutz MP, Bhatt S, Bohan J, et al: Coadministration of disulfiram and lorazepam in the treatment
1838 of alcohol dependence and co-occurring anxiety disorder: An open-label pilot study. Am J Drug Alcohol
1839 Abuse 42(5):490-499, 2016

1840 Book SW, Thomas SE, Randall PK, Randall CL: Paroxetine reduces social anxiety in individuals with a co-
1841 occurring alcohol use disorder. J Anxiety Disord 22(2):310-318, 2008 PMID: 17448631

1842 Bouchery EE, Harwood HJ, Sacks JJ, et al: Economic costs of excessive alcohol consumption in the U.S.,
1843 2006. Am J Prev Med 41(5):516-524, 2011

1844 Bradley KA, Kivlahan DR: Bringing patient-centered care to patients with alcohol use disorders. JAMA
1845 311(18):1861-1862, 2014

1846 Brady KT, Sonne S, Anton RF, et al: Sertraline in the treatment of co-occurring alcohol dependence and
1847 posttraumatic stress disorder. Alcohol Clin Exp Res 29(3):395-401, 2005 PMID: 15770115

1848 Branas CC, Han S, Wiebe DJ: Alcohol Use and Firearm Violence. Epidemiol Rev 38(1):32-45, 2016

1849 Brewer C, Wong VS: Naltrexone: report of lack of hepatotoxicity in acute viral hepatitis, with a review of
1850 the literature. Addict Biol 9(1):81-87, 2004

1851 Briggs, Gerald G, Roger K, et al: Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and
1852 Neonatal Risk. Philadelphia, Wolters Kluwer/Lippincott Williams & Wilkins Health, 2015

1853 Brito JP, Domecq JP, Murad MH, et al: The Endocrine Society guidelines: when the confidence cart goes
1854 before the evidence horse. J Clin Endocrinol Metab 98(8):3246–3252, 2013 23783104

1855 Brown ES, Carmody TJ, Schmitz JM, et al: A randomized, double-blind, placebo-controlled pilot study of
1856 naltrexone in outpatients with bipolar disorder and alcohol dependence. Alcohol Clin Exp Res
1857 33(11):1863-1869, 2009 PMID: 19673746

1858 Bujarski S, O'Malley SS, Lunny K, Ray LA: The effects of drinking goal on treatment outcome for
1859 alcoholism. J Consult Clin Psychol 81(1):13-22, 2013

1860 Bush K, Kivlahan DR, McDonell MB, et al: The audit alcohol consumption questions (audit-c): an effective
1861 brief screening test for problem drinking. ambulatory care quality improvement project (acquip). alcohol
1862 use disorders identification test. Arch Intern Med 158(16):1789-1795, 1998

1863 CAMPRAL® (acamprosate calcium) [package insert]: St. Louis, MO, Forest Pharmaceuticals, Inc, 2005

1864 Carroll K, Ziedonis D, O'Malley SS, et al: Pharmacologic interventions for alcohol- and cocaine-abusing
1865 individuals: A pilot study of disulfiram vs. naltrexone. Am J Addict 2(1):77-79, 1993

Carstairs SD: Ondansetron Use in Pregnancy and Birth Defects: A Systematic Review. Obstet Gynecol 127(5):878-883, 2016 27054939

Centers for Disease Control and Prevention (CDC): Quitting smoking among adults--United States, 2001-2010. MMWR Morb Mortal Wkly Rep 60(44):1513-1519, 2011

Center for Substance Abuse and Treatment: Incorporating alcohol pharmacotherapies into medical practice. (Treatment improvement protocol (TIP); no. 49). Substance Abuse and Mental Health Services Administration (SAMHSA), Rockville, MD, 2009

Chang G, McNamara TK, Orav EJ, Wilkins-Haug L: Brief intervention for prenatal alcohol use: the role of drinking goal selection. J Subst Abuse Treat 31(4):419-424, 2006 17084796

Chapman C, Slade T, Hunt C, Teesson M: Delay to first treatment contact for alcohol use disorder. Drug Alcohol Depend 147:116-121, 2015

Charlet K, Heinz A: Harm reduction-a systematic review on effects of alcohol reduction on physical and mental symptoms. Addict Biol [Epub ahead of print] 27353220

Charney DA, Heath LM, Zikos E, et al: Poorer drinking outcomes with citalopram treatment for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res 39(9):1756-1765, 2015

Chavez LJ, Williams EC, Lapham G, Bradley KA: Association between alcohol screening scores and alcohol-related risks among female veterans affairs patients. J Stud Alcohol Drugs 73(3): 391-400, 2012

Chen AC, Davis CM, Kahler CW et al: 5-httlpr moderates naltrexone and psychosocial treatment responses in heavy drinking men who have sex with men. Alcohol Clin Exp Res 38(9):2362-2368, 2014

Cherpitel CJ: Screening for alcohol problems in the U.S. General population: Comparison of the cage, raps4, and raps4-qf by gender, ethnicity, and service utilization. Rapid alcohol problems screen. Alcohol Clin Exp Res 26(11):1686-1691, 2002

Chick J, Anton R, Checinski K, et al: A multicentre, randomized, double-blind, placebo-controlled trial of naltrexone in the treatment of alcohol dependence or abuse. Alcohol Alcohol 35(6):587-593, 2000a PMID: 11093966

Chick J, Howlett H, Morgan MY, et al: United Kingdom Multicentre Acamprosate Study (UKMAS): a 6-month prospective study of acamprosate versus placebo in preventing relapse after withdrawal from alcohol. Alcohol Alcohol 35(2):176-187, 2000b PMID: 10787394

Chick J, Aschauer H, Hornik K: Efficacy of fluvoxamine in preventing relapse in alcohol dependence: a one-year, double-blind, placebo-controlled multicentre study with analysis by typology. Drug Alcohol Depend 74(1):61-70, 2004 PMID: 15072808

Chou R, Gordon DB, de Leon-Casasola OA, et al: Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. J Pain 17(2):131-157, 2016a

Chou SP, Goldstein RB, Smith SM, et al: The Epidemiology of DSM-5 Nicotine Use Disorder: results from the national epidemiologic survey on alcohol and related conditions-III. J Clin Psychiatry 77(10):1404-1412. 2016b

Coller JK, Cahill S, Edmonds C, et al: OPRM1 A118G genotype fails to predict the effectiveness of naltrexone treatment for alcohol dependence. Pharmacogenet Genomics 21(12):902-905, 2011 PMID: 21946895

Collins SE, Grazioli VS, Torres NI, et al: Qualitatively and quantitatively evaluating harm-reduction goal setting among chronically homeless individuals with alcohol dependence. Addict Behav 45:184-190, 2015

Compton WM, Dawson DA, Goldstein RB, Grant BF: Crosswalk between DSM-IV dependence and DSM-5 substance use disorders for opioids, cannabis, cocaine and alcohol. Drug Alcohol Depend 132(1-2):387-390, 2013

Conigrave KM, Davies P, Haber P, Whitfield JB: Traditional markers of excessive alcohol use. Addiction, 98 Suppl 2:31-43, 2003

Cornelius JR, Salloum IM, Cornelius MD, et al: Preliminary report: double-blind, placebo-controlled study of fluoxetine in depressed alcoholics. Psychopharmacol Bull 31(2):297-303, 1995

Cornelius JR, Salloum IM, Ehler JG, et al: Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. Arch Gen Psychiatry 54(8):700-705, 1997b PMID: 9283504

Corrêa Filho JM, Baltieri DA: A pilot study of full-dose ondansetron to treat heavy-drinking men withdrawing from alcohol in Brazil. Addict Behav 38(4):2044-2051, 2013 PMID: 23396176

Coskunol H, Gökden O, Ercan ES, et al: Long-term efficacy of sertraline in the prevention of alcoholic relapses in alcohol-dependent patients: a single-center, double-blind, randomized, placebo-controlled, parallel-group study. Current Therapeutic Research 63(11):759-771, 2002 PMID: 2003140542

Council of Medical Specialty Societies (CMSS): Principles for the Development of Specialty Society Clinical Guidelines. Chicago, IL, Council of Medical Specialty Societies, 2012

Dasgupta A: Alcohol biomarkers: An Overview Alcohol and Its Biomarkers: Clinical Aspects and Laboratory Determination. San Diego, CA, Elsevier, 2015 (pp. 91-120)

Darvishi N, Farhadi M, Haghtalab T, Poorolajal J: Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis. PLoS One 10(5):e0126870, 2015

Dawson DA, Smith SM, Saha TD, et al: Comparative performance of the audit-c in screening for dsm-iv and dsm-5 alcohol use disorders. Drug Alcohol Depend 126(3): 384-388, 2012

Del Fiol G, Huser V, Strasberg HR, et al: Implementations of the HL7 context-aware knowledge retrieval ("Infobutton") standard: challenges, strengths, limitations, and uptake. J Biomed Inform 45(4):726-735, 2012

Delker E, Brown Q, Hasin DS: Alcohol consumption in demographic subpopulations: an epidemiologic overview. Alcohol Res 38(1):7-15, 2016

De Sousa A: A one-year pragmatic trial of naltrexone vs disulfiram in the treatment of alcohol dependence. Alcohol 39(6):528-531, 2004 PMID: 15525790

De Sousa A: An open randomized study comparing disulfiram and acamprosate in the treatment of alcohol dependence. Alcohol 40(6):545-548, 2005 PMID: 16043433

De Sousa AA, De Sousa J, Kapoor H: An open randomized trial comparing disulfiram and topiramate in the treatment of alcohol dependence. J Subst Abuse Treat 34(4):460-463, 2008 PMID: 17629442

Dhalla S, Kopec JA: The cage questionnaire for alcohol misuse: A review of reliability and validity studies. Clin Invest Med 30(1): 33-41, 2007

Dieperink E, Fuller B, Isenhart C, et al: Efficacy of motivational enhancement therapy on alcohol use disorders in patients with chronic hepatitis C: a randomized controlled trial. Addiction 109(11):1869-1877, 2014

Djulbegovic B, Trikalinos TA, Roback J, et al: Impact of quality of evidence on the strength of recommendations: an empirical study. BMC Health Serv Res 9:120, 2009 19622148

do Amaral RA, Malbergier A: Effectiveness of the CAGE questionnaire, gamma-glutamyltransferase and mean corpuscular volume of red blood cells as markers for alcohol-related problems in the workplace. Addict Behav 33(6):772-781, 2008

Donovan DM, Kivlahan DR, Doyle SR, et al: Concurrent validity of the alcohol use disorders identification test (audit) and audit zones in defining levels of severity among out-patients with alcohol dependence in the combine study. Addiction 101(12):1696-1704, 2006

Drake RE, Essock SM, Shaners A, et al: Implementing Dual-Diagnosis Services for Clients with Severe Mental Illness. In R. N. Rosenthal (Ed.), Dual-Diagnosis (pp. 53-68). New York, NY: Routledge, 2013

Dunlap LJ, Zarkin GA, Bray JW, et al: Revisiting the cost-effectiveness of the COMBINE study for alcohol dependent patients: the patient perspective. Med Care 48(4):306-313, 2010

Dunn KE, Strain EC: Pretreatment alcohol drinking goals are associated with treatment outcomes. Alcohol Clin Exp Res 37(10):1745-1752, 2013

Durand MA, Carpenter L, Dolan H, et al: Do interventions designed to support shared decision-making reduce health inequalities? A systematic review and meta-analysis. PLoS One 9(4):e94670, 2014

Epstein EE, McCrady BS: A Cognitive-Behavioral Treatment Program for Overcoming Alcohol Problems. Oxford, UK, Oxford University Press, 2009

Fagan KJ, Irvine KM, McWhinney BC, et al: Diagnostic sensitivity of carbohydrate deficient transferrin in heavy drinkers. BMC Gastroenterol 14:97, 2014

Feinn R, Tennen H, Kranzler HR: Psychometric properties of the short index of problems as a measure of recent alcohol-related problems. Alcohol Clin Exp Res 27(9):1436-1441, 2003

Ferri M, Amato L, Davoli M: Alcoholics Anonymous and other 12-step programmes for alcohol dependence. Cochrane Database Syst Rev (3), 2006 CD005032

Fleming MF, Anton RF, Spies CD: A review of genetic, biological, pharmacological, and clinical factors that affect carbohydrate-deficient transferrin levels. Alcohol Clin Exp Res 28(9):1347-1355, 2004

Florez G, Garcia-Portilla P, Alvarez S, et al: Using topiramate or naltrexone for the treatment of alcohol-dependent patients. Alcohol Clin Exp Res 32(7):1251-1259, 2008 PMID: 18482157

Florez G, Saiz PA, Garcia-Portilla P, et al: Topiramate for the treatment of alcohol dependence: comparison with naltrexone. Eur Addict Res 17(1):29-36, 2011 PMID: 20975274

Foa EB, Williams MT: Methodology of a randomized double-blind clinical trial for comorbid posttraumatic stress disorder and alcohol dependence. Ment Health Subst Use 3(2):131-147, 2010

Foa EB, Yusko DA, McLean CP, et al: Concurrent naltrexone and prolonged exposure therapy for patients with comorbid alcohol dependence and PTSD: a randomized clinical trial. JAMA 310(5):488-495, 2013

Fogaca MN, Santos-Galduroz RF, Eserian JK, et al: The effects of polyunsaturated fatty acids in alcohol dependence treatment--a double-blind, placebo-controlled pilot study. BMC Clin Pharmacol 11:10, 2011 PMID: 21787433

Forcehimes AA, Tonigan JS, Miller WR, et al: Psychometrics of the Drinker Inventory of Consequences (DrInC). Addict Behav 32(8):1699-1704, 2007

Forest Pharmaceuticals, Inc. Campral (acamprosate calcium) prescribing information, January 2012, Accessed on February 6, 2017 at http://pi.actavis.com/data_stream.asp?product_group=1928&p=pi&language=E

Fortney JC, Unützer J, Wrenn G, et al: A tipping point for measurement-based care. Psychiatr Serv 68(2):179-188, 2017

Fridberg DJ, Cao D, Grant JE, King AC: Naltrexone improves quit rates, attenuates smoking urge, and reduces alcohol use in heavy drinking smokers attempting to quit smoking. Alcohol Clin Exp Res 38(10):2622-2629, 2014

Fucito LM, Park A, Gulliver SB, et al: Cigarette smoking predicts differential benefit from naltrexone for alcohol dependence. Biol Psychiatry 72(10):832-838, 2012

Fuller RK, Branchey L, Brightwell DR, et al: Disulfiram treatment of alcoholism. A Veterans Administration cooperative study 256(11):1449-1455, 1986 PMID: 3528541

Fuller RK, Roth HP: Disulfiram for the treatment of alcoholism. An evaluation in 128 men. Ann Intern Med 90(6):901-904, 1979 PMID: 389121

Garbutt JC, Kranzler HR, O'Malley SS, et al: Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA 293(13):1617-1625, 2005 PMID: 15811981

Gastpar M, Bonnet U, Boning J, et al: Lack of efficacy of naltrexone in the prevention of alcohol relapse: results from a German multicenter study. J Clin Psychopharmacol 22(6):592-598, 2002 PMID: 12454559

Geerlings PJ, Ansoms C, Van Den Brink W: Acamprosate and prevention of relapse in alcoholics. Results of a randomized, placebo-controlled, double-blind study in out-patient alcoholics in the Netherlands, Belgium and Luxembourg. Eur Addict Res 3(3):129-137, 1997

Gelernter J, Gueorguieva R, Kranzler HR, et al: Opioid receptor gene (OPRM1, OPRK1, and OPRD1) variants and response to naltrexone treatment for alcohol dependence: results from the VA Cooperative Study. Alcohol Clin Exp Res 31(4):555-563, 2007 PMID: 17374034

Glass JE, Bohnert KM, Brown RL: Alcohol screening and intervention among United States adults who attend ambulatory healthcare. J Gen Intern Med 31(7):739-745, 2016

Gorelick DA: Problem drinking and low-dose naltrexone-assisted opioid detoxification. J Stud Alcohol Drugs 72(3):507-513, 2011

Gowing L, Ali R, White JM: Opioid antagonists with minimal sedation for opioid withdrawal. Cochrane Database Syst Rev (4):CD002021, 2009

Gowing L, Ali R, White JM: Opioid antagonists under heavy sedation or anaesthesia for opioid withdrawal. Cochrane Database Syst Rev (1):CD002022, 2010

Grant BF, Goldstein RB, Saha TD, et al: Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. JAMA Psychiatry 72(8):757-766, 2015

Grant BF, Saha TD, Ruan WJ, et al: Epidemiology of DSM-5 Drug Use Disorder: results from the national epidemiologic survey on alcohol and related conditions-III. JAMA Psychiatry 73(1):39-47, 2016

Grant BF, Stinson FS, Dawson DA, et al: Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch Gen Psychiatry 61(8):807-816, 2004

Greenfield SF, Pettinati HM, O'Malley S, et al: Gender differences in alcohol treatment: an analysis of outcome from the COMBINE study. Alcohol Clin Exp Res 34(10):1803-1812, 2010 PMID: 20645934

Gual A, Balcells M, Torres M, et al: Sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder: a randomized controlled trial. Alcohol 38(6):619-625, 2003 PMID: 14633652

Gual A, Lehert P: Acamprosate during and after acute alcohol withdrawal: a double-blind placebo-controlled study in Spain. Alcohol 36(5):413-418, 2001 PMID: CN-00367117

Guardia J, Caso C, Arias F, et al: A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol-dependence disorder: results from a multicenter clinical trial. Alcohol Clin Exp Res 26(9):1381-1387, 2002 PMID: 12351933

Gueorguieva R, Wu R, O'Connor PG, et al: Predictors of abstinence from heavy drinking during treatment in COMBINE and external validation in PREDICT. Alcohol Clin Exp Res 38(10):2647-2656, 2014 PubMed PMID: 25346505

Guglielmo R, Martinotti G, Quatrale M, et al: Topiramate in Alcohol Use Disorders: Review and Update. CNS Drugs 29(5):383-395, 2015

Guyatt GH, Alonso-Coello P, Schünemann HJ, et al: Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 80:3-7, 2016

Guyatt G, Eikelboom JW, Akl EA, et al: A guide to GRADE guidelines for the readers of JTH. J Thromb Haemost 11(8):1603–1608, 2013 23773710

Guyatt G, Gutterman D, Baumann MH, et al: Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians Task Force. Chest 129(1):174–181, 2006 16424429

Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group: Going from evidence to recommendations. BMJ 336(7652):1049–1051, 2008 18467413

Hagedorn HJ, Brown R, Dawes M, et al: Enhancing access to alcohol use disorder pharmacotherapy and treatment in primary care settings: ADaPT-PC. Implement Sci 11:64, 2016

Harasymiw J, Bean P: The early detection of alcohol consumption (edac) test shows better performance than gamma-glutamyltransferase (ggt) to detect heavy drinking in a large population of males and females. Med Sci Monit 13(9):PI19-24, 2007

Harris AH, Bowe T, Hagedorn H, et al: Multifaceted academic detailing program to increase pharmacotherapy for alcohol use disorder: interrupted time series evaluation of effectiveness. Addict Sci Clin Pract 11(1):15, 2016

Harris AH, Ellerbe L, Reeder RN, et al: Pharmacotherapy for alcohol dependence: perceived treatment barriers and action strategies among Veterans Health Administration service providers. Psychol Serv 10(4):410-419, 2013

Hasin DS, Goodwin RD, Stinson FS, Grant BF: Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. Arch Gen Psychiatry 62(10):1097-1106, 2005

Hasin DS, Grant BF: The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) Waves 1 and 2: review and summary of findings. Soc Psychiatry Psychiatr Epidemiol 50(11):1609-1640, 2015

Hasin DS, O'Brien CP, Auriacombe M, et al: DSM-5 criteria for substance use disorders: recommendations and rationale. Am J Psychiatry 170(8):834-851, 2013

Hazlehurst JM, Armstrong MJ, Sherlock M, et al: A comparative quality assessment of evidence-based clinical guidelines in endocrinology. Clin Endocrinol (Oxf) 78(2):183–190, 2013 22624723

Helander A, Dahl H: Urinary tract infection: a risk factor for false-negative urinary ethyl glucuronide but not ethyl sulfate in the detection of recent alcohol consumption. Clin Chem 51(9):1728-1730, 2005

Heinala P, Alho H, Kiianmaa K, et al: Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: a factorial double-blind, placebo-controlled trial. J Clin Psychopharmacol 21(3):287-292, 2001 PMID: 11386491

Herbeck DM, Jeter KE, Cousins SJ, et al: Gender differences in treatment and clinical characteristics among patients receiving extended release naltrexone. J Addict Dis 35(4):305-314, 2016

Hien DA, Levin FR, Ruglass LM, et al: Combining seeking safety with sertraline for PTSD and alcohol use disorders: A randomized controlled trial. Journal of Consulting and Clinical Psychology 83(2): 359-369, 2015

Hietala J, Koivisto H, Anttila P, Niemela O: Comparison of the combined marker ggt-cdt and the conventional laboratory markers of alcohol abuse in heavy drinkers, moderate drinkers and abstainers. Alcohol Alcohol 41(5):528-533, 2006

Higuchi S; Japanese Acamprosate Study Group. Efficacy of acamprosate for the treatment of alcohol dependence long after recovery from withdrawal syndrome: a randomized, double-blind, placebo-controlled study conducted in Japan (Sunrise Study). J Clin Psychiatry 76(2):181-188, 2015

Hock B, Schwarz M, Domke I, et al: Validity of carbohydrate-deficient transferrin (%cdt), gamma-glutamyltransferase (gamma-gt) and mean corpuscular erythrocyte volume (mcv) as biomarkers for chronic alcohol abuse: A study in patients with alcohol dependence and liver disorders of non-alcoholic and alcoholic origin. Addiction 100(10):1477-1486, 2005

Huang MC, Chen CH, Yu JM, et al: A double-blind, placebo-controlled study of naltrexone in the treatment of alcohol dependence in Taiwan. Addict Biol 10(3):289-92, 2005 PMID: 16109592

Humeniuk R, Ali R, Babor TF, et al: Validation of the alcohol, smoking and substance involvement screening test (ASSIST). Addiction 103(6):1039-1047, 2008

Iheanacho T, Issa M, Marienfeld C, Rosenheck R: Use of naltrexone for alcohol use disorders in the Veterans' Health Administration: a national study. Drug Alcohol Depend 132(1-2):122-6, 2013

Institute of Medicine: Clinical Practice Guidelines We Can Trust. Washington, DC, National Academies Press, 2011

Institute of Medicine (US) Committee on Quality of Health Care in America: Crossing the Quality Chasm: A New Health System for the 21st Century. Washington, DC, National Academies Press, 2001. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222274/

Ipser JC, Wilson D, Akindipe TO, et al: Pharmacotherapy for anxiety and comorbid alcohol use disorders. Cochrane Database Syst Rev 1:CD007505, 2015

Isaksson A, Walther L, Hansson T, et al: Phosphatidylethanol in blood (B-PEth): a marker for alcohol use and abuse. Drug Test Anal 3(4):195-200, 2011

Johnson BA, Ait-Daoud N, Akhtar FZ, et al. Oral topiramate reduces the consequences of drinking and improves the quality of life of alcohol-dependent individuals: a randomized controlled trial. Arch Gen Psychiatry 61(9):905-912, 2004a PMID: 15351769

Johnson BA, Ait-Daoud N, Aubin HJ, et al. A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex) in patients with alcohol dependence. Alcohol Clin Exp Res 28(9):1356-1361, 2004b PMID: 15365306

Johnson BA, Ait-Daoud N, Bowden CL, et al: Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361(9370):1677-1685, 2003 PMID: 12767733

Johnson BA, Roache JD, Javors MA, et al: Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: A randomized controlled trial. JAMA 284(8):963-971, 2000

Johnson BA, Rosenthal N, Capece JA, et al: Topiramate for treating alcohol dependence: a randomized controlled trial. JAMA 298(14):1641-1651, 2007 PMID: 17925516

Johnson BA, Rosenthal N, Capece JA, et al: Improvement of physical health and quality of life of alcohol-dependent individuals with topiramate treatment: US multisite randomized controlled trial. Arch Intern Med 168(11):1188-1199, 2008 PMID: 18541827

Johnson BA, Seneviratne C, Wang XQ, et al: Determination of genotype combinations that can predict the outcome of the treatment of alcohol dependence using the 5-HT(3) antagonist ondansetron. Am J Psychiatry 170(9):1020-1031, 2013

Jones AW: Pharmacokinetics of ethanol - issues of forensic importance. Forensic Sci Rev 23(2):91-136, 2011

Jonas DE, Amick HR, Feltner C, et al: Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings [Internet]. Rockville, MD, Agency for Healthcare Research and Quality, 2014. Available from http://www.ncbi.nlm.nih.gov/books/NBK208590/ PubMed PMID: 24945054

Jonas DE, Garbutt JC, Amick HR, et al: Behavioral counseling after screening for alcohol misuse in primary care: a systematic review and meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 157(9):645-654, 2012 PMID: 23007881

Jonas DE, Garbutt JC, Brown JM, et al: Screening, Behavioral Counseling, and Referral in Primary Care to Reduce Alcohol Misuse. Comparative Effectiveness Review No. 64. (Prepared by the RTI International-University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-10056-I.) AHRQ Publication No. 12-EHC055-EF. Rockville, MD, Agency for Healthcare Research and Quality; July 2012. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Kabel DI, Petty F: A placebo-controlled, double-blind study of fluoxetine in severe alcohol dependence: adjunctive pharmacotherapy during and after inpatient treatment. Alcohol Clin Exp Res 20(4):780-784, 1996 PMID: 8800399

Kampman KM, Pettinati HM, Lynch KG, et al: A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. Drug Alcohol Depend 133(1):94-99, 2013

Kaner E, Bland M, Cassidy P, et al: Effectiveness of screening and brief alcohol intervention in primary care (SIPS trial): pragmatic cluster randomised controlled trial. BMJ 346:e8501, 2013

Kelly E, Darke S, Ross J: A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. Drug Alcohol Rev 23(3):319-344, 2004

Kelly AT, Mozayani A: An overview of alcohol testing and interpretation in the 21st century. J Pharm Pract 25(1):30-6, 2012

Kendler KS, Ohlsson H, Sundquist J, Sundquist K: Alcohol use disorder and mortality across the life-span: a longitudinal cohort and co-relative analysis. JAMA Psychiatry 73(6), 575-581, 2016

Kenneson A, Funderburk JS, Maisto SA: Substance use disorders increase the odds of subsequent mood disorders. Drug Alcohol Depend 133(2):338-343, 2013

Kerr-Correa F, Igami TZ, Hiroce V, Tucci AM: Patterns of alcohol use between genders: a cross-cultural evaluation. J Affect Disord 102(1-3):265-275, 2007

Kiefer F, Andersohn F, Otte C, et al: Long-term effects of pharmacotherapy on relapse prevention in alcohol dependence. Acta Neuropsychiatrica 18:233-238, 2004

Kiefer F, Helwig H, Tarnaske T, et al: Pharmacological relapse prevention of alcoholism: clinical predictors of outcome. Eur Addict Res 11(2):83-91, 2005 PMID: 15785069

Kiefer F, Jahn H, Tarnaske T, et al: Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry 60(1):92-99, 2003 PMID: 12511176

Killeen TK, Brady KT, Gold PB, et al: Effectiveness of naltrexone in a community treatment program. Alcohol Clin Exp Res 28(11):1710-1717, 2004 PMID: 15547458

King AC, Cao D, O'Malley SS, et al: Effects of naltrexone on smoking cessation outcomes and weight gain in nicotine-dependent men and women. J Clin Psychopharmacol 32(5):630-636, 2012

Kiritzé-Topor P, Huas D, Rosenzweig C, et al: A pragmatic trial of acamprosate in the treatment of alcohol dependence in primary care. Alcohol Alcohol 39(6):520-527, 2004

Knapp CM, Ciraulo DA, Sarid-Segal O, et al: Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 35(1):34-42, 2015

Knight JR, Shrier LA, Bravender TD, et al: A new brief screen for adolescent substance abuse. Arch Pediatr Adolesc Med 153(6):591-596, 1999

Knopman DS, Hartman M: Cognitive effects of high-dose naltrexone in patients with probable Alzheimer's disease. J Neurol Neurosurg Psychiatry 49(11):1321-2, 1986

Kollmann D, Rasoul-Rockenschaub S, Steiner I, et al: Good outcome after liver transplantation for ald without a 6 months abstinence rule prior to transplantation including post-transplant cdt monitoring for alcohol relapse assessment - a retrospective study. Transpl Int 29(5):559-567, 2016

Korthuis PT, Lum PJ, Vergara-Rodriguez P, et al; CTN-0055 CHOICES Investigators: Feasibility and Safety of Extended-Release Naltrexone Treatment of Opioid and Alcohol Use Disorder in HIV Clinics: A Pilot/Feasibility Randomized Trial. Addiction, 2017 [Epub ahead of print] 28061017

Kranzler HR, Armeli S, Tennen H, et al: A double-blind, randomized trial of sertraline for alcohol dependence: moderation by age of onset [corrected] and 5-hydroxytryptamine transporter-linked promoter region genotype. J Clin Psychopharmacol 31(1):22-30, 2011 PMID: 21192139

Kranzler HR, Armeli S, Tennen H: Post-treatment outcomes in a double-blind, randomized trial of sertraline for alcohol dependence. Alcohol Clin Exp Res 36(4):739-744, 2012 PMID: 21981418

Kranzler HR, Burleson JA, Korner P, et al: Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics. Am J Psychiatry 152(3):391-397, 1995 PMID: 7864265

Kranzler HR, Covault J, Feinn R, et al: Topiramate treatment for heavy drinkers: moderation by a GRIK1 polymorphism. Am J Psychiatry 171(4):445-452, 2014a

Kranzler HR, Tennen H, Armeli S, et al: Targeted naltrexone for problem drinkers. J Clin Psychopharmacol 29(4):350-357, 2009 PMID: 19593174

Kranzler HR, Wesson DR, Billot L: Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res 28(7):1051-1059, 2004 PMID: 15252291

Kranzler HR, Wetherill R, Feinn R, et al: Posttreatment effects of topiramate treatment for heavy drinking. Alcohol Clin Exp Res 38(12):3017-3023, 2014b

Krupitsky E, Nunes EV, Ling W, et al: Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 377(9776):1506-1513, 2011

Krupitsky E, Nunes EV, Ling W, et al: Injectable extended-release naltrexone (XR-NTX for opioid dependence: long-term safety and effectiveness. Addiction 108(9):1628-1637, 2013

Krupitsky E, Zvartau E, Blokhina E, et al: Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. Arch Gen Psychiatry 69(9):973-981, 2012 PMID: 22945623

Krystal JH, Cramer JA, Krol WF, et al: Naltrexone in the treatment of alcohol dependence. N Engl J Med 345(24):1734-1739, 2001 PMID: 11742047

Laaksonen E, Koski-Jannes A, Salaspuro M, et al: A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol 43(1):53-61, 2008 PMID: 17965444

Larney S, Gowing L, Mattick RP, et al: A systematic review and meta-analysis of naltrexone implants for the treatment of opioid dependence. Drug Alcohol Rev 33(2):115-128, 2014

Latt NC, Jurd S, Houseman J, et al: Naltrexone in alcohol dependence: a randomised controlled trial of effectiveness in a standard clinical setting. Med J Aust 176(11):530-534, 2002 PMID: 12064984

Lee A, Tan S, Lim D, et al: Naltrexone in the treatment of male alcoholics-An effectiveness study In Singapore. Drug and Alcohol Review 20(2):193-199, 2001

Lee HS, Mericle AA, Ayalon L, Areán PA: Harm reduction among at-risk elderly drinkers: a site-specific analysis from the multi-site Primary Care Research in Substance Abuse and Mental Health for Elderly (PRISM-E) study. Int J Geriatr Psychiatry 24(1):54-60, 2009

Lenz AS, Rosenbaum L, Sheperis D: Meta-analysis of randomized controlled trials of motivational enhancement therapy for reducing substance use. Journal of Addictions and Offender Counseling 37:66-86, 2016

Levounis P, Arnaout B, Marienfelf C. eds: Motivational Interviewing for Clinical Practice. Arlington, VA, American Psychiatric Association Publishing, 2017

Lhuintre JP, Daoust M, Moore ND, et al: Ability of calcium bis acetyl homotaurine, a GABA agonist, to prevent relapse in weaned alcoholics. Lancet 1(8436):1014-1016, 1985 PMID: 2859465

Lhuintre JP, Moore N, Tran G, et al: Acamprosate appears to decrease alcohol intake in weaned alcoholics. Alcohol 25(6):613-622, 1990 PMID: 2085344

Liangpunsakul S, Qi R, Crabb DW, Witzmann F: Relationship between alcohol drinking and aspartate aminotransferase:Alanine aminotransferase (AST:ALT) ratio, mean corpuscular volume (MCT), gamma-glutamyl transpeptidase (GGT), and apolipoprotein A1 and B in the U.S. Population. J Stud Alcohol Drugs 71(2):249-252, 2010

Lieberman DZ, Cioletti A, Massey SH, et al: Treatment preferences among problem drinkers in primary care. Int J Psychiatry Med 47(3):231-240, 2014

Likhitsathian S, Uttawichai K, Booncharoen H, et al: Topiramate treatment for alcoholic outpatients recently receiving residential treatment programs: a 12-week, randomized, placebo-controlled trial. Drug Alcohol Depend 133(2):440-446, 2013

Ling W, Weiss DG, Charuvastra VC, et al: Use of disulfiram for alcoholics in methadone maintenance programs. A Veterans Administration Cooperative Study. Arch Gen Psychiatry 40(8):851-854, 1983 PMID: 6347118

Litten RZ, Falk D, Ryan M, Fertig J: Research opportunities for medications to treat alcohol dependence: addressing stakeholders' needs. Alcohol Clin Exp Res 38(1):27-32, 2014

LoCastro JS, Youngblood M, Cisler RA, et al: Alcohol treatment effects on secondary nondrinking outcomes and quality of life: the COMBINE study. J Stud Alcohol Drugs 70(2):186-196, 2009 PMID: 19261230

Longabaugh R, Wirtz PW, Gulliver SB, et al: Extended naltrexone and broad spectrum treatment or motivational enhancement therapy. Psychopharmacology (Berl) 206(3):367-376, 2009 PMID: 19639303

Lowe JM, McDonell MG, Leickly E, et al: Determining ethyl glucuronide cutoffs when detecting self-reported alcohol use in addiction treatment patients. Alcohol Clin Exp Res 39(5):905-910, 2015

Lucey MR, Silverman BL, Illeperuma A, O'Brien CP: Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. Alcohol Clin Exp Res 32(3):498-504, 2008

Ma JZ, Ait-Daoud N, Johnson BA: Topiramate reduces the harm of excessive drinking: implications for public health and primary care. Addiction 101(11):1561-1568, 2006 PMID: 17034435

Maenhout TM, Poll A, Vermassen T, et al: Usefulness of indirect alcohol biomarkers for predicting recidivism of drunk-driving among previously convicted drunk-driving offenders: Results from the recidivism of alcohol-impaired driving (road) study. Addiction 109(1):71-78, 2014

Makoul G, Clayman ML: An integrative model of shared decision making in medical encounters. Patient Educ Couns 60(3):301-12, 2006

Malcolm R, O'Neil PM, Sexauer JD, et al: A controlled trial of naltrexone in obese humans. Int J Obes 9(5):347-53, 1985

Mann K, Lemenager T, Hoffmann S, et al; PREDICT Study Team: Results of a double-blind, placebo-controlled pharmacotherapy trial in alcoholism conducted in Germany and comparison with the US COMBINE study. Addict Biol 18(6):937-946, 2013

Mannelli P, Peindl KS, Lee T, et al: Buprenorphine-mediated transition from opioid agonist to antagonist treatment: state of the art and new perspectives. Curr Drug Abuse Rev 5(1):52-63, 2012

Mark TL, Kassed CA, Vandivort-Warren R, et al: Alcohol and opioid dependence medications: prescription trends, overall and by physician specialty. Drug Alcohol Depend 99(1-3):345-349, 2009

Mark TL, Lubran R, McCance-Katz EF, et al: Medicaid coverage of medications to treat alcohol and opioid dependence. J Subst Abuse Treat 55:1-5, 2015

Marienfeld C, Iheanacho T, Issa M, Rosenheck RA: Long-acting injectable depot naltrexone use in the Veterans' Health Administration: a national study. Addict Behav 39(2):434-438, 2014

Marques P, Tippetts S, Allen J, et al: Estimating driver risk using alcohol biomarkers, interlock blood alcohol concentration tests and psychometric assessments: Initial descriptives. Addiction 105(2):226-239, 2010

Martin GW, Rehm J: The effectiveness of psychosocial modalities in the treatment of alcohol problems in adults: a review of the evidence. Can J Psychiatry 57(6):350-358, 2012

Martinotti G, Di Nicola M, De Vita O, et al: Low-dose topiramate in alcohol dependence: a single-blind, placebo-controlled study. J Clin Psychopharmacol 34(6):709-715, 2014

Martins SS, Gorelick DA: Conditional substance abuse and dependence by diagnosis of mood or anxiety disorder or schizophrenia in the U.S. population. Drug Alcohol Depend 119(1-2):28-36, 2011

Mason BJ, Goodman AM, Chabac S, et al. Effect of oral acamprosate on abstinence in patients with alcohol dependence in a double-blind, placebo-controlled trial: the role of patient motivation. J Psychiatr Res 40(5):383-393, 2006 PMID: 16546214

Mason BJ, Kocsis JH, Ritvo EC, Cutler RB: A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. JAMA 275(10):761-767, 1996 PMID: 8598592

Mason BJ, Quello S, Goodell V, et al: Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med 174(1):70-77, 2014

McGrath PJ, Nunes EV, Stewart JW, et al: Imipramine treatment of alcoholics with primary depression: A placebo-controlled clinical trial. Arch Gen Psychiatry 53(3):232-240, 1996 PMID: 8611060

McLean CP, Su YJ and Foa EB: Posttraumatic stress disorder and alcohol dependence: Does order of onset make a difference? J Anxiety Disord 28(8):894-901, 2014

Meyer A, Wapp M, Strik W, Moggi F: Association between drinking goal and alcohol use one year after residential treatment: a multicenter study. J Addict Dis 33(3):234-242, 2014

McCaul ME, Wand GS, Eissenberg T, et al: Naltrexone alters subjective and psychomotor responses to alcohol in heavy drinking subjects. Neuropsychopharmacology 22(5):480-492, 2000a

McCaul ME, Wand GS, Rohde C, Lee SM: Serum 6-beta-naltrexol levels are related to alcohol responses in heavy drinkers. Alcohol Clin Exp Res 24(9):1385-1391, 2000b

McDonell MG, Leickly E, McPherson S, et al: A randomized controlled trial of ethyl glucuronide-based contingency management for outpatients with co-occurring alcohol use disorders and serious mental illness. Am J Psychiatry in press

Micromedex. Acamprosate. Accessed on February 7, 2017a at http://www.micromedexsolutions.com/home/dispatch

Micromedex. Gabapentin. Accessed on February 7, 2017b at http://www.micromedexsolutions.com/home/dispatch

Micromedex. Naltrexone. Accessed on February 7, 2017c at http://www.micromedexsolutions.com/home/dispatch

Micromedex. Ondansetron. Accessed on February 7, 2017d at http://www.micromedexsolutions.com/home/dispatch

Micromedex. Topiramate. Drug Name. Accessed on February 7, 2017e at http://www.micromedexsolutions.com/home/dispatch

Miller WR, Rollnick S: Motivational Interviewing: Helping People Change, 3rd Edition. New York, NY, The Guilford Press, 2013

Miller WR, Tonigan JS, Longabaugh R: The Drinker Inventory of Consequences (DrInC): An instrument for assessing adverse consequences of alcohol abuse. Test manual. (Volume 4, Project MATCH Monograph Series). Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1995

Miller WR, Zweben A, DiClemente CC, Rychtarik RG: Motivational Enhancement Therapy Manual: a clinical research guide for therapists treating individuals with alcohol abuse and dependence. Rockville, MD, National Institute on Alcohol Abuse and Alcoholism, 1994. Project MATCH Monograph Series, Vol. 2. DHHS Publication No. 94-3723. Accessed on February 4, 2017 at https://pubs.niaaa.nih.gov/publications/ProjectMatch/match02.pdf

Minozzi S, Amato L, Vecchi S, et al: Oral naltrexone maintenance treatment for opioid dependence. Cochrane Database Syst Rev (4):CD001333, 2011 21491383

Mitchell AJ, Meader N, Bird V, Rizzo M: Clinical recognition and recording of alcohol disorders by clinicians in primary and secondary care: meta-analysis. Br J Psychiatry 201:93-100, 2012

Mitchell JE, Morley JE, Levine AS, et al: High-dose naltrexone therapy and dietary counseling for obesity. Biol Psychiatry 22(1):35-42, 1987

Moak DH, Anton RF, Latham PK, et al: Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. J Clin Psychopharmacol 23(6):553-562, 2003 PMID: 14624185

Monterosso JR, Flannery BA, Pettinati HM, et al: Predicting treatment response to naltrexone: the influence of craving and family history. Am J Addict 10(3):258-268, 2001 PMID: 11579624

Monti PM, Rohsenow DJ, Swift RM, et al: Naltrexone and cue exposure with coping and communication skills training for alcoholics: treatment process and 1-year outcomes. Alcohol Clin Exp Res 25(11):1634-1647, 2001 PMID: 11707638

Monroe AK, Lau B, Mugavero MJ, et al: Heavy alcohol use is associated with worse retention in HIV care. J Acquir Immune Defic Syndr 73(4):419-425, 2016

Morgenstern J, Kuerbis AN, Chen ACet al: A randomized clinical trial of naltrexone and behavioral therapy for problem drinking men who have sex with men. J Consult Clin Psychol 80(5):863-875, 2012 PMID: 22612306

Morini L, Politi L, Acito S, et al: Comparison of ethyl glucuronide in hair with carbohydrate-deficient transferrin in serum as markers of chronic high levels of alcohol consumption. Forensic Sci Int 188(1-3):140-143, 2009

Morley KC, Teesson M, Reid SC, et al: Naltrexone versus acamprosate in the treatment of alcohol dependence: A multi-centre, randomized, double-blind, placebo-controlled trial. Addiction 101(10):1451-1462, 2006 PMID: 16968347

Morley KC, Teesson M, Sannibale C, et al: Clinical predictors of outcome from an Australian pharmacological relapse prevention trial. Alcohol 45(6):520-526, 2010 PMID: 20952764

Morris PL, Hopwood M, Whelan G, et al: Naltrexone for alcohol dependence: a randomized controlled trial. Addiction 96(11):1565-1573, 2001 PMID: 11784454

Mowbray O, Krentzman AR, Bradley JC, et al: The effect of drinking goals at treatment entry on longitudinal alcohol use patterns among adults with alcohol dependence. Drug Alcohol Depend 132(1-2):182-188, 2013

Moyer VA on behalf of the U.S. Preventive Services Task Force: Screening and behavioral counseling interventions in primary care to reduce alcohol misuse: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 159:210-218, 2013

Mundle G, Ackermann K, Mann K: Biological markers as indicators for relapse in alcohol-dependent patients. Addict Biol 4(2):209-214, 1999

Naranjo CA, Bremner KE, Lanctot KL: Effects of citalopram and a brief psycho-social intervention on alcohol intake, dependence and problems. Addiction 90(1):87-99, 1995 PMID: 7888983

Narayama PL, Gupta AK, Sharma PK: Use of anti-craving agents in soldiers with alcohol dependence syndrome. Medical Journal Armed Forces India 64(4):320-324, 2008

Nava F, Premi S, Manzato E, et al: Comparing treatments of alcoholism on craving and biochemical measures of alcohol consumptionst. J Psychoactive Drugs 38(3):211-217, 2006 PMID: 17165363

Nehlin C, Fredriksson A, Jansson L: Brief alcohol screening in a clinical psychiatric population: Special attention needed. Drug Alcohol Rev 31(4):538-543, 2012

Niemelä O: Biomarker-Based Approaches for Assessing Alcohol Use Disorders. Int J Environ Res Public Health 13(2):166, 2016

Norstrom T, Rossow I: Alcohol Consumption as a Risk Factor for Suicidal Behavior: A Systematic Review of Associations at the Individual and at the Population Level. Arch Suicide Res 20(4):489-506, 2016

Okuda M, Olfson M, Wang S, et al: Correlates of intimate partner violence perpetration: results from a National Epidemiologic Survey. J Trauma Stress 28(1):49-56, 2015

O'Malley SS, Jaffe AJ, Chang G, et al: Naltrexone and coping skills therapy for alcohol dependence. A controlled study. Arch Gen Psychiatry 49(11):881-887, 1992 PMID: 1444726

O'Malley SS, Jaffe AJ, Chang G, et al: Six-month follow-up of naltrexone and psychotherapy for alcohol dependence. Arch Gen Psychiatry 53(3):217-224, 1996 PMID: 8611058

O'Malley SS, O'Connor PG: Medications for unhealthy alcohol use: across the spectrum. Alcohol Res Health 33(4):300-312, 2011

O'Malley SS, Robin RW, Levenson AL, et al: Naltrexone alone and with sertraline for the treatment of alcohol dependence in Alaska natives and non-natives residing in rural settings: a randomized controlled trial. Alcohol Clin Exp Res 32(7):1271-1283, 2008 PMID: 18482155

O'Malley SS, Rounsaville BJ, Farren C, et al: Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs specialty care: a nested sequence of 3 randomized trials. Arch Intern Med 163(14):1695-1704, 2003 PMID: 12885685

O'Malley SS, Sinha R, Grilo CM, et al: Naltrexone and cognitive behavioral coping skills therapy for the treatment of alcohol drinking and eating disorder features in alcohol-dependent women: a randomized controlled trial. Alcohol Clin Exp Res 31(4):625-634, 2007 PMID: 17374042

Oslin D, Liberto JG, O'Brien J, et al: Naltrexone as an adjunctive treatment for older patients with alcohol dependence. Am J Geriatr Psychiatry 5(4):324-332, 1997 PMID: 9363289

Oslin DW, Berrettini W, Kranzler HR, et al: A functional polymorphism of the mu-opioid receptor gene is associated with naltrexone response in alcohol-dependent patients. Neuropsychopharmacology 28(8):1546-1552, 2003

Oslin DW, Leong SH, Lynch KG, et al: Naltrexone vs Placebo for the Treatment of Alcohol Dependence: A Randomized Clinical Trial. JAMA Psychiatry 72(5):430-437, 2015

Oslin DW, Lynch KG, Pettinati HM, et al: A placebo-controlled randomized clinical trial of naltrexone in the context of different levels of psychosocial intervention. Alcohol Clin Exp Res 32(7):1299-1308, 2008 PMID: 18540910

Paille FM, Guelfi JD, Perkins AC, et al: Double-blind randomized multicentre trial of acamprosate in maintaining abstinence from alcohol. Alcohol 30(2):239-247, 1995 PMID: 7662044

Peer K, Rennert L, Lynch KG, et al: Prevalence of DSM-IV and DSM-5 alcohol, cocaine, opioid, and cannabis use disorders in a largely substance dependent sample. Drug Alcohol Depend 127(1-3):215-219, 2013

Pelc I, Le Bon O, Lehert P, et al: Acamprosate in the Treatment of Alcohol Dependence: A 6-Month Postdetoxification Study. In: Soyka M, ed. Acamprosate in Relapse Prevention of Alcoholism. Springer Berlin Heidelberg, 133-142, 1996

Pelc I, Le Bon O, Verbanck P, et al: Calciumacetylhomotaurinate for maintaining abstinence in weaned alcoholic patients: a placebo-controlled double-blind multi-centre study. In: Naranjo CA, Sellers EM, eds. Novel Pharmacological Interventions for Alcoholism. New York, Springer-Verlag, 1992

Pelc I, Verbanck P, Le Bon O, et al: Efficacy and safety of acamprosate in the treatment of detoxified alcohol-dependent patients. A 90-day placebo-controlled dose-finding study. Br J Psychiatry 171:73-77, 1997 PMID: 9328500

Petrakis I, Ralevski E, Nich C, et al: Naltrexone and disulfiram in patients with alcohol dependence and current depression. J Clin Psychopharmacol 27(2):160-165, 2007 PMID: 17414239

Petrakis IL, O'Malley S, Rounsaville B, et al: Naltrexone augmentation of neuroleptic treatment in alcohol abusing patients with schizophrenia. Psychopharmacology (Berl) 172(3):291-297, 2004 PMID: 14634716

Petrakis IL, Poling J, Levinson C, et al: Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. Biol Psychiatry 57(10):1128-37, 2005 PMID: 15866552

Petrakis IL, Poling J, Levinson C, et al: Naltrexone and disulfiram in patients with alcohol dependence and comorbid post-traumatic stress disorder. Biol Psychiatry 60(7):777-783, 2006 PMID: 17008146

Petrakis IL, Ralevski E, Desai N, et al: Noradrenergic vs serotonergic antidepressant with or without naltrexone for veterans with PTSD and comorbid alcohol dependence. Neuropsychopharmacology 37(4):996-1004, 2012 PMID: 22089316

Pettinati HM, Gastfriend DR, Dong Q, et al: Effect of extended-release naltrexone (XR-NTX) on quality of life in alcohol-dependent patients. Alcohol Clin Exp Res 33(2):350-356, 2009 PMID: 19053979

Pettinati HM, Kampman KM, Lynch KG, et al: Gender differences with high-dose naltrexone in patients with co-occurring cocaine and alcohol dependence. J Subst Abuse Treat 34(4):378-390, 2008 PMID: 17664051

Pettinati HM, Oslin DW, Kampman KM, et al: A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry 167(6):668-675, 2010 PMID: 20231324

Pettinati HM, Volpicelli JR, Luck G, et al: Double-blind clinical trial of sertraline treatment for alcohol dependence. J Clin Psychopharmacol 21(2):143-153, 2001 PMID: 11270910

Pettinati HM, Weiss RD, Miller WR, et al: COMBINE Monograph Series, Volume 2. Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as Part of the Treatment for Alcohol Dependence. DHHS Publication No. (NIH) 04-5289. Bethesda, MD, National Institute on Alcohol Abuse and Alcoholism, 2004

Pfohl DN, Allen JI, Atkinson RL, et al: Naltrexone hydrochloride (Trexan): a review of serum transaminase elevations at high dosage. NIDA Res Monogr 67:66-72, 1986

Piano S, Marchioro L, Gola E, et al: Assessment of alcohol consumption in liver transplant candidates and recipients: The best combination of the tools available. Liver Transpl 20(7):815-822, 2014

Pirro V, Valente V, Oliveri P, et al: Chemometric evaluation of nine alcohol biomarkers in a large population of clinically-classified subjects: pre-eminence of ethyl glucuronide concentration in hair for confirmatory classification. Anal Bioanal Chem 401(7):2153-2164, 2011

Poldrugo F: Acamprosate treatment in a long-term community-based alcohol rehabilitation programme. Addiction 92(11):1537-1546, 1997 PMID: 9519495

Project MATCH Research Group: Matching alcoholism treatments to client heterogeneity: Project MATCH post-treatment drinking outcomes. J Stud Alcohol 58:7–29, 1999

Puukka K, Hietala J, Koivisto H, et al: Obesity and the clinical use of serum GGT activity as a marker of heavy drinking. Scand J Clin Lab Invest 67(5):480-488, 2007

Ralevski E, Balachandra K, Gueorguieva R, et al: Effects of naltrexone on cognition in a treatment study of patients with schizophrenia and comorbid alcohol dependence. J Dual Diagn 2(4):53-69, 2006

Ralevski E, Ball S, Nich C, et al: The impact of personality disorders on alcohol-use outcomes in a pharmacotherapy trial for alcohol dependence and comorbid Axis I disorders. Am J Addict 16(6):443-449, 2007 PMID: 18058408

Ralevski E, O'Brien E, Jane JS, et al: Effects of acamprosate on cognition in a treatment study of patients with schizophrenia spectrum disorders and comorbid alcohol dependence. J Nerv Ment Dis 199(7):499-505, 2011a PMID: 21716064

Ralevski E, O'Brien E, Jane JS, et al: Treatment with acamprosate in patients with schizophrenia spectrum disorders and comorbid alcohol dependence. J Dual Diagn 7(1-2):64-73, 2011b

Rashad I, Kaestner R: Teenage sex, drugs and alcohol use: problems identifying the cause of risky behaviors. J Health Econ 23(3):493-503, 2004

Rising Pharmaceuticals. Disulfiram. 2016. Accessed on February 7, 2017 at http://www.risingpharma.com/Files/Prescribing-Info/Package%20Insert-Disulfiram%20Tablets-250mg-500mg.pdf

Rogers E, Sherman S: Tobacco use screening and treatment by outpatient psychiatrists before and after release of the American Psychiatric Association treatment guidelines for nicotine dependence. Am J Public Health 104(1):90-95, 2014

Rohsenow DJ, Colby SM, Monti PM, et al: Predictors of compliance with naltrexone among alcoholics. Alcohol 24(10):1542-1549, 2000

Rohsenow DJ, Miranda R, Jr., McGeary JE, et al: Family history and antisocial traits moderate naltrexone's effects on heavy drinking in alcoholics. Exp Clin Psychopharmacol 15(3):272-281, 2007 PMID: 17563214

Rösner S, Hackl-Herrwerth A, Leucht S, et al: Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev 2010(12) PMID: CD001867

Rubinsky AD, Dawson DA, Williams EC, et al: Audit-c scores as a scaled marker of mean daily drinking, alcohol use disorder severity, and probability of alcohol dependence in a U.S. General population sample of drinkers. Alcohol Clin Exp Res 37(8):1380-1390, 2013

Rubio G, Jimenez-Arriero MA, Ponce G, et al: Naltrexone versus acamprosate: one year follow-up of alcohol dependence treatment. Alcohol 36(5):419-425, 2001 PMID: 11524308

Rubio G, Martinez-Gras I, Manzanares J: Modulation of impulsivity by topiramate: implications for the treatment of alcohol dependence. J Clin Psychopharmacol 29(6):584-589, 2009 PMID: 19910725

Sachs HC; Committee On Drugs: The transfer of drugs and therapeutics into human breast milk: an update on selected topics. Pediatrics 132(3):e796-809, 2013

Saitz R, Palfai TP, Cheng DM, et al: Screening and brief intervention for drug use in primary care: the ASPIRE randomized clinical trial. JAMA 312(5):502-513, 2014

Sass H, Soyka M, Mann K, et al: Relapse prevention by acamprosate. Results from a placebo-controlled study on alcohol dependence. Arch Gen Psychiatry 53(8):673-680, 1996 PMID: 8694680

Schmitz JM, Lindsay JA, Green CE, et al: High-dose naltrexone therapy for cocaine-alcohol dependence. Am J Addict 18(5):356-362, 2009 PMID: 19874153

Schmitz JM, Stotts AL, Sayre SL, et al: Treatment of cocaine-alcohol dependence with naltrexone and relapse prevention therapy. Am J Addict 13(4):333-341, 2004 PMID: 15370932

Sennesael J: Acamprosate pharmacokinetic study after a single oral administration of 2 acamprosate tablets (2 × 333 mg) to subjects with normal or impaired renal function, Lipha, France (1992) (AOTA-CIN IR1-AD 1003 H. (Data on file)) as cited in Saivin S, Hulot T, Chabac S, et al. Clinical pharmacokinetics of acamprosate. Clin Pharmacokinet 35(5):331-45, 1998

Shiffman RN, Dixon J, Brandt C, et al: The GuideLine Implementability Appraisal (GLIA): development of an instrument to identify obstacles to guideline implementation. BMC Med Inform Decis Mak 5:23, 2005 16048653

Skinner MD, Lahmek P, Pham H, Aubin HJ: Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. PLoS One 9(2):e87366, 2014

Slade T, Chiu WT, Glantz M, et al: A cross-national examination of differences in classification of lifetime alcohol use disorder between DSM-IV and DSM-5: findings from the world mental health survey. Alcohol Clin Exp Res 40(8):1728-1736, 2016a

Slade T, Chapman C, Swift W, et al: Birth cohort trends in the global epidemiology of alcohol use and alcohol-related harms in men and women: systematic review and metaregression. BMJ Open 6(10):e011827, 2016b

Staufer K, Andresen H, Vettorazzi E, et al: Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. Hepatology 54(5):1640-1649, 2011

Stoddard J, Zummo J: Oral and long-acting injectable naltrexone: Removal of boxed warning for hepatotoxicity. J Clin Psychiatry 76(12):1695, 2015

Substance Abuse and Mental Health Services Administration: Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD, NSDUH Series H-48, HHS Publication No (SMA) 14-4863, 2014

Substance Abuse and Mental Health Services Administration: The Role of Biomarkers in the Treatment of Alcohol Use Disorders, 2012 Revision. Advisory, Volume 11, Issue 2. Accessed on January 30, 2017 at http://store.samhsa.gov/shin/content/SMA12-4686/SMA12-4686.pdf

Sudhinaraset M, Wigglesworth C, Takeuchi DT: Social and Cultural Contexts of Alcohol Use: Influences in a Social-Ecological Framework. Alcohol Res 38(1):35-45, 2016

Sullivan MA, Bisaga A, Glass A, et al: Opioid use and dropout in patients receiving oral naltrexone with or without single administration of injection naltrexone. Drug Alcohol Depend 147:122-129, 2015

Syed YY, Keating GM: Extended-release intramuscular naltrexone (VIVITROL®: a review of its use in the prevention of relapse to opioid dependence in detoxified patients. CNS Drugs 27(10):851-861, 2013 Review. 24018540

Sylvia LG, Gold AK, Stange JP, et al: A randomized, placebo-controlled proof-of-concept trial of adjunctive topiramate for alcohol use disorders in bipolar disorder. Am J Addict 25(2):94-98, 2016

Tempesta E, Janiri L, Bignamini A, et al: Acamprosate and relapse prevention in the treatment of alcohol dependence: a placebo-controlled study. Alcohol 35(2):202-209, 2000 PMID: 10787398

Tennis P, Chan KA, Curkendall SM, et al: Topiramate use during pregnancy and major congenital malformations in multiple populations. Birth Defects Res A Clin Mol Teratol 103(4):269-275, 2015

Thomas SE, Randall PK, Book SW, Randall CL: A complex relationship between co-occurring social anxiety and alcohol use disorders: what effect does treating social anxiety have on drinking? Alcohol Clin Exp Res 32(1):77-84, 2008 PMID: 18028529

Tiihonen J, Ryynanen OP, Kauhanen J, et al: Citalopram in the treatment of alcoholism: a double-blind placebo-controlled study. Pharmacopsychiatry 29(1):27-29, 1996 PMID: 8852531

Timko C, Schultz NR, Cucciare MA, et al: Retention in medication-assisted treatment for opiate dependence: A systematic review. J Addict Dis 35(1):22-35, 2016

Turncliff RZ, Dunbar JL, Dong Q, et al: Pharmacokinetics of long-acting naltrexone in subjects with mild to moderate hepatic impairment. J Clin Pharmacol 45(11):1259-1267, 2005

U.S. Preventive Services Task Force: Counseling and interventions to prevent tobacco use and tobacco-caused disease in adults and pregnant women: U.S. Preventive Services Task Force reaffirmation recommendation statement. Ann Intern Med 150(8):551-555, 2009

Vagenas P, Di Paola A, Herme M, et al: An evaluation of hepatic enzyme elevations among HIV-infected released prisoners enrolled in two randomized placebo-controlled trials of extended release naltrexone. J Subst Abuse Treat 47(1):35-40, 2014

Verebey KG, Mulé SJ: Naltrexone (Trexan): a review of hepatotoxicity issues. NIDA Res Monogr 67:73-81, 1986

Vickers AP, Jolly A: Naltrexone and problems in pain management. BMJ 332(7534):132-133, 2006

Volpicelli JR, Alterman AI, Hayashida M, et al: Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry 49(11):876-880, 1992 PMID: 1345133

Volpicelli JR, Clay KL, Watson NT, et al: Naltrexone in the treatment of alcoholism: predicting response to naltrexone. J Clin Psychiatry 56 Suppl 7:39-44, 1995 PMID: 7673104

Volpicelli JR, Rhines KC, Rhines JS, et al: Naltrexone and alcohol dependence. Role of subject compliance. Arch Gen Psychiatry 54(8):737-742, 1997 PMID: 9283509

Walther L, de Bejczy A, Lof E, et al: Phosphatidylethanol is superior to carbohydrate-deficient transferrin and gamma-glutamyltransferase as an alcohol marker and is a reliable estimate of alcohol consumption level. Alcohol Clin Exp Res 39(11):2200-2208, 2015

Weston J, Bromley R, Jackson CF, et al: Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database Syst Rev, 11:CD010224, 2016, Review. 27819746

Wetterling T, Dibbelt L, Wetterling G, et al: Ethyl glucuronide (etg): Better than breathalyser or self-reports to detect covert short-term relapses into drinking. Alcohol Alcohol 49(1): 51-54, 2014

Weykamp C, Wielders JP, Helander A, et al: Toward standardization of carbohydrate-deficient transferrin (CDT) measurements: III. Performance of native serum and serum spiked with disialotransferrin proves that harmonization of CDT assays is possible. Clin Chem Lab Med 51(5):991-996, 2013

White A, Castle IJ, Chen CM et al: Converging patterns of alcohol use and related outcomes among females and males in the United States, 2002 to 2012. Alcohol Clin Exp Res 39(9):1712-1726, 2015

Whitfield JB: Gamma glutamyl transferase. Crit Rev Clin Lab Sci 38(4):263-355, 2001

Whiteford HA, Degenhardt L, Rehm J, et al: Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382(9904):1575-1586, 2013

Whitworth AB, Fischer F, Lesch OM, et al: Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet 347(9013):1438-1442, 1996 PMID: 8676626

Williams EC, Hahn JA, Saitz R, et al: Alcohol use and human immunodeficiency virus (HIV) infection: current knowledge, implications, and future directions. Alcohol Clin Exp Res 40(10):2056-2072, 2016

Williams EC, Rubinsky AD, Lapham GT, et al: Prevalence of clinically recognized alcohol and other substance use disorders among VA outpatients with unhealthy alcohol use identified by routine alcohol screening. Drug Alcohol Depend 135:95-103, 2014

Williams J, Powell LM, Wechsler H: Does alcohol consumption reduce human capital accumulation? Evidence from the college alcohol study. Appl Econ 35:1227-1239, 2003

Wolaver AM: Effects of heavy drinking in college on study effort, grade point average, and major choice. Contemp Econ Policy 20:415-428, 2002

Wolwer W, Frommann N, Janner M, et al: The effects of combined acamprosate and integrative behaviour therapy in the outpatient treatment of alcohol dependence: a randomized controlled trial. Drug Alcohol Depend 118(2-3):417-422, 2011 PMID: 21621929

Wurst FM, Thon N, Yegles M, et al: Ethanol metabolites: their role in the assessment of alcohol intake. Alcohol Clin Exp Res 39(11):2060-2072, 2015

Yen MH, Ko HC, Tang FI, et al: Study of hepatotoxicity of naltrexone in the treatment of alcoholism. Alcohol 38(2):117-120, 2006

Yoshimura A, Kimura M, Nakayama H, et al: Efficacy of disulfiram for the treatment of alcohol dependence assessed with a multicenter randomized controlled trial. Alcohol Clin Exp Res 38(2):572-578, 2014

Zandberg LJ, Rosenfield D, McLean CP, et al: Concurrent treatment of posttraumatic stress disorder and alcohol dependence: Predictors and moderators of outcome. Journal of Consulting and Clinical Psychology 84(1):43-56, 2016

Zarkin GA, Bray JW, Aldridge A, et al: COMBINE Cost-Effectiveness Research Group: Cost and cost-effectiveness of the COMBINE study in alcohol-dependent patients. Arch Gen Psychiatry 65(10):1214-1221, 2008

Zarkin GA, Bray JW, Aldridge A, et al: The effect of alcohol treatment on social costs of alcohol dependence: results from the COMBINE study. Med Care 48(5):396-401, 2010

Appendixes: Review of Research Evidence

Appendix A. Clinical Questions and Search Strategies

Clinical Questions

The evidence review for both the AHRQ report on pharmacotherapy for alcohol use disorder (Jonas et al., 2014) and this guideline was premised on the following clinical questions:

1A. Which medications are efficacious for improving consumption outcomes for adults with alcohol-use disorders in outpatient settings?

1B. How do medications for adults with alcohol-use disorders compare for improving consumption outcomes in outpatient settings?

2A. Which medications are efficacious for improving health outcomes for adults with alcohol-use disorders in outpatient settings?

2B. How do medications for adults with alcohol-use disorders compare for improving health outcomes in outpatient settings?

3A. What adverse effects are associated with medications for adults with alcohol-use disorders in outpatient settings?

3B. How do medications for adults with alcohol-use disorders compare for adverse effects in outpatient settings?

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

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?

6. Are any of the medications more or less effective for adults with specific genotypes (e.g., related to polymorphisms of the mu-opioid receptor gene [OPRM1])?

Search Strategies

The AHRQ's systematic review on *Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings* (Jonas et al., 2014) served as the predominant source of information for this guideline. The search strategies used by the AHRQ can be found in the appendix of the AHRQ review (Jonas et al., 2014). Since the AHRQ searches were conducted from January 1, 1970 through October 11, 2013, the APA also conducted a search of the literature to supplement the AHRQ review, which ranged from September 1, 2013 to April 24, 2016 and used identical search strategies to those used in the AHRQ review. Databases that were searched for both the AHRQ and APA reviews are: PubMed (MEDLINE), EBSCO used for PsycINFO and CINAHL, EMBASE (uses Elsevier site), and Cochrane (uses Wiley site). Details on the search terms and numbers of the articles found are as follows:

2634 ***PubMed***

Search	Query	Items found
#1	Search “Alcohol-Related Disorders” [MeSH]	101450
#2	Search “Alcoholism” [MeSH]	69036
#3	Search “Alcohol Drinking” [MeSH]	55907
#4	Search alcohol depend*	10367
#5	Search “alcohol misuse”	1872
#6	Search alcohol addiction*	1041
#7	Search “alcohol abuse”	14980
#8	Search problem drink*	2557
#9	Search alcohol problem*	3524
#10	Search “alcohol consumption”	32259
#11	Search harmful alcohol*	386
#12	Search harmful drink*	385
#13	Search (((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol[tiab]))	32042
#14	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13)	169531
#15	Search “Alcohol Deterrents”[MeSH]	1211
#16	Search ((“Naltrexone”[Mesh] OR naltrexone))	8614
#17	Search ReVia	8616
#18	Search Vivitrol	29
#19	Search ((“acamprosate” [Supplementary Concept] OR acamprosate))	735
#20	Search Campral	737
#21	Search ((“Disulfiram”[Mesh] OR Disulfiram))	3960
#22	Search Antabuse	4005
#23	Search ((“Amitriptyline”[Mesh] OR Amitriptyline))	8489
#24	Search ((“aripiprazole” [Supplementary Concept] OR aripiprazole))	2982
#25	Search ((“atomoxetine” [Supplementary Concept] OR atomoxetine))	1366
#26	Search ((“Baclofen”[Mesh] OR Baclofen))	7067
#27	Search ((“Buspirone”[Mesh] OR Buspirone))	2764
#28	Search ((“Citalopram”[Mesh] OR citalopram))	5752
#29	Search ((“Desipramine”[Mesh] OR Desipramine))	7634
#30	Search escitalopram	6211
#31	Search ((“Fluoxetine”[Mesh] OR Fluoxetine))	11983
#32	Search ((“Fluvoxamine”[Mesh] OR Fluvoxamine))	2712
#33	Search ((“gabapentin” [Supplementary Concept] OR gabapentin))	5237
#34	Search ((“Imipramine”[Mesh] OR Imipramine))	12756

#35	Search ((“nalmefene” [Supplementary Concept] OR nalmefene))	339
#36	Search ((“olanzapine” [Supplementary Concept] OR olanzapine))	7659
#37	Search ((“Ondansetron”[Mesh] OR Ondansetron))	4157
#38	Search ((“Paroxetine”[Mesh] OR paroxetine))	5642
#39	Search ((“Prazosin”[Mesh] OR Prazosin))	13129
#40	Search ((“quetiapine” [Supplementary Concept] OR quetiapine))	4056
#41	Search ((“Sertraline”[Mesh] OR Sertraline))	4196
#42	Search ((“topiramate”[Supplementary Concept] OR topiramate))	4003
#43	Search (((“Valproic Acid”[Mesh] OR Valproate))) OR "divalproex"	16643
#44	Search ((“varenicline”[Supplementary Concept] OR varenicline))	1348
#45	Search ((“Viloxazine”[Mesh] OR Viloxazine))	321
#46	Search ((#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45))	120290
#47	Search ((#14 and #46))	4533
#48	Search (((#14 and #46))) AND "humans"[Filter]	3469
#49	Search (((#14 and #46)) AND "humans"[Filter]) AND "english"[Filter]	2867
#50	Search ((((#14 and #46)) AND "humans"[Filter]) AND "english"[Filter]) AND "adult"[Filter]	1273
#51	Search (#50) AND ("1970/01/01"[Date - Publication] : "3000"[Date - Publication])	1253
#52	Search ((comment[pt] OR editorial[pt] OR letter[pt] OR news[pt]))	1635136
#53	Search ((#51 NOT #52))	1185
#54	Search (((#51 NOT #52))) AND ("2013/09/01"[Date - Publication] : "3000"[Date - Publication])	124
#55	Search ((#47 AND (“retraction”[All Fields] OR “Retracted Publication”[pt]))	5
#56	Search #54 NOT #55	124

2635 ***PsycINFO***

Search ID#	Search Terms (using Boolean/Phrase Search Mode)	Actions
S1	“Alcohol-Related Disorders”	280

S2	DE “Alcoholism”	26,797
S3	(DE “Alcohol Drinking Attitudes” OR DE “Alcohol Drinking Patterns") OR (DE "Alcohol Intoxication”)	22,573
S4	alcohol depend*	18,723
S5	“alcohol misuse”	1,647
S6	alcohol addiction*	3,846
S7	“alcohol abuse”	24,544
S8	problem drink*	5,810
S9	alcohol problem*	12,102
S10	“alcohol consumption”	15,177
S11	harmful alcohol*	724
S12	harmful drink*	498
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	24,062
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	82,937
S15	“Alcohol Deterrents”	2
S16	naltrexone	2,986
S17	ReVia	18
S18	Vivitrol	23
S19	acamprosate	416
S20	Campral	14
S21	Disulfiram	654
S22	Antabuse	160
S23	Amitriptyline	2,333
S24	aripiprazole	2,049
S25	atomoxetine	787
S26	Baclofen	1,221
S27	Buspirone	1,400
S28	Citalopram	2,365
S29	Desipramine	2,090
S30	escitalopram	1,185
S31	Fluoxetine	6,074
S32	Fluvoxamine	1,522
S33	gabapentin	1,207
S34	Imipramine	4,044
S35	nalmefene	114
S36	olanzapine	5,556
S37	Ondansetron	446
S38	Paroxetine	3,057
S39	Prazosin	594
S40	quetiapine	3,074

S41	Sertraline	2,469
S42	topiramate	1,450
S43	"Valproic Acid" OR Valproate OR divalproex	4,342
S44	varenicline	562
S45	Viloxazine	109
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	40,367
S47	S14 AND S46	2,411
S48	S14 AND S46 Limiters - English; Age Groups: Adulthood (18 yrs & older); Population Group: Human	1,197
S49	S14 AND S46 Limiters - Published Date: 20130901-20160531; English; Age Groups: Adulthood (18 yrs & older); Population Group: Human	181

2636 ***CINAHL***

Search ID#	Search Terms (using Boolean/Phrase search mode)	References Retrieved
S1	MH "Alcohol-Related Disorders"	1,275
S2	MH "Alcoholism"	12,790
S3	MH "Alcohol Drinking"	19,424
S4	alcohol depend*	4,003
S5	"alcohol misuse"	855
S6	alcohol addiction*	507
S7	"alcohol abuse"	9,104
S8	problem drink*	1,694
S9	alcohol problem*	3,696
S10	"alcohol consumption"	7,140
S11	harmful alcohol*	368
S12	harmful drink*	238
S13	TI ((drinking OR drinker OR drinkers) AND alcohol) OR AB ((drinking OR drinker OR drinkers) AND alcohol)	8,163
S14	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13	43,236
S15	MH "Alcohol Deterrents"	253
S16	naltrexone	1,506
S17	ReVia	11
S18	Vivitrol	50
S19	acamprosate	196
S20	Campral	7
S21	Disulfiram	271
S22	Antabuse	20

S23	Amitriptyline	865
S24	aripiprazole	920
S25	atomoxetine	517
S26	Baclofen	1,005
S27	Buspirone	253
S28	Citalopram	1,217
S29	Desipramine	177
S30	escitalopram	475
S31	Fluoxetine	1,676
S32	Fluvoxamine	227
S33	gabapentin	1,584
S34	Imipramine	343
S35	nalmefene	50
S36	olanzapine	1,747
S37	Ondansetron	936
S38	Paroxetine	1,120
S39	Prazosin	316
S40	quetiapine	1,084
S41	Sertraline	1,028
S42	topiramate	1,165
S43	"Valproic Acid" OR Valproate OR divalproex	2,193
S44	varenicline	555
S45	Viloxazine	5
S46	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45	17,496
S47	S14 AND S46	1,201
S48	S14 AND S46 Limiters - English; Age Groups: Adulthood (18 yrs & older); Population Group: Human	1,196
S49	S14 AND S46 Limiters - Published Date: 20130901-20160531; English; Age Groups: Adulthood (18 yrs & older); Population Group: Human	239

2637 ***EMBASE***

Search ID#	Search Terms	References Retrieved
#1	'alcohol-related disorders'/exp OR 'alcohol-related disorders'	109,688
#2	'alcoholism'/exp	109,506
#3	'drinking behavior'/exp	39,554
#4	'alcohol'/exp AND depend*	37,628

#5	'alcohol misuse'	2,372
#6	'alcohol'/exp AND addiction*	12,146
#7	'alcohol abuse'/exp	29,673
#8	problem AND drink*	9,845
#9	'alcohol'/exp AND problem*	14,123
#10	'alcohol consumption'/exp	90,443
#11	harmful AND alcohol*	3,691
#12	harmful AND drink*	2,250
#13	drinking:ti OR drinker:ti OR drinkers:ti AND alcohol:ti OR (drinking:ab OR drinker:ab OR drinkers:ab AND alcohol:ab)	40,816
#14	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	258,040
#15	'alcohol deterrents'	15
#16	'naltrexone'/exp OR naltrexone	13,218
#17	'revia'/exp OR revia	12,211
#18	'vivitrol'/exp OR vivitrol	12,203
#19	'acamprosate'/exp OR acamprosate	2,082
#20	'campral'/exp OR campral	2,025
#21	'disulfiram'/exp OR disulfiram	8,453
#22	'antabuse'/exp OR antabuse	8,134
#23	'amitriptyline'/exp OR amitriptyline	36,056
#24	'aripiprazole'/exp OR aripiprazole	11,148
#25	'atomoxetine'/exp OR atomoxetine	4,233
#26	'baclofen'/exp OR baclofen	15,835
#27	'buspirone'/exp OR buspirone	8,567
#28	'citalopram'/exp OR citalopram	19,423
#29	'desipramine'/exp OR desipramine	21,591
#30	'escitalopram'/exp OR escitalopram	8,570
#31	'fluoxetine'/exp OR fluoxetine	41,023
#32	'fluvoxamine'/exp OR fluvoxamine	12,745
#33	'gabapentin'/exp OR gabapentin	23,826
#34	'imipramine'/exp OR imipramine	35,132
#35	'nalmefene'/exp OR nalmefene	1,087
#36	'olanzapine'/exp OR olanzapine	28,340
#37	'ondansetron'/exp OR ondansetron	14,436
#38	'paroxetine'/exp OR paroxetine	24,817
#39	'prazosin'/exp OR prazosin	23,785
#40	'quetiapine'/exp OR quetiapine	18,698
#41	'sertraline'/exp OR sertraline	21,836
#42	'topiramate'/exp OR topiramate	17,639
#43	'valproic acid'/exp OR 'valproic acid' OR 'valproate'/exp OR valproate OR divalproex	57,157

#44	'varenicline'/exp OR varenicline	3,309
#45	'viloxazine'/exp OR viloxazine	1,451
#46	#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45	289,719
#47	#14 AND #46	11,439
#48	#47 AND ([adult]/lim OR [aged]/lim) AND [humans]/lim AND [english]/lim AND [embase]/lim AND [1970-2016]/py	2,401
#49	editorial:it OR letter:it OR note:it AND [1970-2016]/py	2,041,776
#50	#48 NOT #49 AND [1970-2016]/py	2,161
#51	#48 NOT #49 AND [2013-2016]/py	545

2638 ***COCHRANE***

ID	Search	Hits
#1	MeSH descriptor: [Alcohol-Related Disorders] explode all trees	3886
#2	MeSH descriptor: [Alcoholism] explode all trees	2638
#3	MeSH descriptor: [Alcohol Drinking] explode all trees	2804
#4	alcohol depend*	5822
#5	"alcohol misuse"	299
#6	alcohol addiction*	1893
#7	"alcohol abuse"	1452
#8	problem drink*	1027
#9	alcohol problem*	3480
#10	"alcohol consumption"	3355
#11	harmful alcohol*	710
#12	harmful drink*	310
#13	(drinking:ti or drinking:ab or drinker:ti or drinker:ab or drinkers:ti or drinkers:ab) and (alcohol:ti or alcohol:ab)	3324
#14	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13	13194
#15	MeSH descriptor: [Alcohol Deterrents] explode all trees	182
#16	[mh Naltrexone] or naltrexone	1559
#17	ReVia	13
#18	Vivitrol	16
#19	acamprosate	256
#20	Campral	8
#21	[mh Disulfiram] or Disulfiram	291
#22	Antabuse	26
#23	[mh Amitriptyline] or Amitriptyline	2536
#24	aripiprazole	917

#25	atomoxetine	407
#26	[mh Baclofen] or Baclofen	475
#27	[mh Buspirone] or Buspirone	569
#28	[mh Citalopram] or Citalopram	1797
#29	[mh Desipramine] or Desipramine	848
#30	escitalopram	1013
#31	[mh Fluoxetine] or Fluoxetine	3173
#32	[mh Fluvoxamine] or Fluvoxamine	963
#33	gabapentin	1402
#34	[mh Imipramine] or Imipramine	2264
#35	nalmefene	120
#36	olanzapine	2653
#37	[mh Ondansetron] or Ondansetron	2431
#38	[mh Paroxetine] or Paroxetine	2402
#39	[mh Prazosin] or Prazosin	1138
#40	quetiapine	1323
#41	[mh Sertraline] or Sertraline	2013
#42	topiramate	979
#43	[mh "Valproic Acid"] or Valproate or Divalproex	1674
#44	[mh Viloxazine] or Viloxazine	151
#45	varenicline	480
#46	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45	25834
#47	#14 and #46	1847
#48	comment:pt or editorial:pt or letter:pt or news:pt	7973
#49	#47 not #48	1838

Additional Target Searches

Search of MEDLINE (PubMed) on January 19, 2017 related to patient preferences and AUD pharmacotherapy

("patient preference" OR "patient preferences" OR "patient choice" OR "patient choices" OR "shared decision making" OR "patient centered") AND ("alcohol use disorder" OR "alcohol use disorders" OR "alcohol abuse" OR "alcohol dependence" OR "alcoholism" OR "alcoholic")	88
Limited to "english"[Language] AND "humans"[Filter]	67

Articles were screened by one reviewer (L.J.F.) for relevance based upon whether the patient population was primarily individuals with AUD and whether specific preferences for AUD treatments were

discussed. Three articles were identified but were of limited relevance as 1 addressed only patients who were undomiciled, 1 was in a primary care setting, and 1 was based on a survey of the Swedish general population. None of the articles commented on preferences for specific pharmacotherapies.

Search of MEDLINE (PubMed) on January 22, 2017 related to use of quantitative measures to detect the presence and severity of alcohol misuse

("audit" OR "promis" OR "rating scale" OR "rating scales" OR "quantitative measure" OR "quantitative measurement" OR "quantitative measurements" OR "quantitative measures" OR "measurement based") AND ("alcohol use disorder" OR "alcohol use disorders" OR "alcohol abuse" OR "alcohol dependence" OR "alcoholism" OR "alcoholic")	4376
Limited to ("english"[Filter] AND "humans"[Filter] AND ("2006"[Date - Publication] : "2016"[Date - Publication])) NOT ("comment"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type])	1859

Articles were screened by one reviewer (L.J.F.) for relevance based upon whether the quantitative measure was used to support a diagnosis of AUD and establish its severity. Articles were excluded if they focused on the use of quantitative measures for screening purposes in community samples or primary care settings. Three articles were identified, one of which was a systematic review of properties of the AUDIT.

Search of MEDLINE (PubMed) on January 22, 2017 related to use of laboratory biomarkers for alcohol use

("biomarker" OR "biomarkers" OR "cdt" OR "carbohydrate deficient transferrin" OR "ast" OR "alt" OR "aspartate amino transferase" OR "alanine amino transferase" OR "ethylglucuronide" OR "ethyl glucuronide" OR "ethyl sulfate" OR "ethylsulfate" OR "ggt" OR "gamma glutamyl transferase" OR "gammaglutamyltransferase" OR "mcv" OR "mean corpuscular volume" OR "phosphatidylethanol" OR "phosphatidyl ethanol" OR "peth") AND ("alcohol use disorder" OR "alcohol use disorders" OR "alcohol abuse" OR "alcohol dependence" OR "alcoholism" OR "alcoholic")	6175
Limited to ("english"[Filter] AND "humans"[Filter] AND ("2006"[Date - Publication] : "2016"[Date - Publication])) NOT ("comment"[Publication Type] OR "editorial"[Publication Type] OR "letter"[Publication Type])	2562

Articles were screened by one reviewer (L.J.F.) for relevance based upon whether the laboratory biomarker was used as part of an initial evaluation of AUD or for ongoing monitoring of alcohol consumption patterns during treatment. Articles were included if they focused on the impact of quantitative measures on patient outcomes and used a randomized controlled design or a controlled or prospective cohort design with at least 50 individuals. Articles that were primarily aimed at establishing threshold values to optimize sensitivity and specificity or optimizing laboratory assay methodologies

were excluded. Three articles were identified of which one was a systematic review that included articles on use of phosphatidylethanol as a possible marker for chronic alcohol consumption or binge drinking. Two articles addressed the utility of biomarkers in identifying relapse of AUD in individuals who had received a liver transplant.

Search of MEDLINE (PubMed) on January 19, 2017 related to use of AUD medications in pregnancy and while breastfeeding

("disulfiram" OR "acamprosate" OR "naltrexone" OR "topiramate" OR "ondansetron" OR "gabapentin") AND ("pregnant" OR "pregnancy" OR "breast feeding" OR "breastfeeding" OR "lactation" OR "lactating" OR "puerperal disorders" OR "puerperium" OR "perinatal" OR "prenatal")	646
Limited to "english"[Language] AND "humans"[Filter] AND ("2006"[Date - Publication] : "2016"[Date - Publication])	229

Articles were screened by one reviewer (L.J.F.) for relevance based upon whether treatment using the medications listed above was at least 3 weeks in duration and not just at delivery or on an as needed basis (e.g., for intermittent nausea). Included articles were randomized controlled trials, clinical trials of at least 50 women, or data from registries (e.g., MotherRisk). Based upon these criteria, 11 articles were identified for full text review for possible citation in the discussion of evidence for guideline statement 14.

Appendix B. Review of Research Evidence Supporting Guideline Statements

Assessment and Determination of Treatment Goals

Statement 1:

APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include assessment of current and past use of tobacco and alcohol as well as any misuse of other substances including prescribed or over-the-counter medications or supplements.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. Expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves the identification and diagnosis of substance use disorders. (See APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015) for additional details. A detailed systematic review to support this statement was outside the scope of this guideline; however, less comprehensive searches of the literature did not yield any studies that related to this recommendation in the context of AUD treatment. Consequently, the strength of research evidence is rated as low. Indirect evidence from outpatient primary care settings suggests that screening for use of tobacco, alcohol, and other substances can be beneficial if coupled with a brief intervention. Screening and intervention for tobacco use has been recommended by the United States Preventive Services Task Force (USPSTF, 2009). Screening for at-risk drinking or AUD has also been recommended by the USPSTF (Moyer et al., 2013) as well as by professional organizations such as the American College of Obstetricians and Gynecologists (2011). Although several randomized controlled outpatient trials have not found a significant benefit of screening and brief intervention for alcohol (Kaner et al., 2013) or substance use (Saitz et al., 2014), screening may increase the likelihood that these disorders will be identified and documented in the clinical record (Williams et al., 2014; Mitchell et al., 2012), which would be expected to improve clinical decision-making. Recognition of these disorders is particularly important given the high rates of comorbidity in individuals with AUD (Chou et al., 2016b; Grant et al., 2016) and the frequent lack of treatment for these disorders (Hasin and Grant, 2015; Centers for Disease Control and Prevention, 2011).

Statement 2:

APA recommends (1C) that the initial psychiatric evaluation of a patient with alcohol use disorder include a quantitative behavioral measure to detect the presence of alcohol misuse and assess its severity.

Evidence for this statement is indirect and comes from studies of screening for AUD and studies of the properties of commonly used alcohol related quantitative measures. The strength of research evidence for this statement is rated as low. Findings from the COMBINE study suggest that, in individuals receiving treatment for AUD, scores on the AUDIT reflect the severity of the disorder (Donovan et al., 2006). Severity of AUD is also reflected by AUDIT or AUDIT-C scores in other outpatient settings and community samples (Williams et al., 2014; Rubinsky et al., 2013; Dawson et al., 2012; Chavez et al., 2012). In primary care settings, the USPSTF (Moyer et al., 2013) recommends screening for alcohol misuse and notes that "both the AUDIT and the abbreviated AUDIT-C have good sensitivity and

specificity for detecting the full spectrum of alcohol misuse across multiple populations." Other scales that have been used for screening purposes in routine care (Dhalla and Kopec, 2007; Cherpitel, 2002; Humeniuk et al., 2008) have been less well studied as an indicator of AUD severity.

The USPSTF notes that their recommendations do not apply to individuals seeking treatment for alcohol misuse, but the ability to implement screening with these measures in primary care settings suggests that they would be feasible to use in outpatient alcohol treatment. In addition to usage for screening in hospital and emergency department settings, quantitative measures have been used for screening purposes in outpatient psychiatric settings, again suggesting the feasibility of implementation in AUD treatment (Nehlin et al., 2012). This recommendation is also consistent with Guideline VII on Quantitative Assessment as part of the APA Practice Guidelines for the Psychiatric Evaluation of Adults (American Psychiatric Association, 2015).

Statement 3:

APA suggests (2C) that physiological biomarkers (e.g., blood phosphatidylethanol [PEth], blood carbohydrate deficient transferrin [CDT] alone and in combination with gamma-glutamyl transferase [GGT]) be used to identify persistently elevated levels of alcohol consumption as part of the initial evaluation of patients with alcohol use disorder or in the treatment of individuals who have an indication for ongoing monitoring of their alcohol use.

Evidence for this statement is indirect and the strength of research evidence for this statement is rated as low. Evidence comes from information on the sensitivity and specificity of physiological biomarkers in detecting alcohol consumption (Wurst et al., 2015; Substance Abuse and Mental Health Services Administration, 2012; Walther et al., 2015; Lowe et al., 2015; Alatalo et al., 2009; Bergstrom et al., 2008; Hietala et al., 2006; Hock et al., 2005). In addition, some (Wetterling et al., 2014; Harasymiw and Bean, 2007), but not all (Bertholet et al., 2014; Liangpunsakul et al., 2010) studies suggest that physiological biomarkers can supplement patient self-report in identifying alcohol use in community samples, primary care, and other medical settings. Research also suggests that physiological biomarkers can be used to identify relapse to drinking (Mundle et al., 1999) and to promote abstinence (McDonell et al., in press) or to demonstrate risk for alcohol-related behaviors such as driving while intoxicated (Maenhout et al., 2014; Marques et al., 2010) or health complications after liver transplant (Kollmann et al., 2016; Piano et al., 2014; Staufer et al., 2011). Additional information on the rationale for using physiological biomarkers in the management of individuals with AUD can be found in the Advisory from the Substance Abuse and Mental Health Services Administration (2012).

Statement 4:

APA recommends (1C) that patients be assessed for co-occurring conditions (including substance use disorders, other psychiatric disorders, and other medical disorders) that may influence the selection of pharmacotherapy for alcohol use disorder.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. Expert opinion suggests that conducting such assessments as part of the initial psychiatric evaluation improves diagnostic accuracy, appropriateness of treatment selection, and treatment safety.

(For additional details, see Guideline I. Review of Psychiatric Symptoms, Trauma History, and Psychiatric Treatment History and Guideline VI. Assessment of Medical Health of the APA Practice Guidelines for the Psychiatric Evaluation of Adults Guideline [American Psychiatric Association, 2015]). A detailed systematic review to support this statement was outside the scope of this guideline; however, less comprehensive searches of the literature did not yield any studies that related to this recommendation in the context of AUD treatment. Consequently, the strength of research evidence is rated as low.

Statement 5:

APA suggests (2C) that the initial goals of treatment of alcohol use disorder (e.g., abstinence from alcohol use, reduction or moderation of alcohol use, other elements of harm reduction) be agreed upon between the patient and clinician and that this be documented in the medical record.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. Also, in choosing pharmacotherapy for AUD and particularly before deciding to prescribe disulfiram, it is essential to know whether the patient has a goal of abstinence from alcohol use or not. More generally, expert opinion suggests that engaging patients in shared decision-making improves the therapeutic alliance and adherence. (For additional details, see Guideline VIII. Involvement of the Patient in Treatment Decision Making in the APA Practice Guidelines for the Psychiatric Evaluation of Adults [American Psychiatric Association, 2015]). There has also been increasing attention to shared decision making in treatment of AUD (Bradley and Kivlahan, 2014) as well as in other areas of medicine (Makoul and Clayman, 2006; Durand et al., 2014).

A detailed systematic review to support this statement was outside the scope of this guideline; however, a less comprehensive search of the literature did not yield any studies that were directly related to this recommendation. Consequently, the strength of research evidence is rated as low. However, secondary analyses of clinical trial data show that patient stated goals of abstinence at study initiation are associated with more days abstinent and greater reductions in alcohol consumption than patient-stated goals of reduced alcohol use (Al-Otaiba et al., 2008; Berger et al, 2016; Gueorguieva et al., 2014; Meyer et al., 2014; Dunn and Strain, 2013; Bujarski et al., 2013; Adamson et al., 2010; Mowbray et al., 2013; Chang et al., 2006). In addition, patient goals sometimes changed in the course of treatment. Several smaller studies also related to determining patient goals at the start of treatment. One small study examined the number and types of goals set in the course of treatment by individuals with AUD who were chronically homeless (Collins et al., 2015). Drinking-related goals were most frequent and typically included reducing drinking and reducing alcohol-related consequences, rather than abstinence-based goals. Quality-of-life goals and health-related goals were also reported throughout the course of treatment. In addition, a small study of at-risk elderly drinkers who were treated in primary care compared enhanced referral to integrated care, which included treatment goal setting among multiple other components (Lee et al., 2009). Individuals receiving integrated care were more likely to access care and had fewer drinks in the past week and fewer binge drinking episodes in the past 3 months than those assigned to receive enhanced referral.

Statement 6:

APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of the patient's legal obligations (e.g., abstinence from alcohol use, monitoring of abstinence) and that this be documented in the medical record.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. A detailed systematic review to support this statement was outside the scope of this guideline; however, based upon prior searches related to psychiatric assessment and treatment planning, we would not anticipate finding any studies with a direct bearing on this recommendation.

Statement 7:

APA suggests (2C) that the initial goals of treatment of alcohol use disorder include discussion of risks to self (e.g., physical health, occupational functioning, legal involvement) and others (e.g., impaired driving) from continued use of alcohol and that this discussion be documented in the medical record.

Evidence for this statement comes from general principles of clinical care in psychiatric practice. A detailed systematic review to support this statement was outside the scope of this guideline; however, evidence does suggest that abstaining from or reducing alcohol consumption is associated with significant health benefits (Charlet and Heinz, in press). In addition, having the patient identify negative consequences of drinking for himself or herself is an element of Motivational Enhancement Therapy (Miller et al., 1994; Miller and Rollnick, 2013). Assessment of drinking consequences has been a part of many studies of treatment for AUD, including Project MATCH (Miller et al., 1995; Project MATCH Research Group, 1999) and the COMBINE study (Anton et al., 2006), although the specific effect of this element on outcomes has not been separated from other elements of treatment.

Nonpharmacotherapy Treatments

Statement 8:

APA recommends (1C) that patients with alcohol use disorder have a documented comprehensive and person-centered treatment plan that includes evidence-based nonpharmacological and pharmacological treatments.

Evidence for this statement comes from general principles of assessment and clinical care in psychiatric practice. A detailed systematic review to support this statement was outside the scope of this guideline; however, less comprehensive searches of the literature did not yield any studies that directly related to this recommendation. Consequently, the strength of research evidence is rated as low.

Expert opinion suggests that, when using pharmacotherapy to treat AUD, it is beneficial for a treatment plan to incorporate non-pharmacological treatments and have a patient-centered focus. Furthermore, major clinical trials of alcohol pharmacotherapy, such as the COMBINE study, include some form of non-pharmacological treatment in all treatment arms. For example, medication management included elements of education, encouragement, approaches to enhancing medication adherence, and supportive interactions to promote abstinence.

In terms of person-centered care, one meta-analysis (Barrio and Gual, 2016) assessed the role of patient-centered care in individuals with AUD. Of the 40 included studies, 5 involved use of pharmacological agents on an "as needed" basis and 35 involved motivational interviewing, with more than one session occurring in 15 of the studies. Despite significant heterogeneity in the studies, a benefit of "as needed" medication was described with positive alcohol-related outcomes in some of the multiple session motivational interviewing studies.

In terms of treatment preferences related to AUD, a study of 399 primary care patients included 65 individuals (68% male) with a score of greater than 8 on the AUDIT (Lieberman et al., 2014). When asked about potential treatments, 68% reported interest in "getting help from my doctor", 37% reported interest in an internet program, and 23% reported interest in Alcoholics Anonymous. In terms of pharmacotherapy, 55% reported interest in "taking a medication that would make it easier to avoid alcohol (but would not make me sick if I drank), with 20% reporting interest in "taking a medication that would make me sick if I drank." Alcohol related treatment preferences were also assessed in a large (N=9005) population-based study in Sweden (Andréasson et al., 2013). Among respondents who reported the highest number of standard drinks per week (>28 for men and >18 for women), approximately 40% expressed a preference for Alcoholics Anonymous or other support group, approximately 40% expressed a preference for psychotherapy, approximately 15% expressed a preference for pharmacotherapy, and approximately 5% expressed a preference for internet-based intervention. Data from the COMBINE study demonstrate that patient views of treatment, including treatment cost-effectiveness, may differ from clinician views (Dunlap et al., 2010). In addition, the time that patients must invest in attending treatment sessions and traveling to treatment is often considerable (Dunlap et al., 2010).

Selection of a Pharmacotherapy

Statement 9:

APA recommends (1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of reducing alcohol consumption or achieving abstinence;**
- **prefer pharmacotherapy or have not responded to nonpharmacological treatments alone; and**
- **have no contraindications to the use of these medications.**

Evidence supporting the use of naltrexone and acamprosate comes from multiple double-blind randomized controlled clinical trials. All trials described below were conducted in the outpatient setting, with subject recruitment typically occurring by print and other media advertising or by referrals (e.g., from inpatient detoxification programs or other outpatient clinicians). Most studies were conducted in Europe or the United States; the remaining studies were conducted in Asia, Australia or South America. Trials were at least 12 weeks in length to be included in the systematic review of evidence, with some extending to 26 weeks or more. Post-treatment follow-up was typically minimal but some trials followed subjects up to a year after treatment discontinuation. The majority of the trials included

psychotherapies or other psychosocial interventions for all treatment groups (e.g., motivational therapies, cognitive behavioral interventions, manual-based medication management approaches).

The vast majority of trials established eligibility for the trial based on DSM-IV criteria or ICD-10 criteria for alcohol dependence as well as numerical descriptions of alcohol use (e.g., days of drinking in past week or month, threshold numbers for drinks per day or drinks per week), typically with lower thresholds for women than for men. In framing the guideline recommendation in terms of DSM-5 AUD, we relied on evidence that DSM-IV alcohol dependence corresponds to DSM-5 AUD of at least moderate severity (Hasin et al., 2013; Peer et al., 2013; Compton et al., 2013). In terms of exclusion criteria, other substance use disorders, besides nicotine and sometimes marijuana, typically precluded participation as did use of psychotropic medications, and significant physical or psychiatric illnesses were also exclusion criteria for most trials. Other exclusion criteria related to ability to consent (e.g., language barriers, cognitive deficits) and to potential safety risks with the medication such as pregnancy or breastfeeding or need for opioid medication (with naltrexone). Study subjects were generally limited to adults, with a mean age of subjects in the mid-40s. The majority of trials had a preponderance of men. Other demographic characteristics were often unreported.

Most study outcomes were focused on abstinence-related outcomes such as any drinking, time to first drink, or time to relapse or alcohol consumption related outcomes such number of drinking days, number of heavy drinking days, drinks per drinking day, or drinks per week. Other important outcomes such as quality of life, accidents, injuries, and mortality were reported infrequently. In trials that included information about adverse events, the methods for identifying such events were frequently unclear. Numbers of serious events (including suicide or suicide attempts) were small, making it impossible to identify whether differences existed among treatment conditions. Some studies only reported information about adverse events that were statistically different from placebo, which could affect the meta-analyses on harms.

Benefits of acamprosate

Table B-1. Acamprosate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNTh	Strength of Evidence Grade
Return to any drinking	16[a]; 4,847	Medium; RCTs	Consistent[b]	Direct	Precise	RD: -0.09 (-0.14 to -0.04)	12	Moderate
Return to heavy drinking	7; 2,496	Low; RCTs	Consistent	Direct	Precise	RD: -0.01 (-0.04 to 0.03)	NA	Moderate[c]
Drinking days	13[d]; 4,485	Medium; RCTs	Consistent	Direct	Precise	WMD: -8.8 (-12.8 to -4.8)	NA	Moderate
Heavy drinking days	1; 100	Medium; RCT	Unknown	Direct	Imprecise	WMD: -2.6 (-11.4 to 6.2)	NA	Insufficient
Drinks per drinking day	1[d]; 116	Low; RCT	Unknown	Direct	Imprecise	WMD: 0.40 (-1.81 to 2.61)	NA	Insufficient
Accidents	0[e];	NA	NA	NA	NA	NA	NA	Insufficient

	0							
Injuries	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 612	Low; RCT	Unknown	Direct	Unknown	NSD[f]	NA	Insufficient
Mortality	8[g]; 2,677	Medium; RCTs	Unknown	Direct	Imprecise	7 (ACA) vs. 6 (PBO)	NA	Insufficient

From Jonas, et al. (2014), Table D-1

[a] 2 additional studies were rated high risk of bias; 1 additional study was rated as unclear risk of bias
[b] Although there was considerable statistical heterogeneity, fourteen of fifteen studies reported point estimates that favored acamprosate; differences were in magnitude of benefit
[c] The relatively small number of studies reporting this outcome raises concern for potential reporting bias, hence the rating of moderate rather than high rating
[d] 1 additional study was rated high risk of bias
[e] The single study that reported this outcome was rated as unclear risk of bias. It reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.
[f] Results were not reported for each treatment group separately, but there were no clinically significant differences across treatment groups
[g] One additional study reported a death but did not specify in which treatment group it occurred.
h Values for NNT were added from Jonas, et al. (2014), Table 37. For values marked NA, NNT was not calculated either because the risk difference (95% CI) was not statistically significant or the effect measure was not one that allows direct calculation of NNT (e.g., WMD).

Abbreviations: ACA = acamprosate; CI = confidence interval; NA = not applicable; NNT = number needed to treat; NSD = no statistically significant difference; PBO = placebo; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

The AHRQ review (Jonas et al., 2014) found that acamprosate treatment at a dose of 666 mg and three times daily (range 1,000 mg to 3,000 mg per day in divided doses) was associated with a decreased likelihood of returning to alcohol use as compared to placebo (Moderate SOE, risk difference [RD], -0.09; 95% CI, -0.14 to -0.04, NNT = 12). Number of drinking days was also reduced with acamprosate treatment relative to placebo (Moderate SOE; weighted mean difference [WMD], -8.8; 95% CI, -12.8 to -4.8; 13 trials). However, for both outcomes, the benefits of acamprosate were primarily seen in studies done outside of the United States. Return to heavy drinking (Moderate SOE) and number of heavy drinking days (Insufficient SOE) showed no effect of acamprosate. The available evidence also did not permit any conclusions about the effect of acamprosate on outcomes such as quality of life, functioning, accidents, injuries, or mortality. In studies that assessed response rates by sex, men and women did not differ on any measure of efficacy.

In the studies with long term use of acamprosate (48 to 52 weeks), there was an 11% absolute reduction in return to any drinking (RD, -0.11; 95% CI, -0.16 to -0.06; 4 trials) and 12.2% fewer drinking days than those treated with placebo over 48 to 52 weeks (WMD, -12.2; 95% CI, -16.4 to -8.0; I^2 0%).

A number of relevant studies that are not included in the AHRQ meta-analysis have shown mixed results for acamprosate. A pragmatic trial in France randomly assigned 422 patients in 149 general practices to standard care (typically outpatient detoxification followed by psychotherapy) or to acamprosate plus standard care (Kiritzé-Topor et al., 2004). The trial reported better outcomes for the acamprosate group on a number of alcohol related measures with an NNT of about 7. A 24-week study (total N=327) with low risk of bias that was conducted in Japan (Higuchi et al., 2015) showed greater rates of abstinence with acamprosate than placebo at 24 weeks (47.2% for acamprosate vs. 36.0% for placebo; p=0.039), but there was no significant effect of treatment on secondary endpoints (i.e., cumulative days of

abstinence during 24 weeks of treatment, time to first relapse, and time to 3 or more days of consecutive drinking). Furthermore, the generalizability of this study to the U.S. may be limited because patients were enrolled upon discharge from 2 months of inpatient detoxification/rehabilitation.

In two additional randomized controlled trials, effects of acamprosate did not differ from placebo. The German PREDICT study (Mann et al., 2013), modeled after the COMBINE study, recruited subjects (total N=426) at time of discharge from medical detoxification (average length of stay 18 days). The time to first heavy drinking (primary outcome) did not differ among the treatment groups. Relapse free survival at 90 days was 48.3% for acamprosate vs. 51.8% for placebo. Another study (total N=100) with low risk of bias in a primary care setting (Berger et al., 2013) found no effect of acamprosate on percent days abstinent (primary outcome), percent heavy drinking days, or change in GGT levels. Nevertheless, both acamprosate and placebo groups showed improvement during the 12-week trial, particularly among individuals with a treatment goal of abstinence.

Grading of the overall supporting body of research evidence for efficacy of acamprosate:

- **Magnitude of effect:** Weak. When present, the magnitude of the effect is small.
- **Risk of bias:** Medium. Studies are RCTs of low to medium bias based on their described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. However, studies from the US showed minimal or no response to acamprosate. The doses of acamprosate and characteristics of subjects in the studies appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and alcohol consumption.
- **Consistency**: Inconsistent. There was considerable heterogeneity as evidenced by I^2 values of 70-80% on return to any drinking and on percent drinking days.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** Present. Although not analyzed as part of the AHRQ meta-analysis, all three trials that examined several doses of acamprosate found at least a trend for improved response at higher doses.
- **Confounding factors (including likely direction of effect):** Absent. No known confounding factors are present that would be likely to reduce the effect of the intervention.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Moderate. A large number of RCTs have been conducted, most of which have low to medium risk of bias. Many of the RCTs are funded by governmental agencies. Although the studies have good applicability and measure outcomes of interest directly, the imprecision and inconsistency of findings are limitations.

Harms of acamprosate

Table B-2 Acamprosate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	13[a]; 4,653	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.006 (-0.003 to 0.015)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	1[b]; 601	Medium; RCT	Unknown	Direct	Imprecise	RD 0.164 (0.095 to 0.234)	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	12[c]; 3,299	Medium; RCTs	Consistent	Direct	Precise	RD 0.099 (0.030 to 0.168)	Moderate
Dizziness	2; 151	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.08 (-0.22 to 0.38)	Low
Headache	6[b]; 1,074	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.001 (-0.052 to 0.05)	Low
Insomnia	3[b]; 251	Medium; RCT	Inconsistent	Direct	Imprecise	RD 0.019 (-0.10 to 0.138)	Low
Nausea	7[b]; 1,758	Low to medium; RCTs	Consistent	Direct	Imprecise	RD 0.006 (-0.012 to 0.023)	Moderate
Numbness / tingling / paresthesias	1[b]; 262	Medium; RCT	Unknown	Direct	Imprecise	RD 0.008 (-0.013 to 0.029)	Insufficient
Rash	1[b]; 35	Low; RCT	Unknown	Direct	Imprecise	RD 0.111 (-0.069 to 0.291)	Insufficient
Suicide attempts or suicidal ideation	1[c]; 581	Medium; RCT	Unknown	Direct	Imprecise	RD 0.007 (-0.005, 0.019)	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	4[b]; 1,817	Medium; RCTs	Consistent	Direct	Precise	RD 0.024 (0.007 to 0.042)	Moderate

FROM Jonas et al., (2014) Table D-33

[a] Three additional studies were rated high or unclear risk of bias

[b] One additional study was rated high or unclear risk of bias

[c] Two additional studies were rated high or unclear risk of bias

Abbreviations: AE = adverse effect; CI = confidence interval; RCT = randomized controlled trial; RD risk difference

The AHRQ review (Jonas et al., 2014) found statistically significant increases in anxiety, diarrhea, and vomiting as compared to placebo, although statistical heterogeneity was high, particularly for diarrhea. In addition to diarrhea, the package insert for acamprosate also lists somnolence as a common side effect (Forest Pharmaceuticals, Inc., 2012). The package insert also notes that acamprosate is contraindicated with severe renal impairment (CrCl 30 mL/min or less) and requires dose adjustments for moderate renal impairment (CrCl of 30 to 50 mL/min). Adverse events of a suicidal nature were described in the package insert as somewhat more common with acamprosate as compared to placebo (1.4% vs. 0.5% in studies of 6 months or less; 2.4% vs. 0.8% in year-long studies) with suicide in 3 of 2272

(0.13%) patients in the pooled acamprosate group and 2 of 1962 patients (0.10%) in the pooled placebo group. However, the AHRQ report notes that evidence was not sufficient to make a determination about the risk of suicide-related events (Jonas et al., 2014).

In studies published since the AHRQ report (Jonas et al., 2014), diarrhea was also common. In Berger et al. (2013), diarrhea occurred in almost one-third of subjects but there was no difference between acamprosate and placebo. In Higuchi et al. (2015), diarrhea occurred more frequently with acamprosate than placebo (12.9% vs. 4.9%, respectively). Mann et al., (2013), diarrhea was also noted to be greater with acamprosate than placebo, whereas anxiety was greater in subjects treated with placebo than in those receiving acamprosate. Other side effects occurred in less than 10% of either group (Berger et al., 2013; Higuchi et al., 2015) without differences in overall side effects (Higuchi et al., 2015) or study attrition due to adverse events (Mann et al., 2013).

Grading of the overall supporting body of research evidence for harms of acamprosate:

- **Magnitude of effect:** Weak. When present, the magnitude of effect is small.
- **Risk of bias:** High. Studies are RCTs of low to medium bias based on their described randomization and blinding procedures and descriptions of study dropouts. However, methods for determining harms are not well-specified and there is potential for selective reporting of results.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of acamprosate and characteristics of subjects in the studies appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured common side effects and dropouts due to adverse events.
- **Consistency:** Inconsistent. There was considerable heterogeneity, particularly in reported rates of diarrhea.
- **Precision:** Imprecise. Confidence intervals for studies are wide in many studies and cross the threshold for clinically significant harms of the intervention.
- **Dose-response relationship:** Unknown. Dose response information on side effects was not well described.
- **Confounding factors (including likely direction of effect):** Absent. No known confounding factors are present that would be likely to modify adverse events of the intervention. Although abnormalities in renal function could affect blood levels of drugs, individuals with significant renal impairment were excluded from the clinical trials.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Low. A large number of RCTs have been conducted, but few have assessed adverse events in a systematic and pre-defined fashion. Many of the RCTs are funded by governmental agencies. Although the studies have good applicability and measure outcomes of interest directly, imprecision and inconsistency of findings are a limitation.

Data abstraction - acamprosate

Table B3. Studies related to acamproate

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Followup)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Anton, 2006; Donovan, 2008; LoCastro, 2009; COMBINE	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA[a] 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153)[a] Other Tx: As randomized; community support group participation (like AA) encouraged	16 (68)	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: NR	Percent drinking days: -0.1 (95%CI -4.21, 4.01) Return to any drinking: -0.02 (95%CI -0.08, 0.04) Return to heavy drinking: -0.04 (95%CI -0.11, 0.04)	Low
Baltieri, 2004	Design: DBRCT Setting: Outpatient Country: Brazil Funding: NR	ACA 1,998 (40); PBO (35) Other Tx: AA encouraged	12 (24)	ICD-10 alcohol dependence Mean Age: 18 to 60 y % Non-white NR 0% Female Other Dx: 0%	Return to any drinking: -0.22 (95%CI -0.45, 0)	Medium
Berger, 2013; Berger, 2016	Design: DBRCT Setting: 2 outpatient primary care sites Country: U.S. Funding: Forest	ACA 1,998 (51); PBO (49) Other Tx: Brief structured behavioral intervention from primary care physician	12	DSM-IV alcohol dependence Mean Age: 48 y 9% Non-white 38% Female Other Dx: Tobacco use 44%	Percent drinking days: 0.9 (95%CI -11.59, 13.39) Percent heavy drinking days: -2.6 (95%CI -11.38, 6.18) Return to any drinking: 0.12 (95%CI 0, 0.25)	Medium

					Both treatment groups improved with greater response in those with a goal of abstinence No deaths or serious adverse events	
Besson, 1998	Design: DBRCT Setting: 3 outpatient, psychiatric sites Country: Switzerland Funding: Govt, Lipha	ACA 1,300 to 1,998 (55); PBO (55) Other Tx: Routine counseling 100%; Voluntary disulfiram 22% to 24%	52 (108)	DSM-III chronic or episodic alcohol dependence Mean Age: 42 y % Non-white NR 20% Female Other Dx: 0%	Percent drinking days: -19 (95%CI -32.43, -5.57) Return to any drinking: -0.11 (95%CI -0.26, 0.04) Attrition: 65% at 360 days/ 0 at 360 days	Medium
Chick, 2000b	Design: DBRCT Setting: 20 outpatient clinics Country: U.K. Funding: Lipha	ACA 1,998 (289); PBO (292) Other Tx: Usual psychosocial; outpatient treatment program	24	DSM-III alcohol dependence Mean Age: 43 y % Non-white NR 16% Female Other Dx: 0%	Percent drinking days: 2 (95%CI -3.71, 7.71) Return to any drinking: -0.01 (95%CI -0.06, 0.04) Return to heavy drinking: 0.02 (95%CI -0.04, 0.08)	Medium
COMBINE Study Research Group, 2003	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (9); ACA 3,000 + MM (9); NTX 100 + CBI + MM (9); NTX 100 + MM (9); PBO + CBI + MM (9); PBO + MM (8) Other Tx: As randomized	16	DSM-IV alcohol dependence Mean Age: 38 to 42 y 17 to 22% Non-white 22 to 33% Female Other Dx: NR	Acamprosate-naltrexone group adherence was equal to, or better than, adherence with placebo, acamprosate alone or naltrexone alone Adverse events were comparable in all groups. Attrition: 31/11 to 20	Medium
De Sousa, 2005	Design: OLRCT Setting: Outpatient, private psychiatric hospital Country: India	ACA 1,998 (50); DIS 250 (50) Other Tx: Weekly supportive group psychotherapy offered	35	DSM-IV alcohol dependence Exclusions: previous disulfiram or acamprosate treatment Mean Age: 42 to 43 y	Disulfiram had a lower relapse rate than acamprosate (88% vs. 46%, p = 0.0001) and a longer mean time to first relapse (123 d vs. 71 days p = 0.0001). Acamprosate had lower craving scores than disulfiram.	High

	Funding: NR			100% Non-white 0% Female Other Dx: NR		
Geerlings, 1997	Design: DBRCT Setting: 22 outpatient substance use treatment centers Country: Belgium, the Netherlands, and Luxem-bourg Funding: Lipha	ACA 1,332 to 1,998 (128); PBO (134) Other Tx: ACA: benzodiazepines 5%; Placebo: benzodiazepines 6%	26 (52)	DSM-III alcohol dependence Mean Age: 40 to 42 y % Non-white NR 24% Female Other Dx: NR	Percent drinking days: -10 (95%CI -18.66, -1.34) Return to any drinking: -0.12 (95%CI -0.21, -0.02)	Medium
Greenfield, 2010; Fucito, 2012; COMBINE	Design: Secondary data analysis Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153) Other Tx: As randomized;; community support group participation (like AA) encouraged	68	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: 0%	There was a significant naltrexone by CBI interaction for women on two primary outcomes (percent days abstinent and time to first heavy drinking days) and also secondary outcome measures (good clinical response, percent heavy drinking days, and craving). Only the naltrexone by CBI interaction was significant for percent days abstinent. The naltrexone by CBI interaction was significant for time to first heavy drinking day: in men (p=.048) with each treatment showing slower relapse times. A non-significant trend was present in women. Naltrexone or CBI alone was superior to groups receiving neither in the percent of heavy drinking days.	Low
Gual, 2001	Design: DBRCT Setting: Outpatient; multicenter; hospitals	ACA 1,998 (148); PBO (148) Other Tx: NR	26	DSM-III-R alcohol dependence Mean Age: 41 y	Percent drinking days: -10.6 (95%CI -18.11, -3.09)	Medium

	Country: Spain Funding: Lipha			% Non-white NR 20 to 21% Female Other Dx: NR	Return to any drinking: -0.09 (95%CI -0.19, 0.02)	
Higuchi, 2015	Design: DBRCT Setting: Outpatient Country: Japan Funding: Nippon Shinyaku Company	ACA 1998 (163), PBO (184)	24 (24)	ICD-10 alcohol dependence Mean Age: 52.4 y % Non-white NR 12.5% Female Other Dx: NR	Abstinence rates with acamprosate vs. placebo were 47.2% vs. 36.0% with 11.3% (95% CI, 0.6%-21.9%) difference (P = .039) Overall adverse events and diarrhea were common and more frequent with acamprosate	Low
Kiefer, 2003; Kiefer, 2004; Kiefer, 2005	Design: DBRCT Setting: 1 outpatient site Country: Germany Funding: Univ; Meds	ACA 1,998 (40); NTX 50 (40); PBO (40); ACA 1,998 + NTX 50 (40) Other Tx: Group therapy	12	DSM-IV alcohol dependence without any withdrawal symptoms Exclusions: homelessness Mean Age: 46 y % Non-white NR 26% Female Other Dx: 0%	Return to any drinking: -0.17 (95%CI -0.33, -0.02) Return to heavy drinking: -0.13 (95%CI -0.33, 0.08)	Low
Laaksonen, 2008	Design: OLRCT Setting: 6 outpatient sites in 5 cities Country: Finland Funding: Govt	ACA 1,998 or 1,333 (81); DIS 100 to 200 (81); NTX 50 (81) Other Tx: Manual-based CBT	Up to 52 (119)	ICD-10 alcohol dependence Mean Age: 43 y 0% Non-white 29% Female Other Dx: NR	During the continuous medication period (1-12 weeks, the DIS group did significantly better than the NTX and ACA groups in time to first heavy drinking days (p = 0.001), days to first drinking (p = 0.002), abstinence days and average weekly alcohol intake. During the targeted medication period (13-52 weeks), there were no significant differences between the groups in time to first heavy drinking days and days to first drinking while the DIS group reported significantly more	High

					frequent abstinence days than the ACA and NTX groups. During the whole study period (1-52 weeks), the DIS group did significantly better in the time to the first drink compared to the other groups. Attrition: 52/ 5 at 52 weeks	
Lhuintre, 1985	Design: DBRCT Setting: Outpatient; methadone maintenance clinics Country: France Funding: Meds	ACA 1,000 to 2,250 (42); PBO (43) Other Tx: Meprobamate 100% for first month	13	Alcohol dependence indicated by morning withdrawal, >200 g/day daily alcohol intake, or at least two failed treatment attempts; GGT >30 IU/l; and red blood cell volume >96 fl Mean Age: 40 to 43 y % Non-white NR 11% Female Other Dx: NR	Return to any drinking: -0.2 (95%CI -0.4, 0)	High
Lhuintre, 1990	Design: DBRCT Setting: Outpatient substance use disorders clinic Country: France Funding: NR	ACA 1,332 (279); PBO (290) Other Tx: Psychotherapy allowed	12 (12)	At least one sign of alcohol dependence, GGT >2x normal, or mean red blood cell corpuscular volume >98 fl Mean Age: 42 to 43 y % Non-white NR 18% Female Other Dx: NR	Return to any drinking: -0.1 (95%CI -0.16, -0.03) Attrition: 37 / <1	High

Mann, 2012; Mann, 2013, PREDICT	Design: DBRCT Setting: NR Country: Germany Funding: Govt; Meds	ACA 1,998 (172); NTX 50 (169); PBO (86) Other Tx: Medical management	12	Alcohol dependence Mean Age: 45 y % Non-white NR 23% Female Other Dx: NR	Return to heavy drinking: 0.04 (95%CI -0.09, 0.16) Point estimates for heavy drinking relapse free survival from the Kaplan Meier curves were 48.3% for acamprosate, 49.1 % for naltrexone and 51.8% for placebo. Diarrhea was greater in acamprosate treated patients. Attrition: 34/0 to 2	Medium
Mason, 2006	Design: DBRCT Setting: 21 outpatient clinics[b] Country: U.S. Funding: Lipha	ACA 2,000 (258); ACA 3,000 (83); PBO (260) Other Tx: Brief abstinence-oriented protocol-specific counseling and self-help materials 100%	24 (32)	DSM-IV alcohol dependence Mean Age: 44 to 45 y 14 to 15% Non-white 29 to 36% Female Other Dx: Tobacco use 77%	Percent drinking days: -5.9 (95%CI -11.51, -0.29) Return to any drinking: 0.04 (95%CI 0, 0.08) Return to heavy drinking: -0.04 (95%CI -0.12, 0.04)	Low
Morley, 2006; Morley, 2010	Design: DBRCT Setting: 3 outpatient intensive substance use treatment sites Country: Australia Funding: Govt	ACA 1,998 (55); NTX 50 (53); PBO (61) Other Tx: All offered 4 to 6 sessions of manualized compliance therapy; Up-take/ attendance NR	12	DSM-IV alcohol dependence or abuse and with alcohol abstinence for 3-21 days Mean Age: 45 y % Non-white NR 30% Female Other Dx: Substantial levels of emotional distress (anxiety, stress, and depression) Severe concurrent illness (psychiatric or other) –NOS 3	Drinks per drinking days: 0.4 (95%CI -1.81, 2.61) Return to any drinking: -0.02 (95%CI -0.16, 0.12) Return to heavy drinking: -0.02 (95%CI -0.14, 0.19)	Low

Narayama, 2008;	Design: Prospective cohort Setting: Military, outpatient Country: India Funding: NR	ACA 1,332 to 1,998 (28); NTX 50 (26); TOP 100 to 125 (38) Other Tx: Various psycho-therapies were offered	52	ICD-10 alcohol dependence Mean Age: 38 y 100% Non-white 0% Female Other Dx: NR	Topiramate (76.3%) was significantly more effective (p<0.01) in sustaining abstinence, though 57.7% naltrexone and 60.70% acamprosate maintained complete abstinence. 7 topiramate subjects (18.4%) reported decreased relapses compared to 8 naltrexone (30.8%) and 9 acamprosate (32.1%) subjects.	High
Paille, 1995	Design: DBRCT Setting: NR Country: France Funding: NR	ACA 1.3g (188); ACA 2g (173); PBO (177) Other Tx: Supportive psychotherapy 100%; Hypnotics 6 to 7%; Anxiolytics 8 to 12%; Antidepressants 8 to 9%	52 (78)	DSM-III-R alcohol dependence Exclusions: three previous detoxification attempts Mean Age: 43 y % Non-white NR 20% Female Other Dx: NR	Percent drinking days: -10.2 (95%CI -16.53, -3.87) Return to any drinking: -0.07 (95%CI -0.13, -0.01)	Medium
Pelc, 1996; Pelc, 1992	Design: DBRCT Setting: Outpatient; multicenter Country: Belgium Funding: NR	ACA 1,332 to 1,998 (55); PBO (47) Other Tx: Supportive psychotherapy 100%	26	DSM-III alcohol dependence and GGT values above normal Mean Age: 43 y % Non-white NR 31% Female Other Dx: NR	Return to any drinking: -0.19 (95%CI -0.32, -0.07) Attrition: 45% day 90; 65% day 180/ 17%; 21%	High
Pelc, 1997	Design: DBRCT Setting: Outpatient; after inpatient detoxification Country: Belgium, France	ACA 1,332 (63); ACA 1,998 (63); PBO (62) Other Tx: Counseling, social support when needed 100%	13	DSM-III-R alcohol dependence Mean Age: NR y % Non-white NR	Percent drinking days: -22.2 (95%CI -35.7, -8.7) Return to any drinking: -0.27 (95%CI -0.39, -0.14)	Medium

	Funding: Lipha		% Female NR Other Dx: NR		
Poldrugo, 1997	Design: DBRCT Setting: Inpatient for 1-2 weeks then outpatient; multicenter community-based alcohol rehabilitation program Country: Italy Funding: Lipha	ACA 1,332 to 1,998 (122); 26 (52) PBO (124) Other Tx: Community-based rehabilitation program with group sessions, alcohol education, community meetings 100	DSM-III chronic or episodic alcohol dependence Mean Age: 43 to 45 y % Non-white NR 23 to 31% Female Other Dx: 0%	Percent drinking days: -16 (95%CI -30.3, -1.7) Return to any drinking: -0.16 (95%CI -0.28, -0.04)	Medium
Ralevski, 2011; Ralevski, 2011	Design: DBRCT Setting: Outpatient; university and VA health centers Country: U.S. Funding: Govt, Forest	ACA 1,998 (12); PBO (11) 12 Other Tx: Weekly skills training that incorporated CB drug relapse prevention strategies 100%	DSM-IV alcohol dependence and DSM-IV schizophrenia, schizoaffective disorder or psychotic disorder not otherwise specified Mean Age: 51 y 65% Non-white 17% Female Other Dx: Schizophrenia spectrum disorders 100%	Drinks per drinking day: 1.8 (95%CI -3.53, 7.13) Percent drinking days: 3.7 (95%CI -12.5, 19.9) Percent heavy drinking days: 1.9 (95%CI -6.86, 10.66) Attrition: 35/NR	High
Sass, 1996	Design: DBRCT Setting: Psychiatric outpatient Country: Germany Funding: Lipha	ACA 1,332 to 1,998 (136); 48 (96) PBO (136) Other Tx: Counseling / psychotherapy 100%	At least 5 DSM-III-R alcohol dependence criteria Mean Age: 41 to 42 y % Non-white NR 22% Female Other Dx: NR	Percent drinking days: -17.1 (95%CI -27.18, -7.02) Return to any drinking: -0.2 (95%CI -0.31, -0.09)	Medium

Tempesta, 2000	Design: DBRCT Setting: Outpatient Country: Italy Funding: Lipha	ACA 1,998 (164); PBO (166) Other Tx: Medical and behavioral counseling	26 (39)	DSM-III-R alcohol dependence and GGT values >2x normal or mean corpuscular volume (MCV) > 95 fl Mean Age: 46 y % Non-white NR 17% Female Other Dx: 0%	Percent drinking days: -11.7 (95%CI -21.17, -2.23) Return to any drinking: -0.16 (95%CI -0.27, -0.06)	Medium
Whitworth, 1996	Design: DBRCT Setting: Outpatient specialty clinic Country: Austria Funding: Lipha	ACA 1,332 or 1,998 (224); PBO (224) Other Tx: NR	52 (104)	DSM-III chronic or episodic alcohol dependence Mean Age: 42 y % Non-white NR 21% Female Other Dx: NR	Percent drinking days: -10 (95%CI -17.76, -2.24) Return to any drinking: -0.11 (95%CI -0.17, -0.05)	Medium
Wolwer, 2011	Design: DBRCT Setting: Outpatient; 4 university hospitals; 1 non-academic clinic Country: Germany Funding: Govt, Meds	ACA 1,998 + IBT (124); ACA 1,998 + TAU (122)[d]; PBO + IBT (125) Other Tx: NR	24 (52)	DSM-IV alcohol dependence Mean Age: 46 y % Non-white NR 29% Female Other Dx: NR	Return to heavy drinking: 0 (95%CI -0.12, 0.13)	Medium

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Benefits of naltrexone

Table B-4. Naltrexone (any dose and delivery) compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNT[g]	Strength of Evidence Grade
Return to any drinking	21[a]; 4,233	Medium; RCTs	Consistent	Direct	Precise	RD: -0.04 (-0.07 to -0.01)	NC	Moderate
Return to heavy drinking	23[a]; 4,347	Medium; RCTs	Consistent	Direct	Precise	RD: -0.07 (-0.11 to -0.03)	NC	Moderate
Drinking days	19[b]; 3,329	Medium; RCTs	Consistent	Direct	Precise	WMD: -4.57 (-6.61 to -2.53)	NC	Moderate
Heavy drinking days	11[c]; 2034	Medium; RCTs	Consistent	Direct	Precise	WMD: -3.81 (-5.85 to -1.78)	NC	Moderate
Drinks per drinking day	11[d]; 1,422	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.54 (-1.01 to -0.07)	NC	Low
Accidents	0; 0	NA	NA	NA	NA	NA	NC	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Quality of life	4; 1,513	Medium; RCTs	Inconsistent	Direct	Imprecise	Unable to pool data, some conflicting results[e]	NA	Insufficient
Mortality	6[f]; 1,738	Medium; RCTs	Unknown	Direct	Imprecise	1 (NTX) vs. 2 (PBO)	NA	Insufficient

FROM Jonas et al., 2012, Table D-3

[a] 2 additional studies were rated high risk of bias; 2 additional studies were rated as unclear risk of bias
[b] 3 additional studies were rated high risk of bias
[c] 2 additional studies were rated high risk of bias
[d] 5 additional studies were rated high risk of bias
[e] Two studies found no significant difference between naltrexone- and placebo-treated subjects. One study reported that patients receiving injectable naltrexone 380mg/month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs. 6.2, p=0.044). One study measured alcohol-related consequences (with the DrInC) and reported that more subjects who received placebo (N=34) had ≥1 alcohol-related consequence than those who received naltrexone (N=34): 76% vs. 45%, P=0.02.
[f] One additional study reported a death but did not specify in which treatment group it occurred.
[g] Values for NNT were added from Jonas, et al. (2014), Table 37. For values marked NA, NNT was not calculated either because the risk difference (95% CI) was not statistically significant or the effect measure was not one that allows direct calculation of NNT (e.g., WMD); NC indicates that the AHRQ review did not comment on a NNT for these outcomes.

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

Table B-5. Oral naltrexone (50mg) compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNT	Strength of Evidence Grade
Return to any drinking	16; 2,347	Medium; RCTs	Consistent	Direct	Precise	RD: -0.05 (-0.10 to -0.00)	20	Moderate
Return to heavy drinking	19; 2,875	Medium; RCTs	Consistent	Direct	Precise	RD: -0.09 (-0.13 to -0.04)	12	Moderate

Drinking days	15; 1,992	Medium; RCTs	Consistent	Direct	Precise	WMD: -5.4 (-7.5 to -3.2)	NA	Moderate
Heavy drinking days	6; 521	Medium; RCTs	Consistent	Direct	Precise	WMD: -4.1 (-7.6 to -0.61)	NA	Moderate
Drinks per drinking day	9; 1,018	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.49 (-0.92 to -0.06)	NA	Low

FROM Jonas et al., 2012, Table D-4 with values for NNT added from Table 37
Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

3001 **Table B-6. Oral naltrexone (100mg) compared with placebo**

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNT	Strength of Evidence Grade
Return to any drinking	3; 946	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.03 (-0.08 to 0.02)	NA	Low
Return to heavy drinking	2; 858	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.05 (-0.11 to 0.01)	NA	Low
Drinking days	2; 858	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -0.9 (-4.2 to 2.5)	NA	Low
Heavy drinking days	2; 423	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -3.1 (-5.8 to -0.3)	NA	Low
Drinks per drinking day	1; 240	Medium; RCTs	Unknown	Direct	Imprecise	WMD: 1.9 (-1.5 to 5.2)	NA	Insufficient

FROM Jonas et al., 2012, Table D-5 with values for NNT added from Table 37
Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

3002 **Table B-7. Injectable naltrexone compared with placebo**

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNT	Strength of Evidence Grade
Return to any drinking	2; 939	Medium; RCTs	Consistent	Direct	Imprecise	RD: -0.04 (-0.10 to 0.03)	NA	Low
Return to heavy drinking	2; 615	Medium; RCTs	Inconsistent	Direct	Imprecise	RD: -0.01 (-0.14 to 0.13)	NA	Low
Drinking days	1; 315	Medium; RCTs	Unknown	Direct	Imprecise	WMD: -8.6 (-16.0 to -1.2)	NA	Insufficient
Heavy drinking days	2[a]; 926	Medium; RCTs	Consistent	Direct	Imprecise	WMD: -4.6 (-8.5 to -0.56)	NA	Low
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	NA	Insufficient

FROM Jonas et al., 2012, Table D-6 with values for NNT added from Table 37
[a] Contains data from personal communication (B. Silverman, November 14, 2013).

Abbreviations: CI, confidence interval; NA, not applicable; NSD, no significant difference; NTX, naltrexone; PBO, placebo; RCT, randomized controlled trial; RD, risk difference; WMD, weighted mean difference

In the AHRQ review (Jonas et al., 2014), studies of oral naltrexone typically used a dose of 50 mg/day but a few trials used doses of 100 to 150 mg/day; trials of long-acting injectable naltrexone used doses of 150 to 400 mg/month. With naltrexone treatment, 4% fewer subjects returned to any drinking than with placebo (RD, -0.04; 95% CI, -0.07 to -0.01; 21 trials of low or medium bias) and 7% fewer subjects returned to heavy drinking than with placebo (RD, -0.07; 95% CI, -0.11 to -0.03; 23 trials of low or medium bias). For oral naltrexone at a dose of 50 mg/day, the NNT was 20 to prevent 1 person from returning to any drinking with a NNT of 12 to prevent 1 person from returning to heavy drinking. For doses of oral naltrexone of 100 mg/d and for injectable naltrexone, effects were similar to those for oral naltrexone at 50 mg/day but were not statistically significant. As compared to placebo, subjects who received naltrexone also had 4.6% fewer drinking days (WMD, -4.6; 95% CI, -6.6 to -2.5; 19 trials), 3.8% fewer heavy drinking days (WMD, -3.8; 95% CI, -5.8 to -1.8; 11 trials), and 0.5% fewer drinks per drinking day (WMD, -0.54; 95% CI, -1.01 to -0.07; 11 trials). The single study of injectable naltrexone found a large effect size (WMD, -8.6) for fewer drinking days relative to placebo.

Only a limited number of studies assessed factors related to quality of life, and these studies used different measures making comparison or meta-analysis impossible. In addition, quality of life measures were secondary outcomes and studies were not adequately powered to assess these effects. One study found better overall mental health, but not physical health, with long-acting injectable naltrexone at 380 mg/month but no benefit on either measure at a dose of 190 mg/month. A placebo controlled study of 50 mg/day of oral naltrexone found fewer alcohol related consequences in the naltrexone group (76 versus 45%, p=0.02). The other two studies assessing quality of life measures showed no statistical difference with naltrexone as compared to placebo.

One trial did not meet inclusion criteria for the comparative effectiveness review but was described in some detail in the AHRQ report. In this study (O'Malley et al., 2003), individuals all received oral naltrexone with random assignment to 10 weeks of either primary care management (PCM) or cognitive behavioral therapy (CBT). Responders in each group (84.1% for PCM versus 86.5% for CBT) continued with their assigned psychosocial treatment and were randomly assigned to continue naltrexone or switch to placebo. In the CBT group, the rates of abstinence decreased in those assigned to placebo but did not reach statistical significance whereas in the PCM group, the placebo group had a greater reduction in abstinence rates than those who remained on naltrexone (80.8% vs. 51.9%, p=0.03).

Several studies of oral naltrexone published since the AHRQ review have shown minimal benefits. In the German PREDICT study (total N=426), modeled after the COMBINE study, there was no difference among naltrexone, acamprosate, and placebo groups on the time to first heavy drinking (Mann et al., 2013). A 12-week, low risk of bias trial randomly assigned subjects (N=221) to 50 mg/day oral naltrexone or placebo in blocks based on their OPRM1 genotype. (Oslin et al., 2015) There was no difference in the odds of heavy drinking with naltrexone as compared to placebo for either genotype, although significant reductions in heavy drinking occurred in all treatment groups. A 4-arm study (N=200, medium risk of bias) of men who have sex with men investigated oral naltrexone 100 mg/d versus placebo and brief behavioral compliance treatment with and without modified behavioral self-control therapy (MBSCT) (Morgenstern et al., 2012). MBSCT was associated with a 28% decrease in drinks per week and a 35% decrease in heavy drinking days per week whereas treatment with naltrexone did not have a statistically

significant effect. However, naltrexone did increase the likelihood (odds ratio = 3.3) of achieving non-hazardous levels of drinking, which was the stated goal of study subjects.

Although most trials of naltrexone excluded individuals with co-occurring physical or psychiatric illness, one study of naltrexone for smoking cessation conducted a subgroup analysis for individuals who also reported heavy drinking (Fridberg et al., 2014). The total sample included 315 smokers who were randomly assigned to placebo or naltrexone 50 mg/d for 12 weeks. In the subgroup of 69 heavy drinkers (at least 2 heavy drinking episodes per month), weekly alcohol consumption was reduced with naltrexone treatment (IRR 0.71, 95% CI= 0.51-1.0, p=0.049) as was smoking urge. Smoking quit rates with naltrexone as compared to placebo were also significantly better in the heavy drinking subgroup at the end of the study and at 12-month follow-up. Another medium risk of bias study (Foa et al., 2013) was excluded from the AHRQ review due to its study design, but is of relevance to clinical practice. Subjects met DSM-IV criteria for post-traumatic stress disorder and for alcohol dependence and were randomly assigned to receive naltrexone 100 mg/d plus prolonged exposure therapy (N=40), placebo plus prolonged exposure therapy (N=40); naltrexone 100 mg/d plus supportive therapy (N=42); or placebo plus supportive therapy (N=43). Although attrition was relatively high in all groups during the 24 week trial, alcohol craving and the percentage of days drinking alcohol were reduced in all groups, with a greater mean difference in groups that received naltrexone as compared to placebo groups (p=0.008). PTSD severity was reduced in all groups with no significant effect of prolonged exposure over supportive therapy, however those in the prolonged exposure plus naltrexone group were more likely to achieve a low level of PTSD symptoms.

The AHRQ review (Jonas et al., 2014) also examined studies that assessed whether mu-opioid receptor gene polymorphism status was associated with a more robust response to naltrexone. The main single nucleotide polymorphism (SNP) that was tested was an asparagine to aspartate substitution in exon 1 of the mu-opioid receptor (Due to changes in the NCBI Human Genome Reference Assembly, this SNP has been referred to by a number of designations including A118G, Asn40Asp, rs1799971, A355G and Asn102Asp.) The review found no significant difference between A-allele homozygotes and those with at least one G allele in terms of the outcomes return to any drinking (RD, 0.01; 95% CI, -0.2 to 0.2) and return to heavy drinking (RD, 0.14; 95% CI, -0.03 to 0.3) when all available studies were considered together. However, in their conclusions, the AHRQ report also notes that, for return to heavy drinking, "it is possible that patients with at least one G allele of A118G polymorphism of OPRM1 might be more likely to respond to naltrexone." The reasons behind this interpretation are several fold. Of the 7 studies, 3 studies including the COMBINE study (Anton et al., 2008), reported positive associations between OPRM1 polymorphisms and naltrexone response. In the COMBINE study, individuals who received medical management without cognitive behavioral intervention were more likely to have a good clinical outcome if they had at least one Asp40 allele and received naltrexone (87.1%) as compared to Asn40 homozygotes treated with naltrexone (54.8%). About half of those treated with placebo also had a good outcome, irrespective of genotype. This difference in outcomes would be clinically significant. One additional study did not meet a priori inclusion criteria for the systematic review, but it also included information on naltrexone response and OPRM1 genotype (Oslin et al., 2003). This study also found that naltrexone-treated subjects with at least one Asp40 allele as compared to Asn40

homozygotes had significantly lower rates of relapse (p=0.044) and a longer time to return to heavy drinking (p=0.040). When the results of this study were added to the meta-analysis in a sensitivity analysis, a positive association between genotype and response emerged (RD, 0.16; 95% CI, 0.02 to 0.29).

Table B-8. Results of included studies that assessed the association between mu-opioid receptor gene polymorphisms and naltrexone response

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

FROM Jonas et al., 2014 Table 6

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

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

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

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

Abbreviations: N = number; NR = not reported.

Since the AHRQ review, additional studies have not found a relationship between genotype and naltrexone response. As described above, one study of OPRM1 genotype and naltrexone response randomly assigned subjects (N=221) in blocks based on their OPRM1 genotype as well as to 50 mg/day oral naltrexone vs. placebo (Oslin et al., 2015). In this 12-week trial, there was no difference in the odds of heavy drinking with naltrexone as compared to placebo for either genotype. A secondary analysis of OPRM1 genotype has been conducted in a sample of veterans with alcohol dependence and other psychiatric conditions (Arias et al., 2014). Subjects in this 12-week, medium risk of bias study were randomly assigned to placebo alone (N=64), naltrexone 50 mg/day (N=59), disulfiram 250 mg/day plus placebo (N=66), or naltrexone 50 mg/day and disulfiram 250 mg/day (N=65). OPRM1 genotyping was conducted for a subset of 107 European American subjects. No significant interactions were found between genotype and the response to naltrexone.

Taken together, the findings on OPRM1 genotype and naltrexone response did not seem to indicate a current role for OPRM1 genotype determination in clinical practice and no guideline statement was made. However, use of genotype to identify predictors of response remains a promising avenue for research.

Grading of the overall supporting body of research evidence for efficacy of naltrexone:

- **Magnitude of effect:** Weak. When present for specific outcomes, the magnitude of the effect is small.

- **Risk of bias:** Medium. Studies are RCTs of low to medium bias based on their described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of naltrexone appear to be representative of outpatient clinical practice, but in some studies, the proportion of females in the trial was small.
- **Directness:** Direct. Studies measured abstinence and heavy drinking rates as well as measures of alcohol consumption.
- **Consistency:** Inconsistent. There was considerable heterogeneity as evidenced by I^2 values on drinking related outcomes.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** Unclear. Studies typically used a single dose of naltrexone and, when comparisons were available, outcomes were at least as good, and in some instances, better, for 50 mg/day of oral naltrexone as compared to 100 mg/day.
- **Confounding factors (including likely direction of effect):** Unclear. Some studies suggest a possible effect of genetic polymorphisms on treatment response, which could confound study interpretation.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Moderate. A large number of RCTs have been conducted, most of which have low to medium risk of bias. Many of the RCTs are funded by governmental agencies. Although the studies have good applicability and measure outcomes of interest directly, the imprecision and inconsistency of findings are a limitation. Another limitation is that the majority of trials use oral formulations at a dose of 50 mg/day; the strength of research evidence is less robust for other formulations (i.e., long-acting injections) and doses.

Grading of the overall supporting body of research evidence for predicting efficacy of naltrexone through OPRM1 genetic polymorphism testing:

- **Magnitude of effect:** Unclear. However, if present, the magnitude of the effect is small.
- **Risk of bias:** High. Studies are RCTs of low to medium bias based on their described randomization and blinding procedures and descriptions of study dropouts. However, with one exception, all of the genotyping studies are based on secondary analyses, often with a subset of the original sample.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of naltrexone appear to be representative of outpatient clinical practice; however, many of the studies have few or no women. Some of the studies limit the analysis to Caucasian/European-American subjects.
- **Directness:** Direct. Studies measured abstinence, heavy drinking, and measures of alcohol consumption.

- **Consistency:** Inconsistent. There was considerable heterogeneity as evidenced by I^2 values in the meta-analysis.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit.
- **Dose-response relationship:** Not assessed.
- **Confounding factors (including likely direction of effect):** Likely. Given the known differences in genotype frequency among different races and ethnicities, the inclusion or exclusion of non-Caucasians could influence the study conclusions and the overall meta-analysis.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Low. Although a large number of secondary analyses have been conducted based on government funded RCTs, the applicability, inconsistency, lack of precision, and potential for confounding factors are limitations.

Harms of naltrexone

The AHRQ review (Jonas et al., 2014) found a statistically significant increased risk of withdrawal due to adverse events, dizziness, nausea, and vomiting in individuals treated with naltrexone as compared to placebo. Of studies that reported on mortality, no studies found more than one death in any one treatment group (Jonas et al., 2014). Effects of naltrexone on hepatic enzymes were viewed as intermediate outcomes and not included in the AHRQ meta-analysis (D. Jonas, personal communication). None of the literature identified in the updated literature search provided additional information on harms of naltrexone.

Table B-9. Naltrexone compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Withdrawals due to AEs	17[a]; 2,743	Medium; RCTs	Consistent	Direct	Precise	RD 0.021 (0.009 to 0.034)	Moderate
Anorexia	1; 175	Medium; RCT	Unknown	Direct	Imprecise	RD 0.077 (0.014 to 0.140)	Insufficient
Anxiety	7[b]; 1,461	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.007 (-0.022 to 0.036)	Low
Cognitive dysfunction	1; 123	Medium; RCT	Unknown	Direct	Imprecise	RD 0.190 (0.038 to 0.341)	Insufficient
Diarrhea	11[c]; 2,358	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.013 (-0.011 to 0.038)	Moderate
Dizziness	13[d]; 2,675	Medium; RCTs	Consistent	Direct	Precise	RD 0.063 (0.036 to 0.089)	Moderate
Headache	17[e]; 3,347	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.008 (-0.019 to 0.034)	Low
Insomnia	8[d]; 1,637	Medium; RCTs	Consistent	Direct	Imprecise	RD 0.027 (-0.002 to 0.057)	Low
Nausea	24[f]; 4,655	Medium; RCTs	Consistent	Direct	Precise	RD 0.112 (0.075 to 0.149)	Moderate
Numbness / tingling / paresthesias	1[b]; 123	Medium; RCT	Unknown	Direct	Imprecise	RD -0.008 (-0.185 to 0.168)	Insufficient

Rash	4[c]; 469	Medium; RCTs	Consistent	Direct	Imprecise	RD -0.010 (-0.060 to 0.040)	Low
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 123	Medium; RCT	Unknown	Direct	Imprecise	RD -0.006 (-0.182 to 0.171)	Insufficient
Vision changes (blurred vision)	2; 133	Medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.079 (-0.172 to 0.331)	Low
Vomiting	9[b]; 2,438	Medium; RCTs	Consistent	Direct	Precise	RD 0.043 (0.023 to 0.062)	Moderate

FROM Jonas et al., 2014 Table D-34

[a] Three additional studies were rated high or unclear risk of bias
[b] Two additional studies were rated high or unclear risk of bias
[c] One additional study was rated high or unclear risk of bias
[d] Four additional studies were rated high or unclear risk of bias
[e] Five additional studies were rated high or unclear risk of bias
[f] Seven additional studies were rated as high or unclear risk of bias
Abbreviations: AE = adverse effect; CI = confidence interval; RD = risk difference

Grading of the overall supporting body of research evidence for harms of naltrexone:

- **Magnitude of effect:** Small. When present, the magnitude of effect is small.
- **Risk of bias:** High. Studies are RCTs of low to medium bias based on their described randomization and blinding procedures and descriptions of study dropouts. However, methods for determining harms are not well-specified and there is potential for selective reporting of results.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of naltrexone appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured common side effects and dropouts due to adverse events.
- **Consistency:** Consistent. For adverse events that showed a significant effect (e.g., withdrawal due to adverse events, dizziness, nausea, and vomiting), the findings were consistent across trials.
- **Precision:** Imprecise. Confidence intervals for studies are wide in many studies and cross the threshold for clinically significant harms of the intervention.
- **Dose-response relationship:** Unknown. Dose response information on side effects was not well described.
- **Confounding factors (including likely direction of effect):** Absent. No known confounding factors are present that would be likely to modify adverse events of the intervention.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Moderate. A large number of RCTs have been conducted, but few have assessed adverse events in a systematic and pre-defined fashion. Many of the RCTs are funded by governmental agencies. Although imprecision is a limitation, the studies have good applicability, measure outcomes of interest directly, and are relatively

consistent in finding naltrexone to have greater frequencies of withdrawal due to adverse events, dizziness, nausea, and vomiting as compared to placebo.

3200 Data abstraction - naltrexone

3201 **Table B-10. Studies related to naltrexone**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Followup)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Ahmadi, 2002; Ahmadi, 2004	Design: DBRCT Setting: Outpatient Country: Iran Funding: NR	NTX 50 (58); PBO (58) Other Tx: Individual counseling 100%	12	DSM-IV alcohol dependence Mean Age: 43 y % Non-white NR 0% Female Other Dx: NR	Return to heavy drinking: -0.36 (95%CI -0.53, -0.2) Return to any drinking: -0.19 (95%CI -0.36, -0.02)	High
ALK21-014, 2011	Design: DBRCT Setting: Outpatient Country: Germany, Austria Funding: Alkermes	NTX inj 380 every 4 wks (152); PBO (148) Other Tx: NR	12	NR Mean Age: 46 y % Non-white NR 20% Female Other Dx: NR	Return to heavy drinking: 0.07 (95%CI -0.05, 0.18) Attrition: 37/ 8	Medium
Anton, 1999; Anton, 2001	Design: DBRCT Setting: Outpatient academic site Country: U.S. Funding: Govt, Meds	NTX 50 (68); PBO (63) Other Tx: CBT 100%	12	DSM-III-R alcohol dependence including loss of control over drinking Mean Age: 41 to 44 y 11 to 18% Non-white 27 to 31% Female Other Dx: 0%	Drinks per drinking day: -1.7 (95%CI -3.02, -0.38) Percent drinking days: -8 (95%CI -15.22, -0.78) Return to any drinking: -0.14 (95%CI -0.3, 0.03) Return to heavy drinking: -0.22 (95%CI -0.39, -0.05)	Medium

Anton, 2005	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt, Meds	NTX 50 + CBT (39); NTX 50 + MET (41); PBO + CBT (41); PBO + MET (39) Other Tx: CBT and MET as randomized	12	DSM-IV alcohol dependence , including loss of control over drinking Exclusions: >2 prior detoxification admissions requiring medication Mean Age: 43 to 45 y 8 to 23% Non-white 21 to 27% Female Other Dx: NR	Drinks per drinking day: -0.7 (95%CI -2.06, 0.66) Percent drinking days: -6.8 (95%CI -15.12, 1.52) Return to heavy drinking: -0.17 (95%CI -0.32, -0.02)	Medium
Anton, 2006; Donovan, 2008; LoCastro, 2009; COMBINE	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA[a] 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153)[a] Other Tx: As randomized; community support group participation (like AA) encouraged	16 (68)	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: NR	Percent drinking days: -1.1 (95%CI -5.2, 3) Return to any drinking: -0.04 (95%CI -0.1, 0.02) Return to heavy drinking: -0.06 (95%CI -0.13, 0.01)	Low
Anton, 2008	Design: DBRCT Setting: 11 outpatient sites Country: U.S. Funding: Govt, Meds	NTX 100 (301); PBO (303) Other Tx: MM 100%; CBI 49%; ACA % NR	16	DSM-IV alcohol dependence Mean Age: 45 to 46 y 0% Non-white 30% Female Other Dx: NR	Naltrexone associated with fewer heavy drinking days and trend for more abstinent days over time in subjects with at least 1 copy of the Asp40 allele	Medium
Anton, 2011	Design: DBRCT Setting: Outpatient	NTX 50 (50); PBO (50); NTX 50 + 6 weeks	16	DSM-IV alcohol dependence Exclusion: >1 prior detoxification admission	During the first 6 weeks, naltrexone/gabapentin group had a longer time to relapse, fewer heavy drinking days and fewer drinks per drinking day than placebo and	Medium

	Country: U.S. Funding: Govt	gabapentin, with 1,200 maximum dose (50) Other Tx: Used COMBINE's manual (CBT + MM + 12-step techniques) 100%		Mean Age: 43 to 47 y 13% Non-white 18% Female Other Dx: NR	naloxone alone groups. Time to relapse did not differ at end of study.	
Balldin, 2003	Design: DBRCT Setting: 10 outpatient sites Country: Sweden Funding: DuPont, Meda AB	NTX 50 + CBT (25); NTX 50 +ST (31); PBO + CBT (30); PBO + ST (32) Other Tx: None	26	DSM-IV alcohol dependence Mean Age: 48 to 51 y % Non-white NR 9 to 23% Female Other Dx: 0%	Drinks per drinking day: 0.2 (95%CI -1.47, 1.87) Percent drinking days: -9.9 (95%CI -20.54, 0.74) Percent heavy drinking days: -11 (95%CI -20.95, -1.05) Return to any drinking: 0.03 (95%CI -0.03, 0.09) Return to heavy drinking: 0.01 (95%CI -0.07, 0.1)	Low
Baltieri, 2008; Baltieri, 2009	Design: DBRCT Setting: Outpatient Country: Brazil Funding: Govt	TOP to 200 - 400 (52); NTX 50 (49); PBO (54) Other Tx: Psychosocial 100%; AA recommended	12	ICD-10 alcohol dependence Mean Age: 44 to 45 y 29% Non-white 0% Female Other Dx: Tobacco use 66%	Percent heavy drinking days: -7.5 (95%CI -23.48, 8.48) Percent drinking days: -8.3 (95%CI -23.93, 7.33) Return to any drinking: -0.01 (95%CI -0.18, 0.17) Smokers relapsed more rapidly than non-smokers. Attrition: 45	High
Brown, 2009	Design: DBRCT Setting: Outpatient; university health center	NTX 50 (20); PBO (23) Other Tx: CBT 100%	12	Alcohol dependence and bipolar I or II disorder, with current depressed or mixed mood state	Drinks per drinking day: -1.8 (95%CI -3.67, 0.07) Return to heavy drinking: -0.28 (95%CI -0.55, -0.01)	High

	Country: U.S. Funding: Govt			Exclusions: severe mood symptoms Mean Age: 41 y 26% Non-white 49% Female Other Dx: Bipolar (current depressed or mixed mood) 100%; Cannabis abuse 21%; Cocaine abuse 12%; Amphetamine abuse 7%	Attrition: 48/17	
Carroll, 1993	Design: OLRCT Setting: Outpatient Country: U.S. Funding: Govt	DIS 250 (9); NTX 50 (9) Other Tx: Weekly individual psychotherapy 100%	12	DSM-III-R alcohol abuse/dependence and cocaine dependence Mean Age: 32 y 39% Non-white 72% Female Other Dx: Cocaine dependence 100%	Subjects taking disulfiram showed lower percentage of alcohol use days compared to those taking naltrexone (4.0% vs. 26.3%, t = 3.73, p<0.01). Subjects taking disulfiram also reported fewer total days using alcohol (2.4. vs. 10.4 days, t = 3.00, p<0.01), fewer total drinks (2.3 vs. 27.0, t = -2.00, p=0.06), and more total weeks of abstinence (mean 7.2 vs. 1.1 weeks, t = 4.72, p<0.001) compared to those taking naltrexone. Attrition: 67/ 22	High
Chick, 2000a	Design: DBRCT Setting: 6 outpatient sites; five alcohol treatment units and one academic hepatology department Country: U.K. Funding: DuPont	NTX 50 (90); PBO (85) Other Tx: Usual psychosocial treatment program	12	DSM-III-R alcohol dependence or abuse Mean Age: 43 y % Non-white NR 25% Female Other Dx: 0%	Return to any drinking: 0.01 (95%CI -0.11, 0.13) Return to heavy drinking: 0 (95%CI -0.14, 0.14) Attrition: 59% at 12 weeks; 19% lost to follow-up	Medium
Coller, 2011	Design: Open-label	NTX 50 (100)	12	DSM-IV alcohol dependence	Alcohol use decreased significantly as did GGT and MCV values with no differences	Medium

	Setting: Outpatient Country: Australia Funding: Govt	Other Tx: CBI 100%		Exclusions: naltrexone use in last 6 months Mean Age: 43 y % Non-white NR 43% Female Other Dx: NR	among OPRM1 A118G genotype groups, A/A (65) or A/G and G/G (35).	
COMBINE Study Research Group, 2003	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (9); ACA 3,000 + MM (9); NTX 100 + CBI + MM (9); NTX 100 + MM (9); PBO + CBI + MM (9); PBO + MM (8) Other Tx: As randomized	16	DSM-IV alcohol dependence Mean Age: 38 to 42 y 17 to 22% Non-white 22 to 33% Female Other Dx: NR	Acamprosate-naltrexone group adherence was equal to, or better than, adherence with placebo, acamprosate alone or naltrexone alone Adverse events were comparable in all groups. Attrition: 31/11 to 20	Medium
De Sousa, 2004	Design: OLRCT Setting: Outpatient Country: India Funding: NR	DIS 250 (50); NTX 50 (50); Other Tx: Supportive group psychotherapy 100%	52	DSM-IV alcohol dependence Exclusions: previous naltrexone and/or disulfiram treatment Mean Age: 43 to 47 y % Non-white NR 0% Female Other Dx: NR	Disulfiram associated with greater reduction in relapse, greater survival time until the first relapse, and more days of abstinence than naltrexone: At study endpoint, relapse was 14% with disulfiram vs. 56% with naltrexone. Naltrexone had lower composite craving scores than disulfiram.	High
Florez, 2008	Design: OLRCT Setting: Outpatient substance use disorders clinic Country: Spain Funding: NR	TOP to 200[a] (51); NTX 50 (51) Other Tx: Therapy based on Relapse Prevention Model 100%	26	ICD-10 alcohol dependence Mean Age: 47 y 0% Non-white 15% Female Other Dx: Personality disorders; 27%	Topiramate and naltrexone were both effective but did not differ in efficacy as measured by a composite alcohol use metric.	High

Florez, 2011	Design: OLRCT Setting: Outpatient substance use disorders clinic Country: Spain Funding: NR	TOP 200 (91); NTX 50 (91) Other Tx: BRENDA 100%; At least monthly meeting with psychiatrist 100%	26	ICD-10 alcohol dependence Mean Age: 47 to 48 y % Non-white NR 15% Female Other Dx: Personality disorders 23%	At 3 and 6 months, patients with topiramate reported lower scores than those with naltrexone on craving and alcohol related measures. Disability related measures were also less with topiramate at 6 months. Topiramate also was associated with fewer drinks per drinking day and fewer heavy drinking days at 3 and 6 months compared to naltrexone. The percentage of days abstinent and total drinking days were comparable for topiramate and naltrexone.	High
Foa, 2013; Foa and Williams, 2010; McLean,.2014; Zandberg, 2016	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 100 + PE (40); NTX 100 + SuppTx (42); PBO + PE (40); PBO + SuppTx (43) Other Tx: Single blind randomization to prolonged exposure therapy (12 weekly 90 min sessions then 6 biweekly sessions) vs. supportive therapy; BRENDA provided to all subjects	24 (52)	DSM-IV alcohol dependence and PTSD Mean Age: 42.7 y 70% Non-white 34.5% Female Other Dx: PTSD 100%	Percentage of days drinking alcohol and craving were reduced in all groups with largest effect in groups that received naltrexone (p=0.008). PTSD severity was reduced in all groups with no significant effect of prolonged exposure versus supportive therapy Low PTSD symptoms were more likely with prolonged exposure plus naltrexone.	Medium
Fogaca, 2011	Design: DBRCT Setting: Outpatient Country: Brazil Funding: Govt	NTX 50 (20); PBO (20); NTX 50 + PUFA (20); PUFA (20) Other Tx: None	12	DSM-IV alcohol dependence; male; age 30 to 50 Mean Age: NR y % Non-white NR 0% Female Other Dx: NR	All groups showed improvement at 3 months (p<0.001) on “drinking days”, Short Alcohol Dependence Data (SADD), and craving scores in all groups with no difference in treatment groups. Attrition: 46/15 (between PUFAs group and NTX+PUFAs)	High

Garbutt, 2005; Pettinati, 2009; Lucey, 2008	Design: DBRCT Setting: Inpatient and outpatient, public hospitals, private and VA clinics, and tertiary care medical centers Country: U.S. Funding: Alkermes	NTX inj 380 every 4 weeks (208); NTX inj 190 every 4 weeks (210); PBO (209) Other Tx: BRENDA standardized supportive therapy 100%	26	DSM-IV alcohol dependence with goal of reduced drinking or abstinence Mean Age: 45 y 17% Non-white 32% Female Other Dx: NR	Percent heavy drinking days: -5.14 (95%CI -10.04, -0.23) Return to any drinking: -0.01 (95%CI -0.05, 0.03) Attrition: 39 / 1- 3	Medium
Gastpar, 2002	Design: DBRCT Setting: 7 outpatient sites Country: Germany Funding: DuPont	NTX 50 (84); PBO (87) Other Tx: Psychosocial treatment	12	DSM-III-R alcohol dependence or abuse Mean Age: 43 y 0% Non-white 28% Female Other Dx: 0%	Return to any drinking: -0.03 (95%CI -0.18, 0.12) Return to heavy drinking: -0.01 (95%CI -0.16, 0.14) Attrition: 36/5	Medium
Gelernter, 2007	Design: DBRCT Setting: Multisite VAMCs Country: U.S. Funding: VA	NTX 50 (149); PBO (64) Other Tx: NR	13	DSM-IV alcohol dependence Mean Age: 50 y 26% Non-white 0% Female Other Dx: Cannabis and cocaine 27%; major depression 13.9%; social phobia 7.7%; generalized anxiety disorder 5.1%; PTSD 13.6%; antisocial personality disorder 8.1%; tobacco use 71.8%	Treatment condition, age, and the number of drinks per drinking day at baseline were significant ($p < 0.05$) predictors of the relapse rate and time to relapse. No significant interactions were found between individual single nucleotide polymorphism (SNP) and naltrexone treatment response. In the subsample of patients with genotype information for OPRM1Asn40Asp, OPRK1, or OPRD1 rs678849, naltrexone treatment significantly reduced the odds of relapse. Subjects in the placebo group were about twice as likely to relapse as subjects in the naltrexone group. Attrition: 65	High

Greenfield, 2010; Fucito, 2012; COMBINE	Design: Secondary data analysis Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153) Other Tx: As randomized;; community support group participation (like AA) encouraged	68	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: 0%	There was a significant naltrexone by CBI interaction for women on two primary outcomes (percent days abstinent and time to first heavy drinking days) and also secondary outcome measures (good clinical response, percent heavy drinking days, and craving). Only the naltrexone by CBI interaction was significant for percent days abstinent. The naltrexone by CBI interaction was significant for time to first heavy drinking day: in men (p=.048) with each treatment showing slower relapse times. A non-significant trend was present in women. Naltrexone or CBI alone was superior to groups receiving neither in the percent of heavy drinking days.	Low
Guardia, 2002	Design: DBRCT Setting: 7 outpatient sites Country: Spain Funding: Pharmazam/Zambon	NTX 50 (101); PBO (101) Other Tx: Psychosocial	12	DSM-IV alcohol dependence Mean Age: NR y % Non-white NR 25% Female Other Dx: NR	Drinks per drinking day: -0.51 (95%CI -1.03, 0.01) Percent drinking days: -2.3 (95%CI -9.31, 4.71) Return to any drinking: -0.01 (95%CI -0.15, 0.13) Return to heavy drinking: -0.11 (95%CI -0.2, -0.02) Attrition: 41/0-7	Medium
Heinala, 2001	Design: DBRCT Setting: Outpatient Country: Finland Funding: Govt	NTX 50 daily for 12 wks then targeted + CS (34); PBO + CS (33); NTX 50 daily for 12 wks then targeted + ST (29); PBO + ST (25) Other Tx: None	32	DSM-IV alcohol dependence Mean Age: 46 y % Non-white NR 29% Female Other Dx: 0%	There was a significant treatment effect for rate of relapse to heavy drinking with an interaction between the medication and the type of therapy, with best response for the coping/naltrexone group. Among patients never relapsed to heavy drinking, naltrexone showed a significantly better response than placebo in the coping	High

					groups (p=0.08). In patients who relapsed to heavy drinking: 19.1% of the coping/naltrexone group relapsed only once compared to 3.2% of the coping/placebo group. Coping/naltrexone had better outcomes on reported alcohol consumption (mean +/-SD g/wk) than the other three groups (231+/-40 for coping/naltrexone, 354+/-62 for coping/placebo, 357+/-81 for supportive/naltrexone, and 326+/-80 for supportive/placebo. Attrition: 32	
Huang, 2005	Design: DBRCT Setting: 1 wk alcohol treatment inpatient unit, then outpatient site Country: Taiwan Funding: NR	NTX 50 (20); PBO (20) Other Tx: Weekly individual psychotherapy sessions 100%	14	Subjects admitted for alcohol detoxification and meeting DSM-III-R alcohol dependence Mean Age: 38 to 43 y 100% Non-white 0% Female Other Dx: NR	Return to heavy drinking: 0.05 (95%CI -0.18, 0.28)	High
Johnson, 2004b	Design: DBRCT Setting: 4 outpatient sites Country: U.S., France, the Netherlands Funding: Univ; Meds	NTX inj 400 every 28 days (25); PBO inj (5) Other Tx: Psychosocial support 100%	17	DSM-IV alcohol dependence Mean Age: 43 y 37% Non-white 27% Female Other Dx: NR	Drinks per drinking day: -2.2 (95%CI -3.19, -1.21) Percent heavy drinking days: -13 (95%CI -44.48, 18.48) Percent drinking days: -6.8 (95%CI -53.75, 40.15) Attrition: 30/12	High
Kiefer, 2003; Kiefer, 2004; Kiefer, 2005	Design: DBRCT Setting: 1 outpatient site	ACA 1,998 (40); NTX 50 (40); PBO (40); ACA 1,998 + NTX 50 (40)	12	DSM-IV alcohol dependence without any withdrawal symptoms	Return to any drinking: -0.28 (95%CI -0.44, -0.11)	Low

	Country: Germany Funding: Univ; Meds	Other Tx: Group therapy		Exclusions: homelessness Mean Age: 46 y % Non-white NR 26% Female Other Dx: 0%	Return to heavy drinking: -0.25 (95%CI -0.45, -0.05)	
Killeen, 2004	Design: DBRCT Setting: Outpatient community substance use treatment center Country: U.S. Funding: Govt	NTX 50 + TAU (54); PBO + TAU(43); TAU alone (48) Other Tx: Several types and intensities	12	Current alcohol use disorder Exclusions: >10 days outpatient treatment past 3 months Mean Age: 37 y 24% Non-white 37% Female Other Dx: Comorbid psychiatric disorder 51%; other substance use disorder 35%	Drinks per drinking day: 1.6 (95%CI -0.55, 3.75) Percent drinking days: -1.2 (95%CI -9.31, 7.33) Percent heavy drinking days: -2.9 (95%CI -9.94, 4.14) Return to any drinking: 0 (95%CI -0.21, 0.22) Return to heavy drinking: 0.08 (95%CI -0.13, 0.28)	Medium
King, 2012; Fridberg, 2014	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 50 (34); PBO (35) Other Tx: Behavioral therapy and open-label nicotine patch	12 (52)	Healthy smokers with heavy drinking Mean Age: 35.5 y 37% Non-white 38% Female Other Dx: Nicotine dependence 100%	Weekly alcohol consumption was reduced with naltrexone (IRR 0.71, 95% CI= 0.51-1.0, p=0.049). Smoking quit rates were 23 % naltrexone vs. 15% placebo at 12-month follow-up.	Medium
Kranzler, 2004	Design: DBRCT Setting: Outpatient Country: U.S.	NTX inj once a month 150 (185); PBO inj (157) Other Tx: MET 100%	12	DSM-IV alcohol dependence Mean Age: 44 y 17 to 18% Non-white	Percent drinking days: -8.6 (95%CI -16.01, -1.19) Percent heavy drinking days: -3.4 (95%CI -10.24, 3.44)	Medium

	Funding: Drug Abuse Sciences			33 to 37% Female Other Dx: NR	Return to any drinking: -0.08 (95%CI -0.15, 0) Return to heavy drinking: -0.07 (95%CI -0.16, 0.02)	
Kranzler, 2009	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 50 targeted (38); NTX 50 once daily (45); PBO targeted (39); PBO once daily (41) Other Tx: Brief coping skills training 100%	12	Average weekly alcohol consumption of ≥24 standard drinks for men and ≥18 standard drinks for women Exclusions: recent unsuccessful attempt to reduce drinking or past/current significant alcohol withdrawal symptoms Mean Age: 49 y 3% Non-white 42% Female Other Dx: Substance use disorder <1%; Social phobia 3%; Antisocial personality disorder 3%; Dysthymic disorder <1%; Agoraphobia without panic disorder <1%; OCD <1%; GAD <1%	The difference between the targeted naltrexone group and the mean of the other three groups was not significant (p = 0.038) but the targeted naltrexone group drank 16.5% less per day than the other groups. Heavier drinkers reported greater decreases in drinks per day during the study period (b = -0.004, SE = 0.002, p = 0.038). Men in the targeted naltrexone group had fewer drinks per drinking day than the daily naltrexone group (p = 0.014). The targeted naltrexone group drank 19% less on drinking days than the other groups.	Medium
Krystal, 2001; VACS425	Design: DBRCT Setting: Multisite outpatient Country: U.S. Funding: VA; Meds	NTX 50 for 12 months (209); NTX 50 for 3 months then PBO (209); PBO (209) Other Tx: 12-step facilitation	12 or 52	DSM-IV alcohol dependence Exclusions: homelessness; alcohol related disability pension Mean Age: 49 y 37% Non-white	Percent drinking days: -2.7 (95%CI -6.62, 1.22) Return to any drinking: -0.06 (95%CI -0.14, 0.02) Return to heavy drinking: -0.06 (95%CI -0.15, 0.02) Drinks per drinking day: 0.2 (95%CI -1.38, 1.78)	Medium

				3% Female Other Dx: 0%		
Laaksonen, 2008	Design: OLRCT Setting: 6 outpatient sites in 5 cities Country: Finland Funding: Govt	ACA 1,998 or 1,333 (81); DIS 100 to 200 (81); NTX 50 (81) Other Tx: Manual-based CBT	Up to 52 (119)	ICD-10 alcohol dependence Mean Age: 43 y 0% Non-white 29% Female Other Dx: NR	During the continuous medication period (1-12 weeks, the DIS group did significantly better than the NTX and ACA groups in time to first heavy drinking days (p = 0.001), days to first drinking (p = 0.002), abstinence days and average weekly alcohol intake. During the targeted medication period (13-52 weeks), there were no significant differences between the groups in time to first heavy drinking days and days to first drinking while the DIS group reported significantly more frequent abstinence days than the ACA and NTX groups. During the whole study period (1-52 weeks), the DIS group did significantly better in the time to the first drink compared to the other groups. Attrition: 52/ 5 at 52 weeks	High
Latt, 2002	Design: DBRCT Setting: 4 hospital-based; outpatient sites Country: Australia Funding: Govt	NTX 50 (56); PBO (51) Other Tx: No extensive psychosocial interventions	12 (26)	DSM-IV alcohol dependence Mean Age: 45 y % Non-white NR 30% Female Other Dx: 0%	Percent drinking days: -0.9 (95%CI -26.7, 24.9) Return to heavy drinking: -0.19 (95%CI -0.37, -0.01) Attrition: 31/0-3	Medium
Lee, 2001	Design: DBRCT Setting: Inpatient, for 1 month then outpatient Country: Singapore	NTX 50 (35); PBO (18) Other Tx: Intensive inpatient rehabilitation program; postdischarge	12	DSM-IV alcohol dependence Mean Age: 45 y ≥88% Non-white	Return to any drinking: -0.07 (95%CI -0.35, 0.21) Attrition: 66% at 12 wks; 26% with missing data/15-18%	High

	Funding: Meds	therapy encouraged 100%		0% Female Other Dx: NR		
Longabaugh, 2009	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 50 for 24 weeks + BST (36); NTX 50 for 12 weeks then PBO for 12 weeks + BST (35); NTX 50 for 24 weeks + MET (33); NTX 50 for 12 weeks then PBO for 12 weeks + MET (38)[c] Other Tx: None[d]	12-24 (72)	DSM-IV alcohol dependence Mean Age: 44 to 46 y 6 to 14% Non-white 33 to 43% Female Other Dx: NR	With 12 additional weeks of NTX the median time to first heavy drinking day was longer for those in the BST group than for those in the other three groups (61 days vs. between 11 and 20 days, Wilcoxon chi-square=5.05, p<0.03). With 12 additional weeks of NTX the median time to first drink was longer for those in the BST group than for the other three groups (27.5 days vs. between 2 and 10 days, Wilcoxon chi-square=6.12,p<0.02). Neither percentage of abstinent days nor percentage of heavy drinking days was significantly greater for the BST/NTX condition than any other condition.	Medium
Mann, 2012; Mann, 2013, PREDICT	Design: DBRCT Setting: NR Country: Germany Funding: Govt; Meds	ACA 1,998 (172); NTX 50 (169); PBO (86) Other Tx: Medical management	12	Alcohol dependence Mean Age: 45 y % Non-white NR 23% Female Other Dx: NR	Return to heavy drinking: 0.03 (95%CI -0.1, 0.16) Point estimates for heavy drinking relapse free survival from the Kaplan Meier curves were 48.3% for acamprosate, 49.1 % for naltrexone and 51.8% for placebo. Attrition: 34/0 to 2	Medium
Monterosso, 2001	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 100 (121); PBO (62) Other Tx: BRENDA[b]	12	DSM-III-R alcohol dependence Mean Age: 46 y 27% Non-white 27% Female	Percent heavy drinking days: -3.9 (95%CI -7.58, -0.22)	Medium

				Other Dx: NR		
Monti, 2001; Rohsenow, 2007; Rohsenow, 2000	Design: DBRCT Setting: 2 weeks partial hospital (pre-medication) 52 weeks outpatient Country: U.S. Funding: Govt	NTX 50 (64); PBO (64) Other Tx: Brief physician outpatient contacts (intensive therapy occurred prior to medication portion of trial)	12 (52)	DSM-IV alcohol abuse or dependence Mean Age: 39 y 3% Non-white 24% Female Other Dx: Cocaine use 23%; Sedative use 8%; Opiate use 4%	Return to heavy drinking: -0.05 (95%CI -0.2, 0.11) Drinks per drinking day: -3.83 (95%CI -5.55, -2.11)	Medium
Morgenstern, 2012; Chen, 2014	Design: DBRCT Setting: NR Country: U.S. Funding: Govt	NTX 100 + MBSCT (51); NTX 100 (51); PBO + MBSCT (50); PBO (48) Other Tx: BBCET 100%	12	Average weekly consumption of at least 24 standard drinks per week over the previous 90 days and being sexually active with other men; 90% with DSM-IV alcohol dependence Mean Age: 40 y 26% Non-white 0% Female Other Dx: HIV 15%; Any drug use 67%	Among those receiving usual care only, those received naltrexone were significantly more likely to have non-hazardous drinking during the treatment period than those who received placebo (OR = 3.33, CI 95% = 2.14,17.42). For those receiving MBSCT, naltrexone had no significant effect (OR = 0.53, CI95% = 0.26, 1.07).	Medium
Morley, 2006; Morley, 2010	Design: DBRCT Setting: 3 outpatient intensive substance use treatment sites Country: Australia Funding: Govt	ACA 1,998 (55); NTX 50 (53); PBO (61) Other Tx: All offered 4 to 6 sessions of manualized compliance therapy; Up-take/ attendance NR	12	DSM-IV alcohol dependence or abuse and with alcohol abstinence for 3-21 days Mean Age: 45 y % Non-white NR 30% Female	Drinks per drinking days: =1.2 (95%CI -3.43, 1.03) Percent drinking days: -1.3 (95%CI -14.56, 11.96) Return to any drinking: -0.01 (95%CI -0.13, 0.15)	Low

				Other Dx: Substantial levels of emotional distress (anxiety, stress, and depression) Severe concurrent illness (psychiatric or other) –NOS 3	Return to heavy drinking: 0.03 (95%CI -0.13, 0.20)	
Morris, 2001	Design: DBRCT Setting: Outpatient Country: Australia Funding: Govt, Meds	NTX 50 (55); PBO (56) Other Tx: Group psychoeducation and social support	12	DSM-III-R alcohol dependence Mean Age: 47 y % Non-white NR 0% Female Other Dx: PTSD 23%; GAD 32%; Panic disorder 4%; MDD 6%; BPD 1%	Percent drinking days: -11 (95%CI -26.34, 4.34) Return to any drinking: -0.09 (95%CI -0.23, 0.05) Return to heavy drinking: -0.26 (95%CI -0.43, -0.09)	Medium
Narayana, 2008	Design: Prospective cohort Setting: Military, outpatient Country: India Funding: NR	ACA 1,332 to 1,998 (28); NTX 50 (26); TOP 100 to 125 (38) Other Tx: Various psycho-therapies were offered	52	ICD-10 alcohol dependence Mean Age: 38 y 100% Non-white 0% Female Other Dx: NR	Topiramate (76.3%) was significantly more effective (p<0.01) in sustaining abstinence, though 57.7% naltrexone and 60.70% acamprosate maintained complete abstinence. 7 topiramate subjects (18.4%) reported decreased relapses compared to 8 naltrexone (30.8%) and 9 acamprosate (32.1%) subjects.	High
Nava, 2006	Design: OLRCT Setting: Outpatient Country: Italy Funding: Govt	GHB 50 (28); NTX 50 (24); DIS 200 (28) Other Tx: Cognitive behavioral therapy	52	DSM-IV-TR alcohol dependence Exclusions: any withdrawal syndrome; HIV antibodies; homelessness Mean Age: 38.5 to 42.7 y % Non-white NR 15%% Female	At the end of the study, no statistical difference was found among groups in terms of the number of withdrawn, abstinent, non-abstinent, and relapsed patients A significant reduction in alcohol intake, craving, and laboratory makers of alcohol abuse was found in all groups. The GHB group showed greater decreases in alcohol craving and in laboratory markers of	High

				Other Dx: 0%	alcohol abuse compared to the naltrexone and disulfiram groups. Attrition: 31/17	
O'Malley, 1992; O'Malley, 1996	Design: DBRCT Setting: Outpatient; university alcohol treatment unit Country: U.S. Funding: Govt, Meds	NTX 50 + CS (29); NTX 50 + ST (23); PBO + CS (25); PBO + ST (27)	12 (38)	DSM-III-R alcohol dependence Mean Age: 41 y 7% Non-white 26% Female Other Dx: NR	Drinks per drinking day: -1.75 (95%CI -4.07, 0.57) Percent drinking days: -5.6 (95%CI -11.07, -0.13) Return to any drinking: -0.2 (95%CI -0.38, -0.02) Return to heavy drinking: -0.19 (95%CI -0.38, -0.01)	Medium
O'Malley, 2007	Design: DBRCT stratified by eating disorder Setting: University mental health center Country: U.S. Funding: Govt	NTX 50 (57); PBO (50) Other Tx: CBCST 100%, based on manualized approach used in Project MATCH	12	DSM-IV alcohol dependence Exclusions: >30 days abstinence; obesity or significant underweight Mean Age: 40 y 11% Non-white 100% Female Other Dx: Eating disorder 28%	Return to any drinking: 0.1 (95%CI -0.05, 0.25) Return to heavy drinking: 0.04 (95%CI -0.14, 0.22)	Medium
O'Malley, 2008	Design: DBRCT Setting: Alaskan outpatient site Country: U.S. Funding: Govt, Meds	NTX 50 (34); PBO (34); NTX 50 + Sertraline 100 (33)[a] Other Tx: MM 100%	16	DSM-IV alcohol dependence Mean Age: 40 y 70% Non-white 34% Female Other Dx: NR	Drinks per drinking day: -0.3 (95%CI -0.7, 0.1) Percent drinking days: -9.1 (95%CI -10.55, -7.65) Percent heavy drinking days: -7.5 (95%CI -8.91, -6.09) Return to any drinking: -0.24 (95%CI -0.43, -0.04)	Medium

					Return to heavy drinking: -0.18 (95%CI -0.38, 0.03) Attrition: 33 /15	
O'Malley, 2008	Design: DBRCT Setting: Alaskan outpatient site Country: U.S. Funding: Govt, Meds	NTX 50 (34); PBO (34); NTX 50 + Sertraline 100 (33)[a] Other Tx: MM 100%	16	DSM-IV alcohol dependence Mean Age: 40 y 70% Non-white 34% Female Other Dx: NR	There was a statistically significant advantage of naltrexone over placebo but no additional benefit from the addition of sertraline to naltrexone on total abstinence (NX vs. PL p = 0.04, NX vs. NX-SER p = 0.56) or the percentage who reported a drinking related problem during treatment (NX vs. PL p =0.04, NX vs. NX + SER p = 0.85) Time to first heavy drinking day was longer, but not significantly greater for the naltrexone only group compared to placebo (NX vs. PL p =0.14, NX vs. NX + SER p = 0.84). Treatment efficacy was not dependent on the presence of an Asn40allele. Attrition: 33 /15	Medium
Oslin, 1997	Design: DBRCT Setting: Outpatient substance use disorders clinic and VAMC Country: U.S. Funding: DuPont Merck	NTX 100 on Monday and Wednesday, 150 on Friday (21); PBO (23) Other Tx: Group therapy and case manager 100%	12	DSM-III-R alcohol dependence Mean Age: 58 y 64% Non-white % Female NR Other Dx: 0%	Percent drinking days: -4.6 (95%CI -12.76, 3.56) Return to any drinking: -0.06 (95%CI -0.34, 0.21) Return to heavy drinking: -0.2 (95%CI -0.45, 0.04)	Medium
Oslin, 2008	Design: DBRCT Setting: Outpatient psychiatry clinic Country: U.S.	NTX 100 + CBT (40); NTX 100 + BRENDA[b] (39); NTX 100 + doctor only (41); PBO + CBT (40); PBO + BRENDA[b]	24	DSM-IV alcohol dependence Mean Age: 41 y 27% Non-white 27% Female	Drinks per drinking day: 1.86 (95%CI -1.47, 5.19) Percent drinking days: -0.4 (95%CI -6.14, 5.34) Percent heavy drinking days: -2 (95%CI -6.2, 2.2)	Medium

	Funding: Govt	(40); PBO + doctor only (40) Other Tx: None		Other Dx: NR	Return to any drinking: -0.01 (95%CI -0.11, 0.09) Return to heavy drinking: -0.03 (95%CI -0.15, 0.1)	
Oslin, 2015	Design: DBRCT, block randomized by Asn40 allele genotype Setting: Outpatient Country: U.S. Funding: Govt	NTX 50 (111); PBO (110) Other Tx: Medical management	12	DSM-IV alcohol dependence; European or Asian descent Mean Age: 48.5 y 1.8% Non-white 14.1% Female Other Dx: NR	Time dependent decrease in heavy drinking for all groups (GEE score test $\chi 21 = 12.18$, $P = .001$),with no significant group × time interactions.	Low
Petrakis, 2004; Ralevski, 2006	Design: DBRCT Setting: MIRECC outpatient sites Country: U.S. Funding: VA	NTX 50 (16); PBO (15) Other Tx: CBT + psychiatric treatment as usual; Neuroleptics 52%; Benzodiazepines 16%; Thymoleptics 39%	12	DSM-IV alcohol dependence or abuse and schizophrenia or schizoaffective disorder Mean Age: 46 y 19% Non-white 0% Female Other Dx: Schizophrenia or schizoaffective disorder 100%	Drinks per drinking day: 2.98 (95%CI -4.63, 10.59) Percent drinking days: -8.7 (95%CI -19.16, 1.76) Percent heavy drinking days: -1.5 (95%CI -4.49, 1.49)	Medium
Petrakis, 2005; Ralevski, 2007; Petrakis, 2007; Petrakis, 2006; VAMIRECC	Design: DBRCT Setting: Outpatient VA Country: U.S. Funding: Govt	DIS 250 (66); NTX 50 (59); PBO (64); NTX 50 + DIS 250 (65) Other Tx: Psychiatric treatment as usual 100%	12	DSM-IV alcohol dependence and other axis I disorder Exclusions: psychosis Mean Age: 47 y 26% Non-white 3% Female	Either naltrexone or disulfiram had significantly fewer drinking days per week [$F(1,246) = 5.71$, $p = .02$] and more consecutive days of abstinence [$F(1,246) = 4.49$, $p = 04$] than those assigned to placebo. No significant differences were found between groups in terms of the percent days of abstinence, percent of heavy drinking days,	High

				Other Dx: Axis I disorder 100%	and the number of subjects with total abstinence. Disulfiram showed greater reductions over time of GGT [F(1,454) = 5.85, p < 02] compared to naltrexone. Disulfiram treated subjects reported a significantly greater change over time in craving compared with the naltrexone treated subjects (z = 3.98, p < .01).	
Petrakis, 2005; Ralevski, 2007; Petrakis, 2007; Petrakis, 2006; VAMIRECC	Design: DBRCT Setting: Outpatient VA Country: U.S. Funding: Govt	DIS 250 (66); NTX 50 (59); PBO (64); NTX 50 + DIS 250 (65) Other Tx: Psychiatric treatment as usual 100%	12	DSM-IV alcohol dependence and other axis I disorder Exclusions: psychosis Mean Age: 47 y 26% Non-white 3% Female Other Dx: Axis I disorder 100%	Percent drinking days: -1.9 (95%CI -6.46, 2.66) Percent heavy drinking days: -2 (95%CI -6.25, 2.25) Return to any drinking: 0.01 (95%CI -0.16, 0.18)	Medium
Petrakis, 2012	Design: DBRCT Setting: Outpatient; multiple psychiatric centers, primarily VA Country: U.S. Funding: VA	DMI 200 + PBO (24)[b]; Paroxetine 40 + PBO (20); DMI 200 + NTX 50 (22); Paroxetine 40 + NTX 50 (22) Other Tx: Clinical management; compliance enhancement therapy 100%	12	DSM-IV alcohol dependence and PTSD Exclusions: psychosis Mean Age: 47 y 25% Non-white 9% Female Other Dx: PTSD 100%	Compared to paroxetine, desipramine significantly reduced the percentage of heavy drinking days (F1.844 = 7.22, p = 0.009) and drinks per drinking days (F1.84 = 5.04, p = 0.027). There was a significant interaction for time by desipramine/paroxetine treatment on drinks per week (ATS6.82 = 2.46, p= 0.018): desipramine subjects had a greater reduction in their drinking over time compared with paroxetine subjects. Naltrexone, compared to placebo, significantly decreased craving (F1582.0 = 6.39, p = 0.012; naltrexone = 19.88 (SD = 12.89) and placebo = 21.1 (SD =12.89) at baseline vs. naltrexone =	High

				6.7 (SD = 14.07) and placebo = 8.3 (SD = 13.38) at endpoint). GGT declined more in the desipramine treated participants (F1229.5 = 5.08, p = 0.02; desipramine baseline = 55.2, paroxetine baseline =86.4; desipramine week 4 = 48.7, paroxetine week 4 = 46.1; desipramine week 8 =41.7, paroxetine week 8 =47.1; desipramine week 12 =37.5, paroxetine week 12 = 57.1). Attrition: 44.3/20 favoring DMI	
Pettinati, 2008	Design: DBRCT Setting: University-affiliated outpatient substance use disorder treatment research facility Country: U.S. Funding: Govt, Meds	NTX 150 (82); PBO (82); Subjects also randomized to either CBT or BRENDA (2x2 design) Other Tx: NR	12	DSM-IV alcohol dependence and cocaine dependence Mean Age: 39 y 76% Non-white 29% Female Other Dx: Cocaine dependence 100%	Drinks per drinking day: -1.7 (95%CI -3.29, -0.11) Percent drinking days: -2.3 (95%CI -6.85, 2.25) Percent heavy drinking days: -2.72 (95%CI -6.16, 0.72) Attrition: 36/10	Medium
Pettinati, 2010	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt, Meds	SERT 200 (40); NTX 100 (49); PBO (39); SERT 200 + NTX 100 (42) Other Tx: CBT 100%	14	DSM-IV alcohol dependence and major depression Mean Age: 43 y 35% Non-white 38% Female Other Dx: Depression 100%	Return to any drinking: 0.03 (95%CI -0.15, 0.2) Attrition: 43/6.5	Medium
Schmitz, 2004	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	NTX 50 + RPT (20); NTX 50 + DC (20); PBO + RPT (20); PBO + DC (20) Other Tx: RPT or DC as randomized	12	DSM-IV alcohol dependence and cocaine dependence Mean Age: 36 y 71% Non-white	Drinks per drinking day: 2 (95%CI -1.14, 5.14) Percent drinking days: -0.4 (95%CI -6.91, 6.11) Attrition: 69/NR	High

				16% Female Other Dx: Cocaine dependence 100%		
Schmitz, 2009	Design: DBRCT Setting: Outpatient substance use disorders clinic Country: U.S. Funding: Govt	NTX 100 + CBT (20); NTX 100 + CBT and CM (25); PBO + CBT (27); PBO + CBT and CM (14) Other Tx: CBT 100%	12	DSM-IV alcohol dependence and cocaine dependence Mean Age: 34 y 84 to 93% Non-white 13% Female Other Dx: Cocaine use disorder 100%	The probability of drinking days (any drinking) showed an effect for time, F (1, 365) = 5.27, p ≤.02: each successive week in treatment, the odds of drinking decreased by a factor of 0.94 (95% CI, 0.89–0.99). Mean percent drinking days: 40% for naltrexone with CBT, 33% for naltrexone with CBT+CM, 23% for placebo with CBT, and 33% for placebo with CBT+CM. In the CBT group, the odds of heavy drinking decreased by a factor of 0.81 over time in treatment (95% CI, 0.74–0.88), whereas for participants in the CBT+CM group, the odds of heavy drinking remained stable overtime (OR = 0.99, 95% CI, 0.92–1.06). For participants receiving naltrexone, the odds of a heavy drinking day decreased over time by a factor of 0.83 (95% C.I. 0.78–0.88). For participants receiving placebo, the odds of heavy drinking did not change over time (OR = 0.96, 95% CI, 0.87–1.07) Attrition: 76/NR	High
Volpicelli, 1995; Volpicelli, 1992	Design: DBRCT Setting: Substance use disorder treatment unit of a VAMC Country: U.S. Funding: Govt, Meds	NTX 50 (54); PBO (45) Other Tx: Outpatient treatment program and group therapy 100%	12	Score >5 on the Michigan Alcohol Screening Test (MAST) Mean Age: NR y ≥78% Non-white 0% Female	Return to heavy drinking: -0.19 (95%CI -0.37, -0.02) Return to any drinking: -0.08 (95%CI -0.27, 0.12)	Medium

				Other Dx: NR		
Volpicelli, 1997	Design: DBRCT Setting: Outpatient substance use disorders clinic; university/VA treatment research center Country: U.S. Funding: Govt, Meds	NTX 50 (48); PBO (49) Other Tx: Counseling 100%	12	DSM-III-R alcohol dependence and completed medical detoxification for alcohol withdrawal Exclusions: alcohol abstinence >21 days Mean Age: 38 to 39 y 60 to 65% Non-white 18 to 26% Female Other Dx: NR	Percent drinking days: -4.6 (95%CI -10.1, 0.9) Return to any drinking: -0.09 (95%CI -0.28, 0.1) Return to heavy drinking: -0.18 (95%CI -0.37, 0.02)	Medium

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Benefits of acamprosate compared with naltrexone

The AHRQ meta-analysis (Jonas et al., 2014) found no statistically significant difference between naltrexone and acamprosate on return to any drinking (RD, 0.02; 95% CI, -0.03 to 0.08; 3 trials), return to heavy drinking (RD, 0.01; 95% CI, -0.05 to 0.06; 4 trials), or drinking days (WMD, -2.98; 95% CI, -13.4 to 7.5). Patient characteristics did not appear to be associated with a preferential response to either medication.

Table B-11. Acamprosate compared with naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	3; 800	Low; RCTs	Consistent	Direct	Imprecise	RD: 0.02 (-0.03 to 0.08)[a]	Moderate
Return to heavy drinking	4; 1,141	Low; RCTs	Consistent	Direct	Imprecise	RD: 0.01 (-0.05 to 0.06)[a]	Moderate
Drinking days	2; 720	Low; RCTs	Inconsistent	Direct	Imprecise	WMD: -2.98 (-13.42 to 7.45)[a]	Low
Heavy drinking days	1; 612	Low; RCT	Unknown	Direct	Unknown	Significant NTX by CBI interaction, P=0.006	Insufficient
Drinks per drinking day	2; 720	Low; RCTs	Inconsistent	Direct	Unknown	Unable to pool data[b]	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1[c]; 612	Low; RCT	Unknown	Direct	Imprecise	NSD for all measures except SF-12v2 physical health, which favored NTX+CBI	Insufficient
Mortality	0[d]; 0	NA	NA	NA	NA	NA	Insufficient

FROM Jonas et al., 2014 Table D-8

[a] Positive value indicates that naltrexone is favored

[b] Two trials reported some information about drinks per drinking day, but not enough data for us to conduct quantitative synthesis. One trial conducted in Australia reported no statistically significant difference between acamprosate and naltrexone (mean, SD: 7.5, 6.1 vs. 5.9, 6.1; P not reported).[7] The COMBINE study reported that analyses of alternative summary measures of drinking, including drinks per drinking day (P=0.03), were consistent with those for the co-primary end points (percent days abstinent from alcohol and time to first heavy drinking day), all showing a significant naltrexone by CBI interaction.

[c] One additional study was rated high risk of bias.[8] It found that quality of life improved for both groups over the 52 week follow-up compared with baseline, but found no difference between the acamprosate and naltrexone groups.

[d] One study that reported this outcome was rated high risk of bias; another reported one death but did not specify in which treatment group it occurred

Abbreviations: ACA = acamprosate; CBI = combined behavioral intervention; CI = confidence interval; NA = not applicable; NTX = naltrexone; RCT = randomized controlled trial; RD = risk difference; WMD = weighted mean difference

The COMBINE study (Anton et al., 2006) found that "patients receiving medical management with naltrexone, combined behavioral intervention (CBI), or both fared better on drinking outcomes than those who received placebo, but acamprosate showed no evidence of efficacy, with or without CBI."

Analyses of alternative summary measures of drinking, including drinks per drinking day (p=0.03) and heavy drinking days per month (p=0.006) were consistent with those for the coprimary end points (percentage of days abstinent from alcohol and time to first heavy drinking day) in showing a significant naltrexone by CBI interaction. Although the CBI and naltrexone treatment combination showed a statistically significant difference in quality of life measures, the AHRQ review noted this was unlikely to be clinically significant (Jonas et al., 2014). By three years, median but not mean costs (treatment cost plus social costs of AUD such as health care, arrests, and motor vehicle accidents) were diminished in the COMBINE study by a number of treatment combinations that included pharmacotherapy (Zarkin et al., 2010). Treatment arms that were cost-effective, from a policy (Dunlap et al., 2010) and patient-centered standpoint (Zarkin et al., 2008), were medical management (MM) with placebo, MM plus naltrexone therapy, and MM plus combined naltrexone and acamprosate therapy.

The only study identified in the updated literature search that included a head-to-head comparison of acamprosate and naltrexone was the medium risk of bias German PREDICT study (total N=426) (Mann et al., 2013). This trial was modeled after the COMBINE study and found no difference among naltrexone, acamprosate and placebo groups on the time to first heavy drinking. Point estimates for heavy drinking relapse free survival from the Kaplan Meier curves were 48.3% for acamprosate, 49.1% for naltrexone and 51.8% for placebo. A secondary analysis of adherent patients also showed no significant differences among the treatment groups.

Grading of the overall supporting body of research evidence for head-to-head comparison of acamprosate and naltrexone benefits:

- **Magnitude of effect:** None.
- **Risk of bias:** Low. Studies are RCTs that are generally of low bias based on their described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of acamprosate and naltrexone appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and heavy drinking rates as well as measures of alcohol consumption.
- **Consistency:** Consistent. There was some heterogeneity as evidenced by increased I^2 values on one drinking related outcome but confidence intervals are overlapping.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** Unclear. Studies used a single dose of naltrexone and acamprosate.
- **Confounding factors (including likely direction of effect):** Unclear. Some studies suggest a possible effect of genetic polymorphisms on treatment response, which could confound study interpretation.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Moderate. A number of RCTs have been conducted, most of which are governmentally funded and have a low risk of bias. Although the studies have good applicability, imprecision is a limitation. Another limitation is that the trials use oral

formulations of naltrexone without considering the long-acting injectable formulation.

Harms of acamprosate compared with naltrexone

In terms of adverse events, the risks of headache, nausea, and vomiting were noted to be slightly higher for those treated with naltrexone as compared to acamprosate in the AHRQ review (Jonas et al., 2014). The number of deaths in head-to-head studies of naltrexone and acamprosate was extremely small and no statistical comparison was possible (Jonas et al., 2014). In the PREDICT trial, diarrhea was significantly greater with acamprosate and nervousness/anxiety was greater in placebo subjects. Serious adverse events (9.9% of patients during active treatment and 17.4% during follow-up) and related dropouts (6.3%) did not differ among the treatment groups.

Table B-12. Acamprosate compared with Naltrexone

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)[a]	Strength of Evidence Grade
Withdrawals due to AEs	2[b]; 953	Medium; RCT	Consistent	Direct	Imprecise	RD 0.015 (-0.04 to 0.07)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	4[b]; 836	Low to medium; RCTs	Consistent	Direct	Imprecise	RD 0.18 (-0.02 to 0.37)	Moderate
Dizziness	2[b]; 144	Low to medium; RCT	Inconsistent	Direct	Imprecise	RD 0.08 (-0.23 to 0.39)	Low
Headache	3[b]; 301	Medium; RCT	Inconsistent	Direct	Imprecise	RD -0.056 (-0.120 to 0.008)	Low[d]
Insomnia	2; 144	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RD 0.07 (-0.20 to 0.34)	Low
Nausea	4[c]; 836	Low to medium; RCTs	Consistent	Direct	Imprecise	RD -0.08 (-0.18 to 0.02)	Low[e]
Numbness / tingling / paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	2; 648	Low; RCTs	Consistent	Direct	Precise	RD -0.06 (-0.11 to -0.01)	Moderate

FROM Jonas et al., 2014 Table D-35

[a] In this column, a positive value favors naltrexone
[b] One additional study was rated high or unclear risk of bias
[c] Two additional studies were rated high risk of bias
[d] The additional study rated as high risk of bias found similar results as the medium risk of bias studies. Meta-analysis including all three found a higher risk of headache with naltrexone than with acamprosate: RD -0.087 (-0.159 to -0.015)
[e] Meta-analysis including the two additional studies rated as high or unclear risk of bias found a higher risk of nausea with naltrexone than with acamprosate: RD -0.096 (-0.178 to -0.015)
Abbreviations: ACA = acamprosate; AE = adverse effect; CI = confidence interval; NTX = naltrexone; RCT = randomized controlled trial; RD = risk difference

Grading of the overall supporting body of research evidence for head-to-head comparison of acamprosate and naltrexone harms:

- **Magnitude of effect:** Very small. When present, the magnitude of effect is very small.
- **Risk of bias:** Medium. Studies are RCTs of low bias based on their described randomization and blinding procedures and descriptions of study dropouts. However, methods for determining harms are not always well-specified and there is potential for selective reporting of results.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of acamprosate and naltrexone appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured common side effects and dropouts due to adverse events.
- **Consistency:** Inconsistent. As indicated by the high values of I^2, there was substantial heterogeneity in the reported adverse events among the trials.
- **Precision:** Imprecise. Confidence intervals for studies are wide in many studies and cross the threshold for clinically significant harms of the intervention.
- **Dose-response relationship:** Unknown. Studies used a single dose of acamprosate and naltrexone.
- **Confounding factors (including likely direction of effect):** Absent. No known confounding factors are present that would be likely to modify adverse events of the intervention.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Low. Several RCTs have been conducted, some of which have assessed adverse events in a systematic and pre-defined fashion. Many of the RCTs are funded by governmental agencies. However, findings are imprecise and inconsistent, making it difficult to draw conclusions about differences in side effects between the two medications.

3291 Data abstraction - acamprosate-naltrexone

3292 **Table B-13. Studies related to acamprosate-naltrexone head-to-head comparison**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Follow-up)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Anton, 2006; Donovan, 2008; LoCastro, 2009; COMBINE	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153)[a] Other Tx: As randomized; community support group participation (like AA) encouraged	16 (68)	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: NR	Percent drinking days: 1 (95%CI -3.12, 5.12) Return to any drinking: 0.03 (95%CI -0.04, 0.09) Return to heavy drinking: 0.03 (95%CI -0.05, 0.1)	Low
COMBINE Study Research Group, 2003	Design: DBRCT Setting: 11 academic outpatient sites Country: U.S. Funding: Govt, Meds	ACA 3,000 + CBI + MM (9); ACA 3,000 + MM (9); NTX 100 + CBI + MM (9); NTX 100 + MM (9); PBO + CBI + MM (9); PBO + MM (8) Other Tx: As randomized	16	DSM-IV alcohol dependence Mean Age: 38 to 42 y 17 to 22% Non-white 22 to 33% Female Other Dx: NR	Acamprosate-naltrexone group adherence was equal to, or better than, adherence with placebo, acamprosate alone or naltrexone alone Adverse events were comparable in all groups. Attrition: 31/11 to 20	Medium
Greenfield, 2010; Fucito, 2012; COMBINE	Design: Secondary data analysis Setting: 11 academic outpatient sites Country: U.S.	ACA 3,000 + CBI + MM (151); ACA 3,000 + MM (152); NTX 100 + CBI + MM (155); NTX 100 + MM (154); PBO + CBI + MM (156); PBO + MM (153)	68	DSM-IV alcohol dependence Mean Age: 44 y 23% Non-white 31% Female Other Dx: 0%	There was a significant naltrexone by CBI interaction for women on two primary outcomes (percent days abstinent and time to first heavy drinking days) and also secondary outcome measures (good clinical response, percent heavy drinking days, and craving).	Low

	Funding: Govt, Meds	Other Tx: As randomized;; community support group participation (like AA) encouraged			Only the naltrexone by CBI interaction was significant for percent days abstinent. The naltrexone by CBI interaction was significant for time to first heavy drinking day: in men (p=.048) with each treatment showing slower relapse times. A non-significant trend was present in women. Naltrexone or CBI alone was superior to groups receiving neither in the percent of heavy drinking days.	
Kiefer, 2003; Kiefer, 2004; Kiefer, 2005	Design: DBRCT Setting: 1 outpatient site Country: Germany Funding: Univ; Meds	ACA 1,998 (40); NTX 50 (40); PBO (40); ACA 1,998 + NTX 50 (40) Other Tx: Group therapy	12	DSM-IV alcohol dependence without any withdrawal symptoms Exclusions: homelessness Mean Age: 46 y % Non-white NR 26% Female Other Dx: 0%	Time to relapse or time to first drink did not differ between acamprosate and naltrexone treated groups by survival analysis although the combination of naltrexone plus acamprosate was associated with better outcomes than placebo (p<0.01) or than acamprosate alone (p=0.04).	Low
Laaksonen, 2008	Design: OLRCT Setting: 6 outpatient sites in 5 cities Country: Finland Funding: Govt	ACA 1,998 or 1,333 (81); DIS 100 to 200 (81); NTX 50 (81) Other Tx: Manual-based CBT	Up to 52 (119)	ICD-10 alcohol dependence Mean Age: 43 y 0% Non-white 29% Female Other Dx: NR	During the continuous medication period (1-12 weeks, the DIS group did significantly better than the NTX and ACA groups in time to first heavy drinking days (p = 0.001), days to first drinking (p = 0.002), abstinence days and average weekly alcohol intake. During the targeted medication period (13-52 weeks), there were no significant differences between the groups in time to first heavy drinking days and days to first drinking while the DIS group reported significantly more frequent abstinence days than the ACA and NTX groups.	High

				During the whole study period (1-52 weeks), the DIS group did significantly better in the time to the first drink compared to the other groups. Attrition: 52/ 5 at 52 weeks	
Mann, 2012; Mann, 2013, PREDICT	Design: DBRCT Setting: NR Country: Germany Funding: Govt; Meds	ACA 1,998 (172); NTX 50 (169); PBO (86) Other Tx: Medical management	12	Alcohol dependence Mean Age: 45 y % Non-white NR 23% Female Other Dx: NR	Return to heavy drinking: 0.01 (95%CI -0.1, 0.11) Point estimates for heavy drinking relapse free survival from the Kaplan Meier curves were 48.3% for acamprosate, 49.1 % for naltrexone and 51.8% for placebo. Attrition: 34/0 to 2	Medium
Morley, 2006; Morley, 2010	Design: DBRCT Setting: 3 outpatient intensive substance use treatment sites Country: Australia Funding: Govt	ACA 1,998 (55); NTX 50 (53); PBO (61) Other Tx: All offered 4 to 6 sessions of manualized compliance therapy; Up-take/ attendance NR	12	DSM-IV alcohol dependence or abuse and with alcohol abstinence for 3-21 days Mean Age: 45 y % Non-white NR 30% Female Other Dx: Substantial levels of emotional distress (anxiety, stress, and depression) Severe concurrent illness (psychiatric or other) –NOS 3	No significant difference between treatments in the number of days to first lapse (Breslow test: t2= 0.4, P= 0.81) or in the number of days to first relapse (Breslow test: t2= 2.9, P= 0.23) by survival analysis. Regardless of medication group, significant effects for time were found for drinks per drinking day (F1,159= 6.8, P< 0.01), dependence severity (F1,103= 12.81, P< 0.001) but not for craving (F1,103= 2.0, P = 0.16).	Low
Narayama, 2008;	Design: Prospective cohort Setting: Military, outpatient Country: India	ACA 1,332 to 1,998 (28); NTX 50 (26); TOP 100 to 125 (38) Other Tx: Various psycho-therapies were offered	52	ICD-10 alcohol dependence Mean Age: 38 y 100% Non-white 0% Female	Topiramate (76.3%) was significantly more effective (p<0.01) in sustaining abstinence, though 57.7% naltrexone and 60.70% acamprosate maintained complete abstinence.	High

	Funding: NR			Other Dx: NR	7 topiramate subjects (18.4%) reported decreased relapses compared to 8 naltrexone (30.8%) and 9 acamprosate (32.1%) subjects.	
Rubio, 2001	Design: SBRCT Setting: Outpatient Country: Spain Funding: Govt	ACA 1,665-1,998 (80); NTX 50 (77) Other Tx: Supportive group therapy weekly; weekly visits with a psychiatrist for 3 months, then biweekly until end of study	52	DSM-III-R alcohol dependence Exclusions: previous naltrexone or acamprosate treatment Mean Age: 44 y % Non-white NR 0% Female Other Dx: 0%	At the end of 1 year, 41% receiving naltrexone and 17% receiving acamprosate had not relapsed (P= 0.0009), and the accumulated abstinence was greater for naltrexone compared with acamprosate (mean number of days: 243 vs. 180). Naltrexone had longer survival until first relapse than acamprosate (63 days vs. 42 days, p = 0.02). Relapse to some alcohol use occurred on average 12 days later in the naltrexone group (SD = 16) vs. after 6 days in the acamprosate group (SD = 8). Survival analysis of time to first alcohol consumption showed no significant differences between the two groups (the mean number of days: 44 for the naltrexone group and 39 for the acamprosate group; p = 0.34).	High

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Statement 10:

APA suggests (2C) that disulfiram be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of achieving abstinence;**
- **prefer disulfiram or are intolerant to or have not responded to naltrexone and acamprosate;**
- **are capable of understanding the risks of alcohol consumption while taking disulfiram; and**
- **have no contraindications to the use of this medication.**

Benefits of disulfiram

Evidence for the benefits of disulfiram comes from randomized controlled trials, open-label trials, and expert opinion. The AHRQ review (Jonas et al., 2014) included 4 studies conducted at Veterans Administration Medical Centers and found no statistically significant difference between disulfiram 250 mg per day and sham comparators (i.e., placebo, disulfiram 1 mg/d, riboflavin). In the two trials included in the AHRQ review that assessed percentage of drinking days, one reported no significant difference among treatment groups. The other trial limited its reporting to a subset of subjects (those that drank during the trial and that also completed all assessments) and found disulfiram was associated with fewer drinking days (p=0.05) than those who received comparator (49% with Disulfiram 250 mg/day vs. 75.4% with Disulfiram 1 mg/day and 86.5% with riboflavin). In the two RCTs included in the AHRQ analysis that had a medium risk of bias (Fuller et al., 1979; Fuller et al., 1986), treatment adherence was associated with abstinence, regardless of whether the subject was assigned to active disulfiram or control treatment.

In a medium risk of bias trial conducted in Japan (Yoshimura et al., 2014), subjects (total N=109) were randomly assigned according to a 2 x 2 design with disulfiram 200 mg/d vs. placebo and receipt of educational material on drinking harms and craving management vs. no such education. At 26 weeks, there were no differences among groups in the percent of individuals who remained abstinent. However, this study may have limited generalizability because individuals were randomly assigned to disulfiram after a 2 to 3 month inpatient stay.

A single study in the AHRQ review (Petrakis et al., 2005) compared disulfiram, naltrexone, placebo, and the combination of disulfiram plus naltrexone for 12 weeks in Veterans Administration outpatient settings. Naltrexone was given in a double blind fashion but disulfiram was administered as an open-label medication. The trial found no statistically significant difference between disulfiram and naltrexone for number of subjects achieving total abstinence (51 vs. 38, p=0.11), percentage of days abstinent (96.6 versus 95.4, p=0.55), or percentage of heavy drinking days (3.2 vs. 4, p=0.65).

Table B-14. Disulfiram compared with control

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	NNT[d]	Strength of Evidence Grade
Return to any drinking	2[a]; 492	Medium; RCTs	Consistent[b]	Direct	Imprecise	RD: 0.04 (-0.11 to 0.03)	NA	Low
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 290	Medium; RCTs	Inconsistent	Indirect[c]	Imprecise	1 study reported similar percentages and no significant difference; the other reported that DIS was favored among the subset of subjects who drank and had a complete set of assessment interviews (N=162/605 subjects), p=0.05	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	NA	Insufficient

FROM Jonas et al., 2014 Table D-2

[a] 1 additional study was rated high risk of bias.
[b] Inclusion of the study rated high risk of bias would have made this inconsistent, though it would not have changed the conclusion (the meta-analysis still found no statistically significant difference between groups).
[c] We considered this indirect because the larger study did not report the outcome for the randomized sample; it only reported this outcome for the subset (162/605) who drank and who had a complete set of assessment interviews.
[d] NA entry for numbers needed to treat (NNT) indicates that the risk difference (95% CI) was not statistically significant, so we did not calculate a NNT, or that the effect measure was not one that allows direct calculation of NNT (e.g., WMD).

Abbreviations: CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RD = risk difference

A meta-analysis (Skinner et al., 2014) differed from the AHRQ analysis in including open-label as well as randomized controlled trials. Skinner and colleagues (2014) hypothesized that in a double-blinded trial, subjects in both disulfiram and placebo groups would avoid drinking because of having been warned of the potential for adverse events regardless of actual treatment assignment. They included 22 studies

(2414 subjects) and found a significant overall effect but no difference between disulfiram and control groups in the double-blinded RCTs. When only open-label trials were considered disulfiram was significantly better than controls on alcohol related outcomes (Hedge's g = .70; 95%CI = .46-.93), for which control conditions included acamprosate, naltrexone, and no disulfiram. Individual comparisons for each of these control conditions were also statistically significant. As with the RCTs, however, only a small proportion of women were included in the open-label trials which limits generalizability.

Grading of the overall supporting body of research evidence for efficacy of disulfiram:

- **Magnitude of effect:** No effect in double-blind studies, moderate in open-label studies.
- **Risk of bias:** High. Studies are RCTs and a meta-analysis that includes open-label trials. RCTs are of medium to high risk of bias and open-label studies have not been formally rates but are likely to be of high risk of bias.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The double blind studies primarily include subjects from the U.S. Veterans Administration Medical Centers are over-represented among study locations and the vast majority of subjects are men. The doses of disulfiram used in the studies appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and alcohol consumption.
- **Consistency:** Inconsistent. There was considerable heterogeneity in the trial findings in both the AHRQ meta-analysis and the meta-analysis by Skinner et al. (2014), which included open-label trials.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** No data available to assess.
- **Confounding factors (including likely direction of effect):** Present. As noted above, the subjects knowledge of treatment assignment may be important in the desire to maintain abstinence to avoid an aversive experience when drinking.
- **Publication bias:** Possible. The meta-analysis of Skinner et al. (2014), which included open-label trials, noted funnel plot asymmetry suggesting a potential for publication bias. Virtually all of the disulfiram trials were conducted prior to the advent of clinicaltrials.gov.
- **Overall strength of research evidence:** Low. A small number of RCTs have been conducted, most of which have medium to high risk of bias; open-label studies also are likely to have a high risk of bias. The available evidence is limited in its generalizability due to the location of the trials and the small proportion of women in the studies. The imprecision and inconsistency of findings are additional limitations.

Harms of disulfiram:

The data on harms from the studies included in the AHRQ report was insufficient to conduct meta-analyses. One study showed a greater rate of drowsiness in those receiving versus not receiving disulfiram (8% vs. 2%, p=0.03). Several patients discontinued disulfiram due to increased levels of hepatic enzymes. A 4 arm study (2 x 2, disulfiram vs. placebo, naltrexone vs. placebo) showed greater rates of specific side effects in patients taking any study medication but no differences between groups.

In this study, those on disulfiram and placebo experienced 6 of 14 serious adverse events. In the study of Yoshimura and colleagues (2014), 1/53 disulfiram treated subjects had a dermatological problem, 2/53 had liver enzyme elevations, and 1/53 had renal dysfunction whereas no adverse events were noted in placebo-treated subjects. In the study of Petrakis and colleagues (2005), which compared disulfiram, naltrexone, placebo, and the combination of disulfiram plus naltrexone, fever was more common in the disulfiram group than in the naltrexone group (p=0.03) whereas nervousness (p=0.005) and restlessness (p=0.03) were more common in the naltrexone group than in the disulfiram group.

In the meta-analysis of Skinner et al. (2014), data from open-label trials showed considerable heterogeneity but showed a significantly greater number of adverse events with disulfiram as compared to control conditions.

Additional information on potential harms of disulfiram comes from the product labelling (Rising Pharmaceuticals, 2016), which notes that disulfiram should not be given to individuals who have recently received metronidazole, paraldehyde, alcohol (within 12 hours), or alcohol-containing preparations. It is also noted to be contraindicated in the presence of severe myocardial disease or coronary occlusion. When alcohol is taken within 14 days of disulfiram ingestion, it can produce "flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions, there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death." Disulfiram is noted to be contraindicated in the presence of psychosis or with hypersensitivity to disulfiram or thiuram derivatives used in pesticides and rubber production. Hepatic toxicity is also reported to have occurred in individuals receiving disulfiram.

Grading of the overall supporting body of research evidence for harms of disulfiram:

- **Magnitude of effect:** Small. When instructions for avoiding disulfiram-alcohol reactions are followed, the proportion of individuals who experience adverse events is small.
- **Risk of bias:** High. Studies do not pre-specify harm outcomes and do not report them consistently.
- **Applicability:** The included trials all involve individuals with AUD by prior diagnostic criteria. The vast majority of study subjects are men, which limits the generalizability of the findings. The doses of disulfiram used in the trials appear to be representative of outpatient clinical practice.
- **Directness:** Indirect. Studies generally measured adverse events as a general category or assessed the numbers of individuals who required intervention due to an adverse effect.
- **Consistency:** Inconsistent. There was considerable heterogeneity in the findings of the meta-analysis by Skinner et al. (2014), which included open-label trials.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** No data are available to assess.
- **Confounding factors (including likely direction of effect):** Not identified.

- **Publication bias:** Possible. The meta-analysis of Skinner et al. (2014), which included open-label trials, noted funnel plot asymmetry suggesting a potential for publication bias. Virtually all of the disulfiram trials were conducted prior to the advent of clinicaltrials.gov.
- **Overall strength of research evidence:** Low. A small number of double-blinded RCTs have been conducted, but measures of adverse events were minimal and not systematically defined. With data from open-label trials, the imprecision and inconsistency of findings are limitations in addition to the high risk of bias associated with an open-label study design.

3418 Data abstraction - disulfiram

3419 **Table B-15. Studies related to disulfiram**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Followup)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Carroll, 1993	Design: OLRCT Setting: Outpatient Country: U.S. Funding: Govt	DIS 250 (9); NTX 50 (9) Other Tx: Weekly individual psychotherapy 100%	12	DSM-III-R alcohol abuse/dependence and cocaine dependence Mean Age: 32 y 39% Non-white 72% Female Other Dx: Cocaine dependence 100%	Subjects taking disulfiram showed lower percentage of alcohol use days compared to those taking naltrexone (4.0% vs. 26.3%, t = 3.73, p<0.01). Subjects taking disulfiram also reported fewer total days using alcohol (2.4. vs. 10.4 days, t = 3.00, p<0.01), fewer total drinks (2.3 vs. 27.0, t = -2.00, p=0.06), and more total weeks of abstinence (mean 7.2 vs. 1.1 weeks, t = 4.72, p<0.001) compared to those taking naltrexone. Attrition: 67/ 22	High
De Sousa, 2004	Design: OLRCT Setting: Outpatient Country: India Funding: NR	DIS 250 (50); NTX 50 (50) Other Tx: Supportive group psychotherapy	52	DSM-IV alcohol dependence Exclusions: previous naltrexone and/or disulfiram treatment Mean Age: 43 to 47 y % Non-white NR 0% Female Other Dx: NR	Disulfiram associated with greater reduction in relapse, greater survival time until the first relapse, and more days of abstinence than naltrexone: At study endpoint, relapse was 14% with disulfiram vs. 56% with naltrexone. Naltrexone had lower composite craving scores than disulfiram.	High
De Sousa, 2005	Design: OLRCT	ACA 1,998 (50); DIS 250 (50)	35	DSM-IV alcohol dependence	Disulfiram had a lower relapse rate than acamprosate (88% vs. 46%, p = 0.0001) and a	High

	Setting: Outpatient; private psychiatric hospital Country: India Funding: NR	Other Tx: Weekly supportive group psychotherapy offered		Exclusions: previous disulfiram or acamprosate treatment Mean Age: 42 to 43 y 100% Non-white 0% Female Other Dx: NR	longer mean time to first relapse (123 d vs. 71 days p = 0.0001). Acamprosate had lower craving scores than disulfiram.	
De Sousa, 2008	Design: OLRCT Setting: Inpatient and outpatient alcohol treatment center Country: India Funding: NR	TOP 150 (50); DIS 250 (50) Other Tx: Offered weekly supporting group psychotherapy	39	DSM-IV alcohol dependence Exclusions: previous topiramate or disulfiram treatment Mean Age: 43 y 100% Non-white 0% Female Other Dx: NR	Disulfiram had greater mean time to first relapse than topiramate (133 days vs. 79 days, p = 0.0001) and a lower relapse rate at study endpoint (10% vs. 44%; p = 0.0001) Topiramate had less craving than disulfiram.	High
Fuller, 1979	Design: DBRCT Setting: Outpatient; VA Country: U.S. Funding: VA	DIS 250 (43); DIS 1 (43); RIB 50 (42) *Other Tx:* Counseling (unspecified) 100%	52	Admitted for alcohol related illness: or requesting treatment for alcoholism Mean Age: 43 y 61% Non-white 0% Female Other Dx: NR	Complete abstinence rates did not differ between regular dose (23%) and no disulfiram (12%). Median percentages of drinking days in the disulfiram 500/250 mg, disulfiram 1mg, and no disulfiram groups were 31%, 32%, and 37%, respectively.	Medium
Fuller, 1986	Design: DBRCT Setting: Outpatient; 9 VA medical centers Country: U.S.	DIS 250 (202); DIS 1 (204); RIB 50 (199) *Other Tx:* Counseling (loosely defined) % NR	52	Requesting alcohol treatment and meeting National Council on Alcoholism criteria Mean Age: 41 to 42 y	No significant differences among the groups in percentages of those remaining abstinent for the full year: 18.8%, 22.5%, and 16.1% (p = .25) or in the time to first drinking day (p=.26).	Medium

	Funding: VA			47% Non-white 0% Female Other Dx: NR	Of those who reported drinking and provided all scheduled interviews, subjects taking 250 mg of disulfiram had significantly fewer total drinking days (49±8days) compared to those taking either the 1mg of disulfiram (75±12days) or no disulfiram (86.5±14days). Of those reported drinking and provided six or fewer interviews, the differences among the groups in total drinking days were not statistically significant.	
Laaksonen, 2008	Design: OLRCT Setting: 6 outpatient sites in 5 cities Country: Finland Funding: Govt	ACA 1,998 or 1,333 (81); DIS 100 to 200 (81); NTX 50 (81) Other Tx: Manual-based CBT[b]	Up to 52 (119)	ICD-10 alcohol dependence Mean Age: 43 y 0% Non-white 29% Female Other Dx: NR	During the continuous medication period (1-12 weeks, the DIS group did significantly better than the NTX and ACA groups in time to first heavy drinking days (p = 0.001), days to first drinking (p = 0.002), abstinence days and average weekly alcohol intake. During the targeted medication period (13-52 weeks), there were no significant differences between the groups in time to first heavy drinking days and days to first drinking while the DIS group reported significantly more frequent abstinence days than the ACA and NTX groups. During the whole study period (1-52 weeks), the DIS group did significantly better in the time to the first drink compared to the other groups. Attrition: 52/ 5 at 52 weeks	High
Ling, 1983	Design: DBRCT Setting: Outpatient; VA Country: U.S. Funding: VA	DIS 250 + methadone (41); PBO + methadone (41) Other Tx: Methadone 100%	37	Two of four consecutive >0.05% alcohol readings in subjects on methadone maintenance or at risk of clinic discharge for problem behavior	Both groups reported fewer episodes of morning drinking, alcoholic blackouts, fights, binge drinkings, hospitalizations, and alcohol related arrests.	High

				Mean Age: 39 y % Non-white NR % Female NR Other Dx: Heroin use 80%; Marijuana use 36%; Other drug use 67%; Depression 83%; Moderate to high depression 50%	Attrition: 57% at 12 wks; 55% lost to follow-up/ 3% at 12 wks; 22% lost to follow-up	
Nava, 2006	Design: OLRCT Setting: Outpatient Country: Italy Funding: Govt	GHB 50 (28); NTX 50 (24); DIS 200 (28) Other Tx: Cognitive behavioral therapy	52	DSM-IV-TR alcohol dependence Exclusions: any withdrawal syndrome; HIV antibodies; homelessness Mean Age: 38.5 to 42.7 y % Non-white NR 15%% Female Other Dx: 0%	At the end of the study, no statistical difference was found among groups in terms of the number of withdrawn, abstinent, nonabstinent, and relapsed patients A significant reduction in alcohol intak, craving, and laboratory makers of alcohol abuse was found in all groups. The GHB group showed greater decreases in alcohol craving and in laboratory markers of alcohol abuse compared to the naltrexone and disulfiram groups. Attrition: 31/17	High
Petrakis, 2005; Ralevski, 2007; Petrakis, 2007; Petrakis, 2006; VAMIRECC	Design: DBRCT Setting: Outpatient VA Country: U.S. Funding: Govt	DIS 250 (66); NTX 50 (59); PBO (64); NTX 50 + DIS 250 (65) Other Tx: Psychiatric treatment as usual 100%	12	DSM-IV alcohol dependence and other axis I disorder Exclusions: psychosis Mean Age: 47 y 26% Non-white 3% Female Other Dx: Axis I disorder 100%	Return to any drinking: -0.12 (95%CI -0.27, 0.04)	High

Yoshimura, 2014	Design: DBRCT Setting: Outpatient Country: Japan Funding: Govt	DIS 200 + letter (28); DIS 200 no letter (26); PBO + letter (29); PBO no letter (26) Other Tx: Proportion of subjects received letter discussing harms of alcohol use and approaches to manage craving	26	ICD-10 alcohol dependence Mean Age: 52.1 y % Non-white NR 0% Female Other Dx: NP	No difference in the proportion achieving abstinence at 26 wks	Medium

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Statement 11:

APA suggests (2C) that topiramate, gabapentin, or ondansetron be offered to patients with moderate to severe alcohol use disorder who:

- **have a goal of reducing alcohol consumption or achieving abstinence;**
- **prefer topiramate, gabapentin, or ondansetron or are intolerant to or have not responded to naltrexone and acamprosate;**
  and
- **have no contraindications to the use of these medications.**

Benefits of topiramate

Evidence for topiramate comes from multiple randomized controlled trials, some of which included subjects with co-occurring conditions. The AHRQ review (Jonas et al., 2014) included 3 studies of topiramate vs. placebo and 1 study of topiramate vs. naltrexone vs. placebo. The latter study (Baltieri et al., 2008, Baltieri et al., 2009) was rated as having a high risk of bias and showed no significant differences in the two treatments on drinking outcomes. The 2 placebo-controlled trials (total N=521) that had a low or medium risk of bias were included in the AHRQ meta-analysis (Johnson et al., 2003; Johnson et al., 2007). These trials had a duration of 12 to 14 weeks and were both conducted in the U.S. Based on this meta-analysis, the AHRQ review concluded that there was a moderate strength of evidence for topiramate efficacy on drinks per drinking days (WMD: -1.10 95% CI -1.75 to -0.45), percentage of heavy drinking days (WMD: -11.53 95% CI -18.29 to -4.77), and percentage of drinking days. For the latter outcome, it was not possible to combine the results of the two trials but each showed a comparable mean difference (WMD: -8.5 95% CI -15.9 to -1.1; mean difference -11.6 95% CI -3.98 to -19.3). Findings from sensitivity analyses were similar when high risk of bias studies were included.

Table B-16. Characteristics of included double-blind randomized placebo-controlled trials of topiramate

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

	therapy offered

FROM Jonas et al., 2014

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

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

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

A number of subsequent randomized controlled trials have also examined effects of topiramate. In a low risk of bias U.S. government funded trial, topiramate in doses of up to 200 mg/d (N=67) was compared to placebo (N=71) and was associated with a larger (p =0.001) and more rapid (p =0.0001) reduction in heavy drinking and a larger (p=0.03) and more rapid (p=0.01) increase in the number of days abstinent (Kranzler et al., 2014a). Topiramate subjects were more likely to have had no heavy drinking days in the last 4 weeks of treatment (35.8% vs. 16.9% with placebo, OR=2.75, 95% CI=1.24–6.10) and to have abstained from alcohol use at the end of treatment (OR=2.57; 95% CI=1.13–5.84). The odds of a heavy drinking day were greater in the placebo group than the topiramate group (OR=5.33, 95% CI=1.68–7.28) by the last week of treatment. These benefits of topiramate appeared to be limited to individuals who were homozygous for the rs2832407 C-allele of GRIK1 (which encodes the kainate GluK1 receptor subunit). However, at 3- and 6-month follow-up, the beneficial effects of topiramate on percent heavy drinking days and percent days abstinent were no longer significant (Kranzler et al., 2014b). Topiramate (300 mg/d; N=21) was also one of the treatment arms in a 14 week medium risk of bias double-blind randomized controlled trial of several other anticonvulsant agents that included levetiracetam (N=21), zonisamide 400 mg/d (N=19) and placebo (N=24) (Knapp et al., 2015). For topiramate as compared to placebo, significant treatment effects were seen for weekly percent days drinking (P < 0.0001), percent days heavy drinking (P < 0.0001), and drinks consumed per day (P = 0.0007). A 12-week, medium risk of bias, double-blind randomized placebo controlled trial of topiramate (260 mg/d average dose) conducted in Thailand (total N = 106) was limited by 50% attrition rates but showed no significant difference between the treatments in heavy drinking days, time to first heavy drinking day or secondary drinking outcomes (Likhitsathian et al., 2013).

Several smaller studies of topiramate have been conducted in individuals with a co-occurring psychiatric disorder. A small (total N=30) double-blind randomized placebo-controlled trial of flexibly dosed topiramate (up to 300 mg/day) was conducted at a Veterans Affairs Medical Center in individuals with co-occurring PTSD (Batki et al., 2014). This low risk of bias study showed a 51% decrease in drinking days with topiramate as compared to placebo as well as reductions in standard drinks per week but no effect on the percent of heavy drinking days. Another U.S. government-funded, low risk of bias, double-blind randomized placebo-controlled trial of topiramate (300 mg/day) enrolled individuals with co-occurring cocaine dependence (Kampman et al., 2013). During the 13-week trial, 41/87 (47%) of placebo-treated subjects were lost to followup versus 29/83 (35%) with topiramate. However, on primary outcome measures of weekly differences in percent days drinking, percent days heavy drinking, and mean drinks per drinking day, there was no difference between the placebo and topiramate treated groups. An

additional study in individuals with co-occurring bipolar disorder reported the results of 12 randomized participants but had difficulty recruiting subjects due to problems with topiramate tolerability (Silvia et al., 2016).

Table B-17. Topiramate compared with placebo

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength of Evidence Grade
Return to any drinking	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2[b]; 521	Low; RCTs	Consistent	Direct	Imprecise	Trial 1: WMD: -8.5 (-15.9 to -1.1)[b] Trial 2: mean difference -11.6 (-3.98 to -19.3)	Moderate[b]
Heavy drinking days	2[b]; 521	Low; RCTs	Consistent	Direct	Imprecise	WMD: -11.53 (-18.29 to -4.77)	Moderate[b]
Drinks per drinking day	2[b]; 521	Low; RCT	Consistent	Direct	Imprecise	WMD: -1.10 (-1.75 to -0.45)	Moderate[b]
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	1; 371	Low; RCT	Unknown	Direct	Imprecise	4.4% (TOP) vs. 11.7% (PBO); p=0.01	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	1; 371	Low; RCT	Unknown	Direct	Imprecise	0 (TOP) vs. 1 (PBO)	Insufficient

FROM Jonas et al., 2014 Table D-26

[a] One study conducted in Brazil, rated as high risk of bias, reported this outcome. It reported that more patients treated with topiramate returned to any drinking than with placebo (24/52 versus 15/54).

[b] One additional study reporting this outcome was rated as high risk of bias. Our meta-analysis found a lower percentage of drinking days for patients treated with topiramate than for those who received placebo both without and with including the trial rated as high risk of bias (WMD, -9.7; 95% CI, -16.4 to -3.1). Our meta-analysis found a lower percentage of heavy drinking days for patients treated with topiramate than for those who received placebo both without and with including the trial rated as high risk of bias (WMD, -11.4; 95% CI, -20.4 to -2.4). Our meta-analysis found no statistically significant difference between topiramate and placebo when only including the trial rated as low risk of bias, but found a statistically significant reduction of 1.2 drinks per drinking day when including the trial rated as high risk of bias (WMD, -1.2; 95% CI, -2.2 to -0.2). We were unable to include "trial 2" (N=150), rated as medium risk of bias, in our meta-analyses due to differences in the type of data reported, but its findings are shown in the SOE table, and were generally consistent with those of the low risk of bias trial ("trial 1", N=371).

Abbreviations: CI = confidence interval; NA = not applicable; PBO = placebo; RCT = randomized controlled trial; TOP = topiramate; WMD = weighted mean difference

Grading of the overall supporting body of research evidence for efficacy of topiramate:

- **Magnitude of effect:** Moderate. When present for specific outcomes, the magnitude of the effect is moderate.
- **Risk of bias:** Medium. Studies are RCTs of low to high bias based on their described randomization and blinding procedures and descriptions of study dropouts, with the largest trials having low to medium risk of bias.

- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of topiramate appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and heavy drinking rates as well as measures of alcohol consumption.
- **Consistency:** Inconsistent. There was considerable heterogeneity in the study findings with a proportion of trials showing no effect of topiramate.
- **Precision:** Imprecise. Confidence intervals for studies cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** Unclear. No dose-response relationship studies were done.
- **Confounding factors (including likely direction of effect):** Unclear. One study suggests a possible effect of genetic polymorphisms on treatment response, which could confound study interpretation.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Low to Medium. A number of RCTs have been conducted, with low to high risk of bias. Several of the RCTs are funded by governmental agencies. Other studies show inconsistent findings or had high rates of attrition.

Harms of topiramate

Studies of topiramate in other disorders have reported a number of treatment related side effects. In the studies of topiramate for AUD that were included in the AHRQ report (Jonas et al., 2014), the most notable side effects of topiramate as compared to placebo were cognitive dysfunction and numbness/tingling/paresthesias. In the study of Likhitsathian et al. (2013), parethesias were more common in the topiramate group as compared to placebo (45.3% vs. 17%). Kampman et al. (2013) also found a greater frequency of paresthesias in topiramate treated subjects as compared to placebo treated subjects (20% vs. 3%). Knapp et al. (2015) also noted paresthesias in 19% of topiramate subjects and erectile dysfunction in 14% of topiramate subjects. In addition, Knapp et al. (2015) found a significant effect of topiramate on the mental slowing subscale of the A-B Neurotoxicity Scales relative to placebo (P = 0.008). Batki et al. (2014) found no significant differences in side effects between topiramate and placebo treated subjects.

Table B-18. Results of meta-analyses and risk difference calculations for adverse events: topiramate compared with placebo

Outcome	N trials	N subjects	RD	95% CI	I^2	SOE
Withdrawal due to adverse events	2	521	0.06	-0.12 to 0.25	93.4%	Low
Withdrawal due to adverse events—SA	3	599	0.06	-0.06 to 0.18	86.9%	
Anorexia	1	371	0.13	0.06 to 0.20	NA	Insufficient
Cognitive dysfunction	2	521	0.08	0.01 to 0.16	38.5%	Moderate
Diarrhea	1	371	0.04	-0.03 to 0.10	NA	Insufficient
Diarrhea—SA	2	477	0.00	-0.07 to 0.08	61.1%	
Dizziness	2	521	0.10	-0.01 to 0.22	65.0%	Low
Dizziness—SA	3	627	0.08	0.01 to 0.14	51.5%	

Headache	1	371	-0.08	-0.17 to 0.01	NA	Insufficient
Insomnia	1	371	0.03	-0.05 to 0.11	NA	Insufficient
Insomnia—SA	2	477	0.03	-0.03 to 0.10	0.0%	
Nausea	1	371	-0.06	-0.13 to 0.01	NA	Insufficient
Nausea—SA	2	477	-0.02	-0.11 to 0.06	62.0%	
Numbness/tingling/paresthesias	2	521	0.40	0.32 to 0.47	0.0%	Moderate
Numbness/tingling/paresthesias—SA	3	627	0.29	0.05 to 0.52	93.1%	
Taste abnormalities	1	371	0.18	0.11 to 0.25	NA	Insufficient

FROM Jonas et al., 2014 Table 31; Values for strength of evidence are from Table D-37

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

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

Grading of the overall supporting body of research evidence for harms of topiramate:

- **Magnitude of effect:** Moderate. When present, the magnitude of effect is moderate for cognitive dysfunction and for numbness/tingling/paresthesias.
- **Risk of bias:** High. Studies are RCTs of low to high bias based on their described randomization and blinding procedures and descriptions of study dropouts. However, methods for determining harms are not well-specified and there is potential for selective reporting of results.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. The doses of topiramate appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured common side effects and dropouts due to adverse events.
- **Consistency:** Consistent. For adverse events that showed a significant effect (cognitive dysfunction and numbness/tingling/paresthesias), the findings were consistent across trials.
- **Precision:** Precise. Confidence intervals for cognitive dysfunction and for numbness/tingling/paresthesias are relatively narrow.
- **Dose-response relationship:** Unknown. Dose response information on side effects was not well described.
- **Confounding factors (including likely direction of effect):** Possible and may reduce reported side effects. Given the high rates of attrition in some of the studies and the lack of systematic assessment of side effects, it is possible that attrition occurred due to unrecognized adverse events.
- **Publication bias:** Not identified. No publication bias was noted by the AHRQ review; however, they note that they were unable to assess for publication bias for early clinical trials (prior to clinicaltrials.gov).
- **Overall strength of research evidence:** Moderate. A number of RCTs have been conducted, but few have assessed adverse events in a systematic and pre-defined fashion. Many of the RCTs are funded by governmental agencies. Nevertheless, the studies are relatively consistent in reporting increased likelihood of cognitive dysfunction and numbness/tingling/paresthesias with topiramate, which is consistent with reported side effects in clinical trials for other indications.

3550 Data abstraction - topiramate

3551 **Table B-19. Studies related to topiramate**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Follow-up)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Baltieri, 2008; Baltieri, 2009	Design: DBRCT Setting: Outpatient Country: Brazil Funding: Govt	TOP to 200 - 400 (52); NTX 50 (49); PBO (54) Other Tx: Psychosocial 100%; AA recommended	12	ICD-10 alcohol dependence Mean Age: 44 to 45 y 29% Non-white 0% Female Other Dx: Tobacco use 66%	Time to first relapse was greater with topiramte than placebo 7.8 wks vs. 5.0 wks. Naltrexone was not significantly different from either of the other groups: 5.7 wks. Cumulative abstinence duration was also greater with topiramate (8.2 wks vs. NTX 6.6 wks vs. PBO: 5.6 wks) as was the mean number of weeks with heavy drinking but the rate of complete abstinence at study endpoint was comparable in the 3 groups. Smokers relapsed more rapidly than non-smokers. Attrition: 45	High
Batki, 2014	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	TOP to 300 (14); PBO (16) Other Tx: Medical management	12	DSM-IV alcohol dependence and PTSD Mean Age: NR y 47% Non-white 7% Female Other Dx: PTSD 100%; SUD 33%	Topiramate associated with 51% fewer drinking days but no effect on heavy drinking days. No difference in adverse events between groups or cognition at end of trial. PTSD severity was reduced in topiramate group.	Low
De Sousa, 2008	Design: OLRCT	TOP 150 (50); DIS 250 (50)	39	DSM-IV alcohol dependence	Disulfiram had greater mean time to first relapse than topiramate (133 days vs. 79 days,	High

	Setting: Inpatient and outpatient alcohol treatment center Country: India Funding: NR	Other Tx: Offered weekly supporting group psychotherapy		Exclusions: previous topiramate or disulfiram treatment Mean Age: 43 y 100% Non-white 0% Female Other Dx: NR	p = 0.0001) and a lower relapse rate at study endpoint (10% vs. 44%; p = 0.0001) Topiramate had less craving than disulfiram.	
Florez, 2008	Design: OLRCT Setting: Outpatient substance use disorders clinic Country: Spain Funding: NR	TOP up to 200 (51); NTX 50 (51) Other Tx: Therapy based on Relapse Prevention Model 100%	26	ICD-10 alcohol dependence Mean Age: 47 y 0% Non-white 15% Female Other Dx: Personality disorders; 27%	Topiramate and naltrexone were both effective but did not differ in efficacy as measured by a composite alcohol use metric.	High
Florez, 2011	Design: OLRCT Setting: Outpatient substance use disorders clinic Country: Spain Funding: NR	TOP 200 (91); NTX 50 (91) Other Tx: BRENDA 100%; At least monthly meeting with psychiatrist 100%	26	ICD-10 alcohol dependence Mean Age: 47 to 48 y % Non-white NR 15% Female Other Dx: Personality disorders 23%	At 3 and 6 months, patients with topiramate reported lower scores than those with naltrexone on craving and alcohol related measures. Disability related measures were also less with topiramate at 6 months. Topiramate also was associated with fewer drinks per drinking day and fewer heavy drinking days at 3 and 6 months compared to naltrexone. The percentage of days abstinent and total drinking days were comparable for topiramate and naltrexone.	High
Johnson, 2003; Ma, 2006; Johnson, 2004a	Design: DBRCT Setting: 1 outpatient site Country: U.S. Funding: Ortho McNeil	TOP 25-300 (75); PBO (75) Other Tx: None	12	DSM-IV alcohol dependence Mean Age: 41 y % Non-white NR 28 to 40% Female	Drinks per drinking day: -1.2 (95%CI -2.023, -0.3777) Percent heavy drinking days: -14.9 (95%CI -22.556, -7.244)	Medium

				Other Dx: 0%		
Johnson, 2004a	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	TOP 25-300 (75); PBO (75) Other Tx: Medication compliance management	12	DSM-IV alcohol dependence Abstinence not required at study entry Mean Age: 41.5 y 36% Non-white 29% Female Other Dx: NR	Topiramate had significant improvements on all drinking outcomes, including 27% fewer heavy drinking days vs. placebo (p<001) as well as improvements on reported abstinence and not seeking alcohol (OR=2.63; 95% CI, 1.52-4.53;p=.001), the odds of overall well-being (OR=2.17; 95% CI, 1.16-2.60;p=.01), overall life satisfaction (OR=2.28; 95%CI, 1.21-4.29;p=.01), and reduced harmful drinking consequences (OR=–0.07; 95% CI, –0.12 to –0.02,p=.01) Topiramate had more frequent adverse events compared to placebo: dizziness (28.0% vs. 10.7%; p=.01), paresthesia (57.3% vs. 18.7%; p<.001), psychomotor slowing (26.7% vs. 12.0%; p=.02), memory or concentration impairment (18.7% vs. 5.3%; p=.01), and weight loss (54.7% vs. 26.7%; P=.001). Attrition: 35/11	Low
Johnson, 2007; Johnson, 2008	Design: DBRCT Setting: 17 academic outpatient sites Country: U.S. Funding: Ortho McNeil	TOP 50-300 , mean 171 (183) ; PBO (188) Other Tx: BBCET 100%	14	DSM-IV alcohol dependence Exclusions: >4 unsuccessful inpatient treatment attempts Mean Age: 47 to 48 y 15 % Non-white 26 to 28% Female Other Dx: NR	Drinks per drinking day: -0.93 (95%CI -1.986, 0.126) Percent drinking days: -8.5 (95%CI -15.88, -1.12) Percent heavy drinking days: -8 (95%CI -15.919, -0.081) Attrition: 31%; 6% lost to follow-up/15%; 4% lost to follow-up	Low
Kampman, 2013	Design: DBRCT Setting: Outpatient Country: U.S.	TOP to 300 (83); PBO (87) Other Tx: Individual cognitive behavioral	13	In 30 day period in past 90 days had at least 48/60 drinks (women/men) with 2 or more heavy drinking days	No difference in weekly percent days drinking, weekly percent days heavy drinking and mean drinks per drinking day.	Low

	Funding: Govt	coping skills (Project MATCH)		DSM-IV cocaine dependence Mean Age: 44 y 83% Non-white 21% Female Other Dx: Cocaine dependence 100%	Paresthesias occurred in 20% of topiramate treated subjects and 3% of placebo subjects. Attrition: 59/12 favoring TOP	
Knapp, 2015	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	TOP 300 (21); Levetiracetam 2000 (21); Zonisamide 400 (19); PBO (24) Other Tx: Brief Behavioral Compliance Enhancement Treatment	14	DSM-IV alcohol dependence Mean Age: 47 y 9% Non-white 43.5% Female Other Dx: NR	Significant treatment effects were seen for weekly percent days drinking (P < 0.0001), percent days heavy drinking (P < 0.0001), and drinks consumed per day (P = 0.0007) for topiramate as compared to placebo. Significant effect of topiramate on the mental slowing subscale of A-B Neurotoxicity Scales (p = 0.008) Paresthesias (19%) and erectile dysfunction (14%) more common with topiramate.	Medium
Kranzler, 2014	Design: DBRCT Setting: Outpatient Country: U.S. Funding: VA	TOP to 200 (67); PBO (71) Other Tx: Medical management	12	Average weekly use of standard drinks > 23 for men and >17 for women; goal of reducing but not abstaining from alcohol; majority with DSM-IV alcohol dependence Mean Age: 51.1 y 12% Non-white 38% Female Other Dx: Lifetime MDD 19%	Topiramate was associated with a larger and more rapid decrease in heavy drinking and days with drinking. At end of treatment, topiramate group were more likely to have abstained from alcohol use (OR=2.57; 95% CI=1.13–5.84) and have no heavy drinking days (35.8% vs. 16.9% with placebo, odds ratio=2.75, 95% CI=1.24–6.10). Topiramate subjects reported significantly greater rates of adverse events, specifically numbness/tingling, change in taste, loss of appetite, weight loss, difficulty concentrating, and difficulty with memory.	Low

Likhitsathian, 2013	Design: DBRCT Setting: Outpatient Country: Thailand Funding: Govt	TOP up to mean dose 260 (53); PBO (53) Other Tx: MET and medical management	12	At least 1 of 4 weeks prior to admission with more than 34 standard drinks per week Mean Age: 41.5 y % Non-white NR 0% Female Other Dx: NR	Both groups had reduced drinking but no difference in heavy drinking days or time to first heavy drinking day between groups. Paresthesias were more common with topiramate (45.3% vs. 17%)	Medium
Narayana, 2008	Design: Prospective cohort Setting: Military, outpatient Country: India Funding: NR	ACA 1,332 to 1,998 (28); NTX 50 (26); TOP 100 to 125 (38) Other Tx: Various psycho-therapies were offered	52	ICD-10 alcohol dependence Mean Age: 38 y 100% Non-white 0% Female Other Dx: NR	Topiramate (76.3%) was significantly more effective (p<0.01) in sustaining abstinence, though 57.7% naltrexone and 60.70% acamprosate maintained complete abstinence. 7 topiramate subjects (18.4%) reported decreased relapses compared to 8 naltrexone (30.8%) and 9 acamprosate (32.1%) subjects.	High
Rubio, 2009	Design: DBRCT Setting: Outpatient Country: Spain Funding: Govt	TOP 250 (31); PBO (32)[a] Other Tx: Supportive group therapy offered	12	DSM-IV alcohol dependence Mean Age: 42 y % Non-white NR 0% Female Other Dx: NR	Drinks per drinking day: -2.3 (95%CI -4.715, 0.115) Percent drinking days: -14.9 (95%CI -30.07, 0.27) Percent heavy drinking days: -17.6 (95%CI -30.565, -4.635)	High

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Benefits of Gabapentin

The AHRQ review (Jonas et al., 2014) did not include any studies with a primary focus on gabapentin. In one included study (Anton et al., 2011), gabapentin was added in one treatment arm as an adjunct to naltrexone during the initial 6 weeks of the trial and was associated with improved outcomes at 6 weeks but not at the end of the trial.

A government-funded low risk of bias, double-blind randomized controlled trial (Mason et al., 2014) compared gabapentin at 900 mg/d (N=54) and 1800 mg/d (N=47) to placebo (N=49). The primary study outcomes, which were rate of complete abstinence (chi sq = 4.19; P = .04) and rate of no heavy drinking (chi sq = 5.39; P = .02), increased linearly with the dose of gabapentin. Sustained 12-week abstinence was 4.1% (95%CI, 1.1%-13.7%) with placebo, 11.1% (95%CI, 5.2%-22.2%) with 900 mg/d of gabapentin and 17.0% (95% CI, 8.9% -30.1%; NNT=8) with 1800 mg/d gabapentin. Corresponding rates of no heavy drinking were 22.5% (95% CI, 13.6%-37.2%), 29.6% (95%CI, 19.1%-42.8%), and 44.7% (95% CI, 31.4%-58.8%; NNT=5), respectively. Significant dose dependent reductions were also noted in the pre-specified secondary outcomes: alcohol craving, sleep, and depression. For subjects who completed the trial, rates of complete abstinence, drinks per week and number of heavy drinking days per week were sustained at 24-week follow-up. The most frequent adverse events were fatigue, insomnia, and headache and rates of these side effects did not differ among the three study arms. Insufficient information was available on side effects of gabapentin to grade the overall supporting body of research evidence for harms.

Grading of the overall supporting body of research evidence for efficacy of gabapentin:

- **Magnitude of effect:** Moderate. When present for specific outcomes, the magnitude of the effect is moderate.
- **Risk of bias:** Low. One large RCT accounts for the preponderance of findings and has a low risk of bias based on the described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from North America. The doses of gabapentin are representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and heavy drinking rates as well as measures of alcohol consumption.
- **Consistency:** Not applicable. Data are predominantly from a single study.
- **Precision:** Imprecise. Confidence intervals for some outcomes cross the threshold for clinically significant benefit of the intervention.
- **Dose-response relationship:** Present. Linear increases in efficacy are noted with increases in gabapentin dose for multiple outcomes.
- **Confounding factors (including likely direction of effect):** Not identified.
- **Publication bias:** Not identified.
- **Overall strength of research evidence:** Low to Moderate. Findings are predominantly from a single study with a low risk of bias, a large sample size and a significant dose-response relationship.

3591 Data abstraction - gabapentin

3592 **Table B-20. Studies related to gabapentin**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Follow-up)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Mason, 2014	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt; Meds	Gabapentin 900 (54); Gabapentin 1800 (47); PBO (49) Other Tx: Manual guided weekly counseling	12	DSM IV alcohol dependence Mean Age: 44.5 y 19% Non-white 43% Female Other Dx: 0%	Linear increase with gabapentin dose of rate of complete abstinence (P = .04), rate of no heavy drinking (P = .02), sustained 12-week abstinence (17.0% with NNT=8 for 1800 mg/d) and rates of no heavy drinking with placebo (44.7% NNT=5 for 1800 mg/d). Adverse events did not differ among groups with the predominant side effects of fatigue (23%), insomnia (18%) and headache (14%).	Low

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Benefits of Ondansetron

One large double-blind placebo-controlled trial was not included in the AHRQ review (Jonas et al., 2014) because the period of active treatment was 11 weeks. This trial randomly assigned individuals with DSM-IIIR alcoholism to receive ondansetron, 1 mcg/kg (n = 67), 4 mcg/kg (n = 77), or 16 mcg/kg (n = 71) twice per day; or identical placebo (n = 56) in addition to weekly standardized group cognitive behavioral therapy (Johnson et al., 2000). Data analysis was stratified according to the age of onset of alcoholism and significant effects of ondansetron (fewer drinks per day, fewer drinks per drinking day) were noted in those with early-onset alcoholism as compared to placebo. However, the same benefits were not seen for individuals with late-onset alcoholism. In addition, rates of attrition were high and no consistent dose response relationship was noted. Ondansetron was noted to be well-tolerated with minimal difference in side effects between ondansetron and placebo treated patients. A subsequent large study (N=283) using a dose of 4 mcg/kg ondansetron compared to placebo suggests that serotonin-related genotype may predict response (Johnson et al., 2013) although these results require further replication.

In a Brazilian study of ondansetron that was rated as having a high risk of bias (Corrêa Filho et al., 2013), subjects (total N=102) were randomly assigned to ondansetron (16 mg/day) or placebo. There was no difference in the percent of drinking days between the groups but the percent of heavy drinking days was less in the ondansetron group as compared to placebo (8% vs. 12%, p=0.02).

Insufficient information was available on side effects of gabapentin to grade the overall supporting body of research evidence for harms.

Grading of the overall supporting body of research evidence for efficacy of ondansetron:

- **Magnitude of effect:** Weak. If an effect is present, it seems to occur predominantly in individuals with early-onset AUD.
- **Risk of bias:** High. Studies are RCTs of medium to high risk of bias based on their described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all involve individuals with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. The studies include subjects from around the world, including North America. Typically, ondansetron is used on a short-term basis rather than a chronic basis but the doses appear consistent with typical doses used in treating nausea or vomiting.
- **Directness:** Direct. Studies measured outcomes related to alcohol consumption.
- **Consistency:** Inconsistent. There was inconsistency in the findings at different doses for the subjects overall.
- **Precision:** Not possible to determine.
- **Dose-response relationship:** Not present. Intermediate doses showed greater benefit for some of the subgroups than higher doses of ondansetron.
- **Confounding factors (including likely direction of effect):** Unclear. Some studies suggest a possible effect of genetic polymorphisms on treatment response, which could confound study interpretation.

- **Publication bias:** Not identified.
- **Overall strength of research evidence:** Low. The studies of ondansetron have medium to high risk of bias, attrition, and inconsistent findings according to patient subgroups.

3635 Data abstraction - ondansetron

3636 **Table B-21. Studies related to ondansetron**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Follow-up)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
CorrêaFilho, 2013	Design: DBRCT Setting: University-based outpatient substance use disorder treatment center Country: Brazil Funding: Govt	Ondansetron 16 (50); PBO (52) Other Tx: Standardized brief cognitive behavioral intervention	12	ICD-10 alcohol dependence Exclusions: current use of disulfiram, naltrexone, or acamprosate Mean Age: 42 to 44 y 60 to 73% Non-white 0% Female Other Dx: NR	Significant effect of ondansetron on percent heavy drinking days (7.8% versus 11.7%) but no effect for percent abstinent days (76.1% placebo vs. 88.6% ondansetron), percent heavy drinking days (9.5% placebo vs. 5.9% for ondansetron) or average drinks consumed per day (1.09 placebo vs. 0.66 for ondansetron) in adherent subjects.. Attrition: 50/ 16	High
Johnson, 2000	Design: DBRCT with randomization balanced for age of onset, sex, and average drinks per day at intake Setting: University-based outpatient program Country: U.S. Funding: Govt, Meds	Ondansetron 1 mcg/kg BID (67); 4 mcg/kg BID (67); 16 mcg/kg BID (67); PBO (56) Other Tx: Group cognitive behavioral therapy	11 after 1 wk placebo lead-in	Score of >5 on MAST; >2 drinks per day; no mandate for abstinence before study initiation Mean Age: 40.6 y 21.4% Non-white 30% Female Other Dx: NR	In individuals with early-onset alcoholism treated with ondansetron (1, 4, and 16 mcg/kg BID) versus placebo, drinks per day (1.89, 1.56, and 1.87 vs. 3.30; P = .03, P = .01, and P = .02, respectively) and drinks per drinking day (4.75, 4.28, and 5.18 vs. 6.90; P = .03, P = .004, and P = .03, respectively) were reduced. With ondansetron 4 mcg/kg BID versus placebo there was a greater percentage of days abstinent (70.10 vs. 50.20; P = .02) and total days abstinent per study week (6.74 vs. 5.92; P = .03). The mean log CDT ratio with ondansetron 1 and 4 mcg/kg BID was reduced compared with placebo (-0.17 and -0.19 vs. 0.12; P = .03 and P = .01,	Low

					respectively) with effect sizes of 0.55 and 0.58, respectively. Adverse events were minor and similar in proportions. Attrition: 42/2-6	
Johnson, 2011	Design: DBRCT with randomization balanced by 5'-HTTLPR genotype Setting: University-based outpatient program Country: U.S. Funding: Govt	Ondansetron 4 mcg/kg BID (150); PBO (143) Other Tx: Group cognitive behavioral therapy	11 after 1 wk placebo lead-in	Score of >8 on AUDIT; no mandate for abstinence before study initiation Mean Age: 44.5 y 15% Non-white 27% Female Other Dx: Nicotine use 53%; Cannabis use 18%; Cocaine use 5%	In subjects with the LL genotype of 5'-HTTLPR, ondansetron reduced drinks per drinking day and increased percentage of days abstinent (mean difference versus placebo, −1.62; 95% CI −2.79 to −0.46; p=0.007; effect size=0.56, and 11.27; 95% CI 1.55 to 21.00; p=0.023; effect size=0.41 with mean difference compared with LS/SS subjects, −1.53; 95% CI −2.59 to −0.47; p=0.005; effect size=0.47, and 9.73; 95% CI 0.95 to 18.50; p=0.03; effect size=0.29). Attrition: 33/7	Low

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

In terms of other medications, the AHRQ review (Jonas et al., 2014) found limited evidence to support the efficacy of valproic acid and insufficient evidence to support the efficacy of other medications. Although additional trials have been conducted for some of these medications (aripiprazole, atomoxetine, baclofen, buspirone, olanzapine, prazocin, quetiapine, risperidone, varenicline) since publication of the AHRQ review, none of the medications had a large enough evidence base to warrant inclusion in a guideline statement.

Recommendations Against Use of Specific Medications

Statement 12:

APA recommends (1B) that antidepressant medications not be used for treatment of alcohol use disorder unless there is evidence of a co-occurring disorder for which an antidepressant is an indicated treatment.

Evidence for this recommendation comes from a number studies of serotonin reuptake inhibitors and tricyclic antidepressants that assessed alcohol-related outcomes in individuals with alcohol dependence and a depressive or anxiety disorder (Jonas et al., 2014). Based on a substantial number of trials that directly assess the efficacy of antidepressant medications in treating AUD, the strength of research evidence is rated as moderate.

The AHRQ review (Jonas et al., 2014) included 7 trials comparing placebo to sertraline in doses of 50-200 mg per day and treatment durations of 12- 26 weeks. Of the 7 studies, 5 were done in the U.S., 3 included only individuals with major depressive disorder and alcohol dependence and 1 included individuals with PTSD and alcohol dependence. Meta-analysis did not show a benefit of sertraline on the alcohol-related outcomes and for the outcome of percent of heavy drinking days the comparison favored placebo (Low strength of research evidence; WMD: 1.85 (0.70 to 3.0)). An additional study (total N=170) compared placebo to naltrexone alone, sertraline alone or the combination of naltrexone and sertraline and reported no difference between sertraline and placebo conditions on abstinence rates. The combination of naltrexone plus sertraline showed greater abstinence rates than either treatment alone (p=0.001) as well as a longer time to relapse to heavy drinking. A subsequent double-blind randomized controlled trial of sertraline 200 mg/d (N=32) vs. placebo (N=37) was conducted in individuals with co-occurring PTSD and alcohol dependence (Pettinatti et al., 2010). Treatment in this low risk of bias trial also included 12 sessions of a "Seeking Safety" intervention. At the end of treatment, at 6-month follow-up and at 12-month follow-up, both sertraline and placebo subjects showed a decreased number of drinks per drinking day, a decrease in heavy drinking days and an increase in seven day abstinence rate. PTSD symptoms showed greater improvement with sertraline than placebo, but there was no specific effect of sertraline treatment as compared to placebo on alcohol related outcomes.

The AHRQ review included 2 trials (Naranjo et al., 1995; Tiihonen et al., 1996) of 12-13 weeks duration that compared citalopram 40 mg per day with placebo. Both trials were rated as having a high risk of bias and neither trial showed an effect of citalopram on drinking related outcomes. A subsequent medium risk of bias 12-week trial of citalopram 40 mg/d (N=138) versus placebo (N=127) found worse

outcomes with citalopram than placebo in terms of the percentage decrease in the frequency of alcohol consumption (p = 0.016), the percentage decrease in the quantity of alcohol consumed per drinking day (p = 0.025), the average number of heavy drinking days (p = 0.007), the drinks per drinking day (p = 0.03), and the money spent on alcohol (p = 0.041) (Charney et al., 2015). When individuals with depression were compared to those without depression, the findings in both subgroups were consistent with findings for the overall sample. In another 12-week study in which all subjects (total N=138) received naltrexone (up to 100 mg/day), there was no significant difference on alcohol use or depression-related outcomes between subjects who were randomly assigned to citalopram (up to 60 mg/day) and those assigned to placebo (Adamson et al., 2015).

The AHRQ review (Jonas et al., 2014) included 3 U.S. trials lasting 12-15 weeks and comparing placebo to fluoxetine in doses from 20-60 mg per day (Cornelius et al., 1995; Kabel et al., 1996; Kranzler et al., 1995). In one of the trials, in which all subjects (N=51) had major depressive disorder, subjects treated with fluoxetine had fewer drinking days (WMD, -11.6; 95% CI, -22.7 to -0.5) and fewer heavy drinking days (4.8 versus 16, p=0.04) than those who received placebo (Cornelius et al., 1995). When the two medium risk of bias trials were combined (Cornelius et al., 1995; Kranzler et al., 1995), meta-analysis found no difference between fluoxetine and placebo in drinking days (WMD, -3.2; 95% CI, -18.2 to 11.9) or heavy drinking days (WMD, -1.2; 95% CI, -4.6 to 2.2).

In a single European trial of fluvoxamine 100-300 mg/day as compared with placebo, there was no difference at 12 weeks of treatment or at 52 weeks of follow-up in the percent of subjects who had returned to drinking or the percent who returned to heavy drinking (Chick et al., 19942004). At 12 weeks, fluvoxamine treated patients had more drinking days in the prior month than placebo treated patients, but the groups did not differ on this outcome at 52 weeks of follow-up.

One randomized trial compared paroxetine (10 to 60 mg/d, mean dose 45 mg/d) to placebo in individuals with social anxiety disorder of whom 79% of 42 subjects also had a co-occurring diagnosis of alcohol dependence (Book et al., 2008; Thomas et al., 2008). After 16 weeks (12 weeks at final paroxetine dose), there was no difference in the mean number of drinks per drinking day or the proportion of drinking days or heavy drinking days for paroxetine-treated patients as compared to placebo-treated patients. In an additional high risk of bias trial (Petrakis et al., 2012), paroxetine with and without naltrexone was compared to desipramine with and without naltrexone in subjects with co-occurring alcohol dependence and PTSD. Individuals who received paroxetine had more heavy drinking days (p=0.009) and drinks per drinking day (p=0.027) than those who received desipramine.

Another U.S. study with a medium risk of bias compared desipramine (median dose=200 mg/day) with placebo. In this trial, 39% also had a diagnosis of depression (Mason et al., 1996). Although 12% of desipramine treated patients returned to heavy drinking as compared to 32% of placebo treated patients, this difference was not statistically significant. A medium risk of bias study of imipramine 50-300 mg/day (mean dose=262 mg/day) as compared to placebo in individuals with depression and alcohol dependence found no significant difference between imipramine and placebo groups on percent return to any drinking, percent with heavy drinking, or number of drinks per drinking day. (McGrath et al., 1996)

Grading of the overall supporting body of research evidence for efficacy of antidepressants:

- **Magnitude of effect:** None. When differences were present for specific outcomes, the magnitude of the effect is small and the effect favored placebo.
- **Risk of bias:** Medium. Studies are RCTs of medium to high bias based on their described randomization and blinding procedures and descriptions of study dropouts.
- **Applicability:** The included trials all have a substantial proportion of subjects with AUD, either by prior diagnostic criteria or other evidence of harmful levels of drinking. In most of the studies, subjects also had a co-occurring diagnosis of depression or an anxiety disorder. The studies include subjects from around the world, including North America. The doses of antidepressant medications appear to be representative of outpatient clinical practice.
- **Directness:** Direct. Studies measured abstinence and heavy drinking rates as well as measures of alcohol consumption. Most studies also included measures related to symptoms of co-occurring disorders.
- **Consistency:** Consistent. Although meta-analysis was not conducted across all studies of antidepressant medications, the main findings of the studies were consistent.
- **Precision:** Not able to assess, since confidence intervals were not calculated for the majority of the studies.
- **Dose-response relationship:** Unclear. Studies typically adjusted medication doses based upon clinical response.
- **Confounding factors (including likely direction of effect):** Not identified.
- **Publication bias:** Not identified.
- **Overall strength of research evidence:** Moderate. A number of RCTs have been conducted, most of which have medium to high risk of bias and moderate sample sizes. Many of the RCTs are funded by governmental agencies. Despite the inclusion of different antidepressants of different classes and subjects with different co-occurring conditions, the studies are consistent in showing no effect or a slightly detrimental effect of antidepressant medication on alcohol-related outcomes.

3741 Data abstraction - antidepressants

3742 **Table B-22. Studies related to antidepressants**

Author, Year; Trial Name	Study characteristics	Treatment administered including study arm, dose (mg/day) and sample size (N) and Co-intervention	Rx Duration, Weeks (Follow-up)	Sample characteristics including diagnostic inclusions and major exclusions	Outcome measures, main results and percent attrition (overall/differential)	Risk of Bias
Charney, 2015	Design: DBRCT Setting: Outpatient Country: Canada Funding: Govt	Citalopram 40 (138); PBO (127) Other Tx: Weekly individual and group psychotherapy	12	DSM-IV alcohol abuse or dependence Mean Age: 45.4 y % Non-white NR 30% Female Other Dx: Depression only 22%; Anxiety only 27%; Mixed anxiety and depression 38%; personality disorder 42%	Citalopram was associated with worse outcomes than placebo on frequency of alcohol consumption (p = 0.016); quantity of alcohol consumed per drinking day (p = 0.025); average number of heavy drinking days (p = 0.007); drinks per drinking day (p = 0.03), and money spent on alcohol (p = 0.041). Median survival time to first relapse was not significantly different with treatment in depressed or non-depressed subjects. Attrition: 47	Medium
Naranjo, 1995	Design: DBRCT Setting: Outpatient research center Country: Canada Funding: Govt, Lundbexk A/S	Citalopram 40 (53); PBO (46) Other Tx: Brief psychosocial intervention 100%	12 (20)	Mild to moderate alcohol dependence with at least 28 drinks per week Mean Age: 45 y % Non-white NR 44% Female Other Dx: NR	Both treatment groups showed a significant decrease in alcohol intake (p<0.001) (35.1% citalopram vs. 38.8% placebo). Citalopram had a significant initial effect; reduced alcohol intake during the first week of the treatment period by 47.9% from baseline compared to 26.1% (p<0.01) decrease in the placebo group. During weeks 2-12, the effects of citalopram and placebo were similar; reductions in alcohol intake were 33.4% and 40.5%, respectively. Percentage of abstinent days in the citalopram group increased from baseline to 27.3% ± 3.6 (p< 0.001). The placebo group increased their	High

					abstinent days from 7.1% ±2.3 during baseline to 23.5% ± 3.1 (p< 0.001). Drinks per drinking day decreased from baseline for citalopram (from 7.6 ± 0.6 to 5.4 ±0.4, p< 0.001) and placebo (from 6.4 ±0.4 to 4.7 ± 0.4, p< 0.001). Th Attrition: 37/ 9	
Tiihonen, 1996	Design: DBRCT Setting: Outpatient; community-based alcohol rehabilitation center Country: Finland Funding: Lundbeck	Citalopram 40 (31); PBO (31) Other Tx: Supportive psychotherapy intervention 100%	13 (17)	DSM-III-R alcohol dependence Mean Age: 45 to 47 y % Non-white NR 0% Female Other Dx: 0%	The citalopram group reported better outcomes than placebo in dropout rates, GGT changes, and the reports of patients and relatives: significant differences in dropout rates (32% vs. 58%, p < 0.05) and in relatives' reports (26% vs. 7%, p < 0.05). Attrition: 45/26	High
Mason, 1996	Design: DBRCT Setting: Psychiatry outpatient departments at 2 urban medical centers Country: U.S. Funding: Govt	DMI median 200 (37); PBO (34) Other Tx: AA and other psychosocial treatments encouraged	26	DSM-III-R alcohol dependence Mean Age: Median=40 y 38% Non-white 17% Female Other Dx: Depression 39%	Kaplan-Meier survival curves showed a significant difference between placebo and desipramine in time to relapse (p=.03). There were more relapses on placebo than on desipramine among depressed patients (40% vs. 8.3%) and among nondepressed patients (26.6% vs. 14.3%), but the differences were not statistically significant. Patients who relapsed had more severe alcohol dependence than those who did not (mean±SD, 24.46±8.8 and 18.7±6.9, respectively) Attrition: 52	High
Petrakis, 2012	Design: DBRCT	DMI 200 + PBO (24)[b]; Paroxetine 40 + PBO (20); DMI 200 + NTX 50	12	DSM-IV alcohol dependence and PTSD Exclusions: psychosis	Compared to paroxetine, desipramine significantly reduced the percentage of heavy drinking days (F1.844 = 7.22, p = 0.009) and	High

	Setting: Outpatient; multiple psychiatric centers, primarily VA Country: U.S. Funding: VA	(22); Paroxetine 40 + NTX 50 (22) Other Tx: Clinical management; compliance enhancement therapy 100%		Mean Age: 47 y 25% Non-white 9% Female Other Dx: PTSD 100%	drinks per drinking days (F1.84 = 5.04, p = 0.027). There was a significant interaction for time by desipramine/paroxetine treatment on drinks per week (ATS6.82 = 2.46, p= 0.018): desipramine subjects had a greater reduction in their drinking over time compared with paroxetine subjects. Naltrexone, compared to placebo, significantly decreased craving (F1582.0 = 6.39, p = 0.012; naltrexone = 19.88 (SD = 12.89) and placebo = 21.1 (SD =12.89) at baseline vs. naltrexone = 6.7 (SD = 14.07) and placebo = 8.3 (SD = 13.38) at endpoint). GGT declined more in the desipramine treated participants (F1229.5 = 5.08, p = 0.02; desipramine baseline = 55.2, paroxetine baseline =86.4; desipramine week 4 = 48.7, paroxetine week 4 = 46.1; desipramine week 8 =41.7, paroxetine week 8 =47.1; desipramine week 12 =37.5, paroxetine week 12 = 57.1). Attrition: 44.3/20 favoring DMI	
Cornelius, 1997; Cornelius, 1995	Design: DBRCT Setting: Inpatient psychiatric institute Country: U.S. Funding: Govt	Fluoxetine 20-40 (25); PBO (26) Other Tx: Usual care: psychotherapy 100%	12	DSM-III-R alcohol dependence and major depression Mean Age: 35 y 53% Non-white 49% Female Other Dx: MDD 100%	Drinks per drinking day: -3 (95%CI -5.4, -0.6) Percent drinking days: -11.6 (95%CI -22.71, -0.49) Return to any drinking: -0.13 (95%CI -0.35, 0.1)	Medium
Kabel, 1996	Design: DBRCT	Fluoxetine 20-60 (15); PBO (13)	15	Alcohol dependence Mean Age: 47 y	Return to any drinking: 0.16 (95%CI -0.2, 0.51) Attrition: 42/10	High

	Setting: Inpatient substance abuse treatment Country: U.S. Funding: Govt	Other Tx: NR; an average of 4 DSM-III-R personality disorders		46% Non-white 0% Female Other Dx: Cocaine use 14%		
Kranzler, 1995	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	Fluoxetine 20-60, mean 47 (51); PBO (50) Other Tx: Group psychotherapy 79%; Individual psychotherapy 21%	12 (38)	DSM-III-R alcohol dependence Mean Age: 40 y 5% Non-white 20% Female Other Dx: Major depression 14%	Drinks per drinking day: 0.5 (95%CI -1.61, 2.61) Percent drinking days: 3.8 (95%CI -2.08, 9.68)	Medium
Chick, 2004	Design: DBRCT Setting: 10 outpatient sites Country: U.K., Ireland, Austria, Switzerland Funding: Solvay-Duphar	Fluvoxamine 100-300 (261); PBO (260) Other Tx: Psychosocial treatment	52	DSM-III-R alcohol dependence Exclusions: not wishing to aim for total abstinence Mean Age: 42 (19-72) y % Non-white NR 35% Female Other Dx: NR	No differences in abstinence at week 52 (fluvoxamine: n = 75, 55% vs. placebo: n = 117, 63%; p = 0.24 by LOCF analysis). At week 12, the percentage of days not drinking since the last assessment was 69% for fluvoxamine and 77% for placebo (p = 0.009). The mean dependence severity was more favorable for the placebo group (p = 0.029) Attrition: 64% non-completers; 21% lost to follow-up	Medium
McGrath, 1996	Design: DBRCT Setting: University-based depression research clinic Country: U.S.	IMI 50-300; mean 262 (36); PBO (33) Other Tx: Weekly relapse prevention psychotherapy	12	DSM-III-R alcohol dependence or abuse and with major depression, dysthymia, or depressive disorder not otherwise specified	Clinical Global Impression Scale (CGI) response to imipramine (52%; CI, 33% to 70%) was significantly better than response to placebo (21%; CI, 9% to 38%). Patients receiving imipramine were significantly less depressed than patients	Medium

	Funding: Govt		Exclusions: history of mania Mean Age: 37 imipramine, 11 placebo[a] y 17 to 22% Non-white 49 to 53% Female Other Dx: MDD 71 to 72%; Bipolar 11 to 12%; Atypical depression 70 to 72%; Other substance abuse 16%	taking placebo by the Hamilton Depression Rating Scale (HAM-D). IMI and placebo did not differ in rates of alcohol abstinence in either the last week (44 vs. 22%) or the last 4 weeks (31 vs. 21%) and did not differ in percent of days drinking, percent days of heavy drinking or standard drinks per drinking day.	
Book, 2008; Thomas, 2008	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt, Meds	Paroxetine titration over 4 16 weeks 10-60; avg. 45 (20); PBO (22) Other Tx: MM 100%; Optional one individual therapy session 67%	DSM-IV alcohol use disorder (abuse: 21% and dependence: 79%) and social anxiety disorder, generalized type Mean Age: 28 to 30 y 0 to 18% Non-white 45 to 50% Female Other Dx: Social anxiety disorder 100%;; MDD ~10%	Drinking outcomes did not change with paroxetine or placebo. Liebowitz Social Anxiety Scale scores were improved with paroxetine vs. placebo by week 7 through week 16. Attrition: 37/NR	Medium
Brady, 2005	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Meds	SERT 150 (49); PBO (45) 12 Other Tx: CBT 100%	DSM-IV alcohol dependence and current PTSD in response to civilian trauma Mean Age: 37 y % Non-white NR 43 to 49% Female Other Dx: PTSD 100%; Depressive disorder 51%; Anxiety disorder 38%	Percent heavy drinking days: 1.8 (95%CI 0.65, 2.95) Drinks per drinking day: 0.5 (95%CI -2.42, 3.42)	Medium

Coskunol, 2002	Design: DBRCT Setting: Inpatient (mean 1 month) followed by 6 months outpatient; substance abuse treatment unit Country: Turkey Funding: Pfizer	SERT 100 (30); PBO (29) Other Tx: Thiamine 500 mg per day 100%; Pyridoxone 500 mg per day 100%; AA during inpatient 100%	26	DSM-III-R alcohol dependence Mean Age: 44 y % Non-white NR 0% Female Other Dx: 0	Return to heavy drinking: -0.19 (95%CI -0.44, 0.06)	Medium
Gual, 2003	Design: DBRCT Setting: 1 outpatient site Country: Spain Funding: NR	SERT 50-150 (44); PBO (39) Other Tx: NR	24	DSM-IV and ICD-10 criteria for alcohol dependence and for major depression or dysthymia or both Mean Age: 47 y % Non-white NR 47% Female Other Dx: Depression/ dysthymia 100%	Percent drinking days: 0.6 (95%CI -46.17, 47.37) Return to heavy drinking: 0.09 (95%CI -0.1, 0.28) Attrition: 45 /2	Medium
Hien, 2015	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt	SERT 200 (32); PBO (37) Other Tx: "Seeking Safety" 12 sessions	12 (12)	DSM IV TR alcohol dependence or alcohol abuse with 2 heavy drinking days in past 90 days; additional inclusion criteria based on consumption patterns Co-occurring DSM-IV TR PTSD Mean Age: 42.2 y 59% Non-white 81% Female	Decreased number of drinks per drinking day, a decrease in heavy drinking days and an increase in seven day abstinence rate in both groups; no effect of sertraline. Seeking safety plus sertraline led to greater reduction in PTSD symptoms than seeking safety plus placebo (79% vs. 48%)	Low

				Other Dx: PTSD or subthreshold PTSD 100% Other SUD 55%		
Kranzler, 2011; Kranzler, 2012	Design: DBRCT Setting: Outpatient; university health center Country: U.S. Funding: Govt, Meds	SERT 50-200 (63); PBO (71) Other Tx: Coping skills training 100%	12 (26)	DSM-IV alcohol dependence Mean Age: 48 y 8% Non-white 19% Female Other Dx: Cannabis use disorder 17%; Cocaine use disorder 19%; Past MDD 21%	Percent heavy drinking days: 6.6 (95%CI -4.63, 17.83) Percent drinking days: 3.8 (95%CI -7.95, 15.55) Attrition: 38/12	Medium
Moak, 2003	Design: DBRCT Setting: 1 outpatient site Country: U.S. Funding: Govt, Meds	SERT 50-200 (38); PBO (44) Other Tx: CBT	12	Mild to moderate alcohol dependence or alcohol abuse and DSM-III-R major depressive episode or dysthymic disorder Exclusions: bipolar affective or psychotic disorder; treatment resistant depression Mean Age: 41 y 1% Non-white 39% Female Other Dx: Depression/ dysthymia 100%	Percent drinking days: 0 (95%CI -11.39, 11.39) Drinks per drinking day: -1.2 (95%CI -2.56, 0.16)	Medium
O'Malley, 2008	Design: DBRCT Setting: Alaskan outpatient site	NTX 50 (34); PBO (34); NTX 50 + Sertraline 100 (33)[a] Other Tx: MM 100%	16	DSM-IV alcohol dependence Mean Age: 40 y 70% Non-white	There was a statistically significant advantage of naltrexone over placebo but no additional benefit from the addition of sertraline to naltrexone on total abstinence (NX vs. PL p = 0.04, NX vs. NX-SER p = 0.56) or the	Medium

	Country: U.S. Funding: Govt, Meds		34% Female Other Dx: NR	percentage who reported a drinking related problem during treatment (NX vs. PL p =0.04, NX vs. NX + SER p = 0.85) Time to first heavy drinking day was longer, but not significantly greater for the naltrexone only group compared to placebo (NX vs. PL p =0.14, NX vs. NX + SER p = 0.84). Treatment efficacy was not dependent on the presence of an Asn40allele. Attrition: 33 /15	
Pettinati, 2001	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt, Meds	SERT 200 (50); PBO (50) 14 Other Tx: 12-step facilitation	DSM-III-R alcohol dependence Mean Age: 44 y 80% Non-white 48% Female Other Dx: Depression 47%	Percent drinking days: -1.27 (95%CI -11.59, 9.05) Attrition: 42/12	Medium
Pettinati, 2010; NA	Design: DBRCT Setting: Outpatient Country: U.S. Funding: Govt, Meds	SERT 200 (40); NTX 100 14 (49); PBO (39); SERT 200 + NTX 100 (42) *Other Tx:* CBT 100%	DSM-IV alcohol dependence and major depression Mean Age: 43 y 35% Non-white 38% Female Other Dx: Depression 100%	Sertraline vs. placebo – total abstinence: 27.5% abstinent vs. 23.1% Time (days) to relapse to heavy drinking: median 23 vs. 26; mean 39.9 vs. 41.7 Attrition: 43/6.5	Medium

Unless noted elsewhere subjects were excluded if they had contraindications for specific medications; were pregnant, breastfeeding or unreliable in using contraception; were receiving psychotropic medications; or had another substance use disorder (except nicotine dependence), other psychiatric conditions, suicidal or homicidal ideas or significant physical illness (including renal or hepatic disease).

Statement 13:

APA recommends (1C) that, in individuals with alcohol use disorder, benzodiazepines not be used unless treating acute alcohol withdrawal or unless a co-occurring disorder exists for which a benzodiazepine is an indicated treatment.

Evidence for this recommendation is indirect and based primarily on expert opinion. Consequently, the strength of research evidence is rated as low. The systematic review of the literature did not yield any references that dealt directly with the use of a benzodiazepine to treat AUD, except in the context of alcohol withdrawal. A Cochrane review of pharmacotherapy for co-occurring AUD and anxiety disorders also did not find any randomized trials of benzodiazepines for anxiety disorders in this population, although studies of naltrexone, acamprosate and disulfiram were excluded from the review (Ipser et al., 2015). One small open-label study (Bogenschutz et al., 2016) assessed use of lorazepam in combination with disulfiram and manual-based medical management in individuals with DSM-IV alcohol dependence and symptoms of anxiety. Subjects had reductions in anxiety, depression and craving and had no signs of misuse or dose escalations for lorazepam but two-thirds of the 41 subjects were no longer adherent to treatment at 16 weeks.

Statement 14:

APA recommends (1C) that, for pregnant or breastfeeding women with alcohol use disorder, pharmacologic treatments not be used unless treating acute alcohol withdrawal with benzodiazepines or unless a co-occurring disorder exists that warrants pharmacologic treatment.

Evidence for this recommendation is indirect and based upon data from case reports, registries, case control studies of birth outcomes and, in some instances, animal studies of teratogenecity and neurodevelopmental effects of medication exposure during pregnancy. Consequently, the strength of research evidence is rated as low. Additional evidence that was considered in making this recommendation was the relatively small effect sizes of these medications for treatment of AUD as discussed with Statements 9, 10, and 11.

Data in pregnant animals suggest a low risk for use of ondansetron, moderate risk for use of naltrexone, high risk for use of acamprosate and possible risks for use of gabapentin and topiramate (Briggs et al., 2015). For disulfiram, Briggs and colleagues (2015) note that there is no animal data available. Data for the use of these medications in pregnant women is limited (Briggs et al., 2015); however, an increased risk of malformation does appear to be associated with use of topiramate (Briggs et al., 2015; Weston et al., 2016; Alsaad et al., 2015; Tennis et al., 2015) but not gabapentin (Weston et al., 2016). No clustering of birth defects have been seen when disulfiram is taken by pregnant women, but samples have been small (Briggs et al., 2015). Risk of malformation also appears to be low with ondansetron use during pregnancy although findings on cardiac septal defects are inconsistent (Carstairs, 2016).

Little data is available on the use of these medications in breastfeeding women but there may be potential for toxicity with disulfiram and naltrexone (Sachs et al., 2013; Briggs et al., 2015) as well as topiramate (Briggs et al., 2015), whereas acamprosate, gabapentin, and ondansetron are noted to be "probably compatible" (Briggs et al., 2015) with breastfeeding.

Statement 15:

APA recommends (1B) that acamprosate not be used by patients who have severe renal impairment.

Evidence for this statement comes from a pharmacokinetic study (Sennesael J, 1992), which shows increases in terminal elimination half-life and peak plasma concentration with decreases in renal clearance of drug from plasma after a single dose of 666 mg of acamprosate. Individuals with moderate (creatinine clearance of 1.8-3.6 L/h/1.73m2) or severe (creatinine clearance of 0.3-1.74 L/h/1.73m2) renal impairment had a mean terminal elimination half-life of 33. 4 h and 46.6 h, respectively, as compared to 18.2 hours for healthy volunteers (with creatinine clearance of > 4.5 L/h/1.73m2). Peak plasma concentrations were 198 mcg/L for health volunteers as compared to 398 mcg/L and 813 mcg/L for individuals with moderate or severe renal impairment, respectively. Based upon the significant curvilinear relationship between renal impairment and pharmacokinetic properties, the overall strength of research evidence was viewed as moderate.

Statement 16:

APA recommends (1B) that, for individuals with mild-to-moderate renal impairment, acamprosate not be used as a first-line treatment and, if used, the dose of acamprosate be reduced compared with recommended doses in individuals with normal renal function.

Evidence for this statement also comes from a pharmacokinetic study (Sennesael J, 1992), as described in Statement 15 above. Evidence for reducing the dose of acamprosate, if it is used, comes from basic principles of pharmacokinetics.

Statement 17:

APA recommends (1C) that naltrexone not be used by patients who have acute hepatitis or hepatic failure.

Evidence for this recommendation is indirect and based primarily on early studies of other conditions (e.g., obesity, dementia) in which some patients had several fold elevations in hepatic transaminase levels with naltrexone treatment (Mitchell et al. 1987; Knopman and Hartman , 1986; Verebey and Mulé , 1986; Pfohl et al., 1986; Malcolm et al., 1985). No data is available for the specific conditions specified in this recommendation (i.e., acute hepatitis, hepatic failure) because individuals with these conditions were excluded from clinical trials. Consequently, the strength of research evidence is rated as low.

Subsequent to the approval of naltrexone for clinical use, the FDA removed the "black box" warning from the package labelling for naltrexone (Stoddard and Zummo, 2015). Studies suggested that elevations of hepatic enzymes in individuals treated with naltrexone occurred at about the same frequency as in individuals treated with placebo (Vagenas et al., 2014; Yen et al., 2006; Brewer and Wong, 2004; Lucey et al., 2008). In addition, a small study suggested that hepatic enzymes did not change and that reducing the dose of naltrexone was not needed in individuals with mild to moderate hepatic impairment (Turncliff et al., 2005).

Statement 18:

APA recommends (1C) that naltrexone not be used as a treatment for alcohol use disorder by individuals who use opioids or who have an anticipated need for opioids.

Evidence for this recommendation is indirect and consequently, the strength of research evidence is rated as low. Multiple studies have used opioid antagonists to hasten opioid discontinuation in individuals with an opioid use disorder (Gowing et al., 2009; Gowing et al., 2010). Although opioid antagonist administration was reliable in producing opioid withdrawal, the extent of any benefit was unclear and potential for complications was noted (Gowing et al., 2009; Gowing et al., 2010). These findings suggest that naltrexone not be given to individuals who are currently using opioids unless there is a clinically appropriate period of opioid abstinence before naltrexone initiation. Expert opinion is consistent with this recommendation. Clinical experience also suggests a need for adjustment to typical regimens for pain management in individuals who are receiving naltrexone (Vickers and Jolly, 2006; Chou et al., 2016a), due to the effects of naltrexone in blocking opioid receptors.

Treatment of Alcohol Use Disorder and Co-Occurring Conditions

Statement 19:

APA recommends (1C) that, in patients with alcohol use disorder and co-occurring opioid use disorder, naltrexone be prescribed to individuals who:

- **wish to abstain from opioid use and either abstain from or reduce alcohol use and**
- **who are able to abstain from opioid use for a clinically appropriate time prior to naltrexone initiation.**

Evidence for this statement is primarily indirect from research findings of naltrexone efficacy in AUD (see Statement 9) and separate studies of naltrexone in individuals with opioid use disorder. Consequently, the strength of research evidence is rated as low. Efficacy has been reported in several studies of long-acting injectable or implanted naltrexone (Sullivan et al., 2015; Syed and Keating, 2013; Krupitsky et al., 2013; Krupitsky et al., 2012; Krupitsky et al., 2011; Timko et al., 2016; Larney et al., 2014) with minimal responses to oral naltrexone (Minozzi et al., 2011), likely related to high percentages of attrition.

One double-blind placebo-controlled trial (Mannelli et al., 2011) randomly assigned individuals with opioid dependence who were undergoing a methadone taper to very-low-dose naltrexone (0.125 or 0.250 mg/day). Of the subjects, 79 of 174 also had problem drinking and this group had reduced withdrawal symptoms, less treatment discontinuation, and less resumption of alcohol use after treatment as compared to those who received placebo. However, the relevance of this study to the guideline statement is limited by the use of low-dose naltrexone and the short duration of the trial in the context of methadone tapering.

In a non-blinded trial, persons infected with HIV with AUD and/or opioid use disorder were randomly assigned to treatment as usual or to extended release naltrexone (Korthuis et al., 2017). Of 35 subjects

with AUD, 8 also had an opioid use disorder. Only two-thirds of those assigned to extended release naltrexone initiated treatment but, of those who did initiate treatment, the medication was well tolerated and rates of treatment retention were greater than in subjects who received treatment as usual. Given the fact that the study had a small sample and was limited to individuals infected with HIV, the relevance to other individuals with co-occurring AUD and opioid use disorder is unclear.