Topic Brief: Updating Pharmacotherapy for Adults with Alcohol Use Disorders in Outpatient Settings

Date: 7/19/2021
Nomination Number: 0958

Purpose: This document summarizes the information addressing a nomination submitted on July 19, 2021, through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue:

The current 2018 American Psychiatric Association (APA) Practice Guideline for the Pharmacological Treatment of Patients with Alcohol Use Disorder (AUD)[1] is informed by a 2014 Agency for Healthcare Research and Quality (AHRQ) evidence report with studies.[2] A number of promising new pharmacologic approaches to the treatment of AUD have emerged since that time, and there are new findings from research regarding differential effectiveness of AUD medications by demographic and genetic characteristics, as well as the presence of co-occurring disorders. An updated systematic review based on current evidence would inform an updated guideline by APA and inform AHRQ initiatives to educate clinicians regarding the full spectrum of available treatment options and help improve clinical management of AUD.
Link to nomination

Recommendation

We identified sufficient primary literature to develop an updated systematic review for all but one of the nomination's key questions (KQ2b).

X Systematic review
□ Technical brief
□ Evidence map
□ Rapid review
□ Rapid response
□ Expanded topic brief

Key Findings

- We found a total of six systematic reviews[3-8] and 39 primary studies[9-46] addressing key questions (KQs) regarding the effectiveness of AUD pharmacotherapies for improving alcohol consumption and health outcomes (KQs 1a-b and 2a), associated harms (KQs 3a-b), effectiveness in primary care settings (KQ4), and variation in effectiveness by patient demographic factors, comorbidities, and genetic characteristics (KQs 5-6).
- We did not find any reviews or primary studies to address KQ2b pertaining to the comparative effectiveness of AUD medications for health outcomes.

- While the reviews and primary studies identified only approximately two thirds of the 31 pharmacologic agents currently used for the treatment of AUD, the literature volume is sufficient to produce an estimated medium to large size systematic review update.

Background

According to the data from the third National Epidemiologic Survey on Alcohol and Related Conditions, approximately 14 percent of American adults met the criteria for AUD in 2013, and 29 percent met AUD criteria within their lifetime.[47]

The Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) defines AUD as "a maladaptive pattern of alcohol use leading to clinically significant impairment or distress," as manifested by specific DSM-V criteria for psychosocial, behavioral, or physiologic symptoms.[48]

AUD is associated with significant morbidity, with alcohol consumption linked to numerous acute and chronic conditions, including heart disease, diabetes mellitus, liver cirrhosis, pancreatitis, various malignancies, as well as depression, anxiety, and other psychiatric disorders.[49] The condition also has high mortality, as approximately 88,000 deaths are directly attributed to alcohol annually, making alcohol use the third leading preventable cause of death in the United States after smoking and obesity.[50]

Despite its high prevalence and myriad negative consequences, AUD remains grossly undertreated. According to the Substance Abuse and Mental Health Services Administration's National Survey on Drug Use and Health, fewer than one in 10 Americans diagnosed with AUD within 12 months received any treatment.[51] As such, the APA's 2018 Practice Guideline for the Pharmacological Treatment of Patients with AUD recommends that all adult primary care patients be screened for unhealthy alcohol use, and that those diagnosed with AUD be initiated on evidence-based pharmacologic treatment.[1]

Three medications (Disulfiram, Naltrexone, and Acamprosate) are approved for the treatment of AUD by the United States Food and Drug Administration. Acamprosate, along with daily and extended-release Naltrexone, are considered first-line pharmacotherapies for adults with moderate to severe AUD. Patients who do not respond to first line treatment are recommended second-line pharmacotherapies using either Disulfiram, Topiramate, or Gabapentin.[52]

A number of other medications from different drug classes, including alpha-1 antagonists (Prazosin and Doxazosin), acetylcholine receptor antagonists (Mecamylamine and Varenicline), and selective serotonin reuptake inhibitors (SSRIs), among others, have also been tried for the treatment of AUD.[53] However, due to limited evidence regarding their efficacy, these treatments are currently considered experimental.

Nomination Summary

The nomination was submitted by a staff member from the AHRQ's Center for Evidence and Practice Improvement, requesting an update of AHRQ's 2014 systematic review on pharmacotherapies for adults with AUD in outpatient settings. This evidence report has been used to support AHRQ dissemination and implementation investments to increase the use of

pharmacologic treatment of AUD in primary care practices, in the "EvidenceNow: Managing Unhealthy Alcohol Use" Initiative[54]. The nominator plans to use the report to inform current and future activities of this initiative, and support AHRQ's Integration Academy activities.

The APA has expressed interest in using an updated review to inform an update of their 2018 guideline on pharmacologic treatment of AUD[1].

The KQs and PICOTS for this nomination were kept the same, barring the inclusion of five new medications (Bupropion, Doxazosin, Exenatide, Mecamylamine, and Modafinil) which began being used "off label" for the treatment of AUD after the 2014 review was published.

Scope

Key Questions:

KQ1(a) Which medications are efficacious for improving consumption outcomes for adults with AUD in outpatient settings?

KQ1(b) How do medications for adults with AUD compare for improvingconsumption outcomes in outpatient settings?

KQ2(a) Which medications are efficacious for improving health outcomes for adults with AUD in outpatient settings?

KQ2(b) How do medications for adults with AUD compare for improving health outcomes in outpatient settings?

KQ3(a) What adverse effects are associated with medications for adults with AUD in outpatient settings?

KQ3(b) How do medications for adults with AUD compare for adverse effects in outpatient settings?

KQ4 Are medications for treating adults with AUD effective in primary care settings?

KQ5 Are any of the medications for adults with AUD 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?

KQ6 Are any of the medications for adults with AUD more or less effective for adults with certain genetic polymorphisms (e.g., of the mu-opioid receptor gene [*OPRM1*]) compared with adults without such polymorphisms?

Table 1. KQ 1-6 PICOTS (population, intervention, comparator, outcome, timing, and setting)

Population	Adults (age 18 years or older) with AUDs
Interventions	Pharmacotherapy for relapse prevention or pharmacotherapy combined with various co-interventions (including both FDA-approved drugs and those being used off label), including: (a) Medications approved by the FDA for treatment of AUDs: • Acamprosate • Disulfiram • Naltrexone (b) Medications used off-label, or those under investigation: • Amitriptyline • Aripiprazole • Atomoxetine

	• Baclofen • Bupropion • Buspirone • Citalopram • Desipramine • Doxazosin • Escitalopram • Exenatide • Fluoxetine • Fluvoxamine • Gabapentin • Imipramine • Mecamylamine • Modafinil • Nalmefene • Olanzapine • Ondansetron • Paroxetine • Prazosin • Quetiapine • Sertraline • Topiramate • Valproate • Varenicline • Vilozaxine Pharmacotherapy combined with nonpharmacologic co-interventions with other treatments for AUDs (e.g., behavioral counseling, cognitive behavioral therapy, motivational enhancement therapy, psychosocial treatments, or self-help such as 12-step programs [e.g., Alcoholics Anonymous]) will be eligible for inclusion, as long as they meet other inclusion/exclusion criteria. (This review will not include pharmacotherapy for alcohol withdrawal)
Comparator	For KQs 1-5, studies must compare one of the medications listed above with placebo or another medication. For KQ 6, studies must compare people who have a genetic polymorphism with people who do not have the polymorphism.
Outcomes	**(a) Consumption outcomes** 1. abstinence/any drinking • rates of continuous abstinence • percentage of days abstinent • time to first drink/lapse • time to heavy drinking/relapse 2. reduction in alcohol consumption • number of heavy drinking days • percent of subjects with no heavy drinking days • number of drinking days • drinks per drinking day • drinks per week **(b) Health outcomes** • accidents • injuries • quality of life

	• function • mortality **(c) Adverse effects of intervention(s)** • withdrawals due to adverse events • nausea/vomiting • diarrhea • anorexia • palpitations • headache • dizziness • cognitive dysfunction • taste abnormalities • paresthesias (numbness, tingling) • metabolic acidosis • glaucoma • vision changes • suicidal ideation • insomnia • anxiety • rash
Timing	Studies with at least 12 weeks of follow-up from the time of medication initiation
Setting	Outpatient health care (i.e., nonlaboratory) settings; KQ 4 applies to primary care settings only (i.e., internal medicine, family medicine, pediatrics, obstetrics/gynecology, or college and university health clinics)

Abbreviations: AUD = Alcohol Use Disorder; FDA = United States Food and Drug Administration; KQ = Key Question

See Appendix A.

Summary of Literature Findings

After reviewing 1,812 titles and abstracts (including 21 systematic review and 1,791 primary study citations) we identified six systematic reviews and 39 primary studies relevant to all but one of this nomination's questions (KQ2b), as further summarized below.
We conducted searches for both systematic reviews and primary literature because none of the found systematic reviews were fully duplicative as they did not address all pharmacotherapies of interest.

Effectiveness of AUD Medications for Consumption Outcomes (KQs 1a-1b)

For KQ1a pertaining to the effectiveness of medications for AUD treatment on alcohol consumption outcomes in outpatient settings, we found three systematic reviews and 10 primary studies.

One 2018 Cochrane review[3] included 11 studies assessing the effectiveness of Baclofen compared to placebo. Another 2020 systematic review[4] examined the effectiveness of combined pharmacotherapies including Naltrexone, Disulfiram, Nefazodone, and Acamprosate compared to nonpharmacologic treatments. Finally, one 2020 systematic review[5] examined the effectiveness of Acamprosate, Disulfiram, Citalopram, Fluoxetine, Fluvoxamine, Modafinil, Naltrexone, and Quetiapine, each compared to placebo, on achieving abstinence from alcohol.

The 10 primary studies found consisted of eight randomized controlled trials (RCTs)[9-11, 14-18] and two prospective studies[12, 13] that examined the effectiveness of 10 additional pharmacotherapies (Doxazosin,[9] extended-release Gabapentin,[10] Mecamylamine,[11] Nalmefene,[12, 17, 18] extended-release Naltrexone,[13] Prazosin,[14] Varenicline,[15] and Citicoline[16]) compared to placebo.

For KQ1b pertaining to the comparative effectiveness of different pharmacotherapies for AUD on alcohol consumption outcomes, we found two systematic reviews[3, 5] and three primary studies, consisting of two RCT[20] and one prospective cross-sectional study.[19]
One 2018 Cochrane review[3] of the effectiveness of Baclofen treatment included one study comparing the effectiveness of Baclofen and Acamprosate monotherapies. Another 2020 systematic review[5] additionally examined the comparative effectiveness of four different SSRIs (Fluvoxamine, Citalopram, Fluoxetine, and Escitalopram), as well as the comparative effectiveness of Naltrexone and Topiramate, Oxcarbazepine, and Aripiprazole treatments.

We also found three primary studies examining the effectiveness of dual pharmacotherapies for improving alcohol consumption. One uncontrolled trial evaluated the effectiveness of combined Quetiapine and Mirtazapine treatment[20] while another uncontrolled trial assessed the effectiveness of combined Bupropion and Naltrexone[19]. One prospective cross-sectional study also examined the effectiveness of Disulfiram and Naltrexone dual therapy.[21]

Effectiveness of AUD Medications for General Health Outcomes (KQs 2a-2b)
For KQ2a pertaining to the effectiveness of AUD pharmacotherapies for improving general health outcomes, we found no systematic reviews and five RCTs[9, 10, 16-18] comparing the effectiveness of extended release Gabapentin,[10] Nalmefene,[17, 18] Doxazosin.[9] and Citicoline[16] versus placebo.

We did not identify any systematic reviews or primary studies addressing KQ2b pertaining to the comparative effectiveness of AUD pharmacotherapies for improving general health outcomes.

Harms Associated with AUD Medications (KQ3a-3b)
For KQ3a pertaining to adverse effects associated with AUD pharmacotherapies, we found three systematic reviews[3-5] and 11 primary studies.[9-11, 13-18, 22] One 2018 Cochrane review[3] examined adverse effects of Baclofen monotherapy. Another 2020 systematic review[4] examined adverse effects associated with Naltrexone, Nefazodone, Acamprosate, and Disulfiram treatments. A third 2020 systematic review[5] additionally assessed adverse effects of three types of SSRI (Citalopram, Fluoxetine, and Fluvoxamine), as well as Quetiapine and Modafinil monotherapies.

Eleven additional primary studies related to KQ3a assessed adverse effects associated with extended-release Gabapentin,[10] Nalmefene,[17, 18] Doxazosin,[9] Prazosin,[14] Mecamylamine,[11] daily and extended-release injectable Naltrexone formulations,[13, 22] extended-release Quetiapine,[34] Varenicline,[15] and Citicoline.[16]

For KQ3b pertaining to the comparative adverse effects of AUD pharmacotherapies, we found two systematic reviews[3, 5] and three primary studies.[19-21] One 2018 Cochrane review[3] included one RCT comparing adverse effects of Baclofen and Acamprosate treatments. Another 2020 systematic review[5] compared the adverse effects associated with Citalopram, Fluoxetine, Fluvoxamine, Quetiapine, and Modafinil pharmacotherapies.

Three primary studies additionally examined the adverse effects associated with combination treatments such as Quetiapine plus Mirtazapine,[20] Bupropion plus Naltrexone,[19] and Disulfiram plus Naltrexone[21] in combination.

Effectiveness for AUD Treatment in Primary Care Settings (KQ4)

For KQ4, pertaining to the effectiveness of pharmacologic AUD treatments for improving both alcohol consumption and general health outcomes that are administered in primary care settings, with found two systematic reviews and one primary study. One 2018 Cochrane review[3] included one RCT specifically conducted in a primary care setting, examining the effectiveness and safety of high-dose Baclofen compared to placebo over a yearlong follow-up. Another 2020 systematic review[5] compared the effectiveness of approximately 20 different pharmacologic treatments for maintaining alcohol abstinence in primary care settings in the United Kingdom. Notably, the review broadly examined the applicability of the included pharmacotherapies for use in primary care settings, and assessed some alcohol consumption related outcomes, but did not examine patient health and functional outcomes. Additionally, one RCT examined the effectiveness of using daily or extended-release Naltrexone for the treatment of AUD in primary care settings.[23]

Variation in Effectiveness by Demographic and Clinical Characteristics (KQ5)

For KQ5 pertaining to variation in the effectiveness of pharmacologic AUD treatments by patient demographics, smoking status and co-occurring disorders, we identified two relevant systematic reviews[6, 7] and 22 primary studies,[22, 24-31, 33-38, 40-43, 55] including eighteen RCTs, one secondary RCT analysis, two prospective cohorts, and one naturalistic study.

One 2018 Cochrane review[6] examined the effectiveness of several SSRIs including Citalopram, Escitalopram, Desipramine, Fluoxetine, and Sertraline monotherapies, in addition to a combination therapy with Escitalopram and Memantine as well as other agents, including Imipramine, Mirtazapine, Nefazodone and Viloxazine. Another 2020 systematic review[7] included seven RCTs examining the effectiveness of Naltrexone treatment using either daily or extended-release formulations for the treatment of AUD among adults with co-occurring HIV.

Four RCTs examined whether the effectiveness of AUD pharmacotherapies varied by demographic characteristics. One RCT[24] assessed variation in the effectiveness of Naltrexone treatment by age. Two other RCTs[25, 26] and one secondary RCT data analysis[40] examined variation in effectiveness of Nalmefene,[25] Naltrexone and/or Acamprosate,[26] and Gabapentin[40] based treatments by race/ethnicity. There were no studies examining whether the effectiveness of AUD pharmacotherapies varied by patients' sex.

Three RCTs examined whether the effectiveness of Varenicline[27, 28] and Naltrexone[29] based treatments were moderated by presence of comorbid tobacco use disorder.

The remaining fifteen primary studies[20, 22, 30-39, 41-43] examined variation in the effectiveness of AUD pharmacotherapies by presence of co-occurring disorders. Four RCTs[22, 30-32] assessed variation in the effectiveness of Naltrexone treatment using either daily or extended-release formulations among adults with AUD and co-occurring HIV. Two RCTs and one prospective cohort evaluated the effectiveness of Baclofen,[41] Nalmefene,[33] and Quetiapine[34] among adults with AUD and co-occurring alcohol-related liver disease.

Three other studies examined whether the effectiveness of N-Acetylcysteine,[35] Mirtazapine,[36] and Lorazepam plus Disulfiram[42] for the treatment of AUD varied by presence of comorbid post-traumatic stress disorder, depression, and anxiety disorders. Four additional studies assessed the effectiveness of Atomoxetine,[37] Topiramate,[38] and Nalmefene[43] among adults with AUD and comorbid attention-deficit/hyperactive disorder, bipolar disorder, post-traumatic brain injury syndrome, and general psychiatric comorbidity, respectively. One study also examined the effectiveness of Olanzapine monotherapy compared to combined Olanzapine and Samidorphan treatment[55] among adults with co-occurring AUD and schizophrenia.

Variation in Effectiveness in Subpopulations with Different Genotypes (KQ6)

For KQ6, pertaining to variation in the effectiveness of AUD pharmacotherapies by patients' genetic characteristics, we found one 2020 systematic review and five primary studies. The systematic review examined whether the presence of the A118G genotype of the OPRM1 gene (the gene encoding for opioid *mu*-receptors within the brain that moderate stimulating effects to alcohol among alcohol-dependent individuals) had a moderate effect on the effectiveness of Naltrexone for the treatment of AUD.

Two RCTs and one pre-post study performed related analyses. Specifically, one RCT[29] additionally examined whether the A118G OPRM1 genotype also moderated Naltrexone attractiveness to lower cue-elicited brain response to alcohol. Another pre-post[46] study examined the treatment benefit of combining outpatient Naltrexone pharmacotherapy with Alcoholics Anonymous Facilitation behavioral counseling among individuals with the same OPRM1 gene mutation. Another RCT[24] examined the effect of OPRM1 gene operator region DNA methylation on the outcome of treatment with Naltrexone for AUD.

The last two RCTs evaluated moderating effects of mutations in two other genes involved in AUD and how they moderated the effectiveness of pharmacologic interventions. The first of these RCTs[44] examined the effectiveness of Topiramate among individuals with AUD who had a rs2832407 GRIK1 gene mutation (the gene encoding for the glutamate receptor within the brain associated with cue-induced brain activation that causes alcohol craving). The second RCT[45] assessed whether the presence of a rs29220 mutation in the GABBR1 gene (the gene encoding for the brain's gamma-aminobutyric acid, or GABA, receptors) may moderate treatment response and possibly predict adverse effects to Baclofen.

Table 2. Literature identified for each KQ

Question	Systematic reviews (8/2018-8/2021)	Primary studies (8/2016-8/2021)
KQ1(a). AUD medication effectiveness for *consumption outcomes*	Total: 3[3-5] • Cochrane – 1[3] • Other – 2[4, 5]	Total: 10[9-18] • RCT – 8[9-16] • Prospective cohort – 2[17, 18] Clinicaltrials.gov: 0
KQ1(b). AUD medication comparative effectiveness for *consumption outcomes*	Total: 2[3, 5] • Cochrane – 1[3] • Other – 1[5]	Total: 3[19-21] • RCT – 2[19, 20] • Prospective cross-sectional – 1[21] Clinicaltrials.gov 0
KQ2(a). AUD medication effectiveness for *health outcomes*	Total: 0	Total: 5[9, 10, 16-18] • RCT – 5[9, 10, 16-18]

Question	Systematic reviews (8/2018-8/2021)	Primary studies (8/2016-8/2021)
		Clinicaltrials.gov: 0
KQ2(b). AUD medication comparative effectiveness for *health outcomes*	Total: 0	Total: 0
KQ3(a). Adverse effects of AUD medications	Total: 3[3-5] • Cochrane – 1[3] • Other – 2[4, 5]	Total: 10[9-11, 13-18, 22] • RCT – 9 • Prospective cohort – 1[13] Clinicaltrials.gov: 0
KQ3(b). Comparative adverse effects of AUD medications	Total: 2[3, 5] • Cochrane – 1[3] • Other – 1[5]	Total: 3[19-21] • RCT – 1[20] • Prospective cohort – 1[19] • Prospective cross-sectional – 1[21] Clinicaltrials.gov: 0
KQ4. AUD medication effectiveness in primary care settings	Total: 2[3, 5] • Cochrane – 1[3] • Other[5]	Total: 1[23] • RCT – 1[23] Clinicaltrials.gov: 0
KQ5. Variation in AUD medication effectiveness by age, sex, race/ ethnicity, tobacco use and co-occurring disorders	Total: 2[6, 7] • Cochrane – 1[6] • Other – 1[7]	Total: 22[20, 22, 24-43, 56] • RCT – 18[20, 22, 24-39, 56] • Secondary RCT analysis – 1[40] • Prospective cohort – 2[41, 42] • Naturalistic study – 1[43] Clinicaltrials.gov: 0
KQ6. Variation in AUD medication effectiveness by genetic characteristics	Total: 1[8] • Other – 1[8]	Total: 6[24, 29, 44-46] • RCT – 5[24, 29, 44, 45] • Prospective cohort – 1[46] Clinicaltrials.gov: 0

Abbreviations: AUD = Alcohol Use Disorder; KQ = Key Question; RCT= Randomized Controlled Trial.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

This nomination met all selection criteria for an evidence review for all but one question (KQ2b) pertaining to the comparative effectiveness of AUD medications for improving health outcomes, for which we did not find any published literature.

An updated systematic review that compared the effectiveness of existing pharmacotherapies for the treatment of AUD, examined the applicability of these treatments within primary care settings, and evaluated how the effectiveness of these treatments may vary by patient demographic and genetic characteristics and the presence of comorbid conditions, would be highly impactful and valuable. This updated review would help inform guidelines for clinicians regarding the current options for evidence-based AUD treatments and inform AHRQ initiatives related to AUD.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years from August 12, 2021, on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
  - EHC Program https://effectivehealthcare.ahrq.gov/
  - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
  - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- University of York Centre for Reviews and Dissemination database https://www.crd.york.ac.uk/CRDWeb/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Campbell Collaboration http://www.campbellcollaboration.org/
- McMaster Health System Evidence https://www.healthsystemsevidence.org/
- UBC Centre for Health Services and Policy Research http://chspr.ubc.ca/
- Joanna Briggs Institute http://joannabriggs.org/
- WHO Health Evidence Network http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen

Impact of a New Evidence Review.

The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in Medline, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from August 12, 2016 through August 12, 2021. We reviewed all identified

titles and abstracts for inclusion and classified relevant studies by KQ and study design to estimate the size and scope of a potential evidence review.

Search Strategy

	MeSH	Other terms
Patients		
Adults	Adult/	Adults OR adult
w/Alcohol Use Disorder	Alcohol-Related Disorders/ Alcoholism/ Alcohol Drinking/ Alcoholics/	"Alcohol use disorder" OR alcoholism OR alcohol depend* OR alcohol misuse OR alcohol addiction* OR alcohol abuse OR problem drink* OR alcohol problem* OR "alcohol consumption" OR harmful alcohol* OR harmful drink* OR ((drinking OR drinker OR drinkers) AND alcohol)
Interventions		
In general	Alcohol Deterrents/ Drug Therapy/ /drug therapy	Pharmacotherapy OR pharmacologic
From original review	Naltrexone/ Acamprosate/ Disulfiram/ Amitriptyline/ Aripiprazole/ Atomoxetine Hydrochloride/ Baclofen/ Buspirone/ Citalopram/ Desipramine/ Fluoxetine/ Fluvoxamine/ Gabapentin/ Imipramine/ Olanzapine/ Ondansetron/ Paroxetine/ Prazosin/ Quetiapine Fumarate/ Sertraline/ Topiramate/ Valproic Acid/ Varenicline/	naltrexone OR Revia OR Vivitrol OR acamprosate OR Campral OR disulfiram OR Antabuse OR amitriptyline OR aripiprazole OR atomoxetine OR baclofen OR buspirone OR citalopram OR desipramine OR escitalopram OR fluoxetine OR fluvoxamine OR gabapentin OR imipramine OR nalmefene OR olanzapine OR ondansetron OR paroxetine OR prazosin OR quetiapine

		OR sertraline OR topiramate OR valproate OR varenicline OR vilozaxine
New additions	Bupropion/ Doxazosin/ Exenatide/ Mecamylamine/ Modafinil/	Bupropion OR Zyban OR doxazosin OR Zoxan OR exenatide OR Byetta OR mecamylamine OR modafinil
Comparators		
As with the original search, this is not specified as we are interested in any comparisons.		
Outcomes		
As with the original search, this is not specified as we are interested in most outcomes.		
Timing		
As with the original search, this is left for human review at the title and abstract stage.		
Setting		
As with the original search, this is left for human review at the title and abstract stage.		
Limits		
humans	"humans"[MeSH Terms]	
English	"English"[Language]	
2016 - current	2016/01/01:3000/12/31[Date - Entry]	

Search Strategy converted to PubMed search syntax
"adult"[MeSH Terms] OR "adult"[Title/Abstract] OR "adults"[Title/Abstract] AND "humans"[MeSH Terms] AND "english"[Language] AND 2016/01/01:3000/12/31[Date - Entry] AND "alcohol related disorders"[MeSH Terms] OR "alcoholism"[MeSH Terms] OR "alcohol drinking"[MeSH Terms] OR "alcoholics"[MeSH Terms] OR ("Alcohol use disorder"[Title/Abstract] OR "alcoholism"[Title/Abstract] OR "alcohol depend*"[Title/Abstract] OR "alcohol misuse"[Title/Abstract] OR

"alcohol addiction*"[Title/Abstract] OR "alcohol abuse"[Title/Abstract] OR "problem drink*"[Title/Abstract] OR "alcohol problem*"[Title/Abstract] OR "alcohol consumption"[Title/Abstract] OR "harmful alcohol*"[Title/Abstract] OR "harmful drink*"[Title/Abstract]) OR (("drinking"[Title/Abstract] OR "drinker"[Title/Abstract] OR "drinkers"[Title/Abstract]) AND "alcohol"[Title/Abstract])
AND
"alcohol deterrents"[MeSH Terms] OR "drug therapy"[MeSH Terms] OR "drug therapy"[MeSH Subheading] OR ("naltrexone"[MeSH Terms] OR "naltrexone"[All Fields] OR "naltrexon"[All Fields] OR "naltrexone s"[All Fields] OR ("naltrexone"[MeSH Terms] OR "naltrexone"[All Fields] OR "naltrexon"[All Fields] OR "revia"[All Fields] OR "naltrexone s"[All Fields]) OR ("naltrexone"[MeSH Terms] OR "naltrexone"[All Fields] OR "naltrexon"[All Fields] OR "naltrexone s"[All Fields] OR "vivitrol"[Supplementary Concept] OR "vivitrol"[All Fields]) OR ("acamprosate"[MeSH Terms] OR "acamprosate"[All Fields] OR "acamprosate s"[All Fields]) OR ("acamprosate"[MeSH Terms] OR "acamprosate"[All Fields] OR "campral"[All Fields]) OR ("disulfiram"[MeSH Terms] OR "disulfiram"[All Fields] OR "disulphiram"[All Fields]) OR ("disulfiram"[MeSH Terms] OR "disulfiram"[All Fields] OR "antabuse"[All Fields] OR "disulphiram"[All Fields]) OR ("amitriptyline"[MeSH Terms] OR "amitriptyline"[All Fields] OR "amitriptylin"[All Fields] OR "amitriptyline s"[All Fields]) OR ("aripiprazole"[MeSH Terms] OR "aripiprazole"[All Fields] OR "aripiprazol"[All Fields] OR "aripiprazole s"[All Fields]) OR ("atomoxetine hydrochloride"[MeSH Terms] OR ("atomoxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "atomoxetine hydrochloride"[All Fields] OR "atomoxetine"[All Fields] OR "atomoxetine s"[All Fields]) OR ("baclofen"[MeSH Terms] OR "baclofen"[All Fields] OR "baclofen s"[All Fields] OR "baclofene"[All Fields]) OR ("buspirone"[MeSH Terms] OR "buspirone"[All Fields] OR "buspiron"[All Fields] OR "buspirone s"[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields] OR "citalopram s"[All Fields]) OR ("desipramine"[MeSH Terms] OR "desipramine"[All Fields] OR "desipramine s"[All Fields]) OR ("citalopram"[MeSH Terms] OR "citalopram"[All Fields] OR "escitalopram"[All Fields]) OR ("fluoxetine"[MeSH Terms] OR "fluoxetine"[All Fields] OR "fluoxetin"[All Fields] OR "fluoxetine s"[All Fields]) OR ("fluvoxamin"[All Fields] OR "fluvoxamine"[MeSH Terms] OR "fluvoxamine"[All Fields]) OR ("gabapentin"[MeSH Terms] OR "gabapentin"[All Fields] OR "gabapentine"[All Fields] OR "gabapentin s"[All Fields]) OR ("imipramine"[MeSH Terms] OR "imipramine"[All Fields] OR "imipramin"[All Fields] OR "imipramine s"[All Fields] OR "imipramines"[All Fields]) OR ("nalmefene"[Supplementary Concept] OR "nalmefene"[All Fields]) OR ("olanzapine"[MeSH Terms] OR "olanzapine"[All Fields] OR "olanzapin"[All Fields] OR "olanzapine s"[All Fields]) OR ("ondansetron"[MeSH Terms] OR "ondansetron"[All Fields] OR "ondansetrone"[All Fields]) OR ("paroxetin"[All Fields] OR "paroxetine"[MeSH Terms] OR "paroxetine"[All Fields] OR "paroxetine s"[All Fields]) OR ("prazosin"[MeSH Terms] OR "prazosin"[All Fields] OR "prazosine"[All Fields] OR "prazosin s"[All Fields]) OR ("quetiapin"[All Fields] OR "quetiapine fumarate"[MeSH Terms] OR ("quetiapine"[All Fields] AND "fumarate"[All Fields]) OR "quetiapine fumarate"[All Fields] OR "quetiapine"[All Fields] OR "quetiapine s"[All Fields]) OR ("sertralin"[All Fields] OR "sertraline"[MeSH Terms] OR "sertraline"[All Fields] OR "sertraline s"[All Fields]) OR ("topiramate"[MeSH Terms] OR "topiramate"[All Fields] OR "topiramate s"[All Fields]) OR ("valproat"[All Fields] OR "valproate s"[All Fields] OR "valproates"[All Fields] OR "valproic acid"[MeSH Terms] OR ("valproic"[All Fields] AND "acid"[All Fields]) OR "valproic acid"[All Fields] OR "valproate"[All Fields]) OR ("vareniclin"[All Fields] OR "varenicline"[MeSH Terms] OR "varenicline"[All Fields] OR "varenicline s"[All Fields])) OR ("bupropion"[MeSH Terms] OR "bupropion"[All Fields] OR "amfebutamone"[All Fields] OR "bupropion s"[All Fields] OR "bupropione"[All Fields] OR ("bupropion"[MeSH Terms] OR "bupropion"[All Fields] OR "amfebutamone"[All Fields] OR "zyban"[All Fields] OR "bupropion s"[All Fields] OR "bupropione"[All Fields]) OR ("doxazosin"[MeSH Terms] OR "doxazosin"[All Fields] OR "doxazosine"[All Fields]) OR ("doxazosin"[MeSH Terms] OR "doxazosin"[All Fields] OR "zoxan"[All Fields]) OR ("exenatide"[MeSH Terms] OR "exenatide"[All Fields] OR "exenatide s"[All Fields]) OR ("exenatide"[MeSH Terms] OR "exenatide"[All Fields] OR "byetta"[All Fields] OR "exenatide s"[All Fields]) OR ("mecamylamine"[MeSH Terms] OR "mecamylamine"[All Fields] OR "mecamylamine s"[All Fields]) OR "modafinil"[MeSH Terms])

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Clinical Trials link

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the United States?	Yes. The nomination is requesting an update of the 2014 AHRQ systematic review of pharmacotherapies for the treatment of AUD.[2]
1b. Is the nomination a request for an evidence report?	Yes.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes. The focus of the proposed review update is comparative effectiveness of pharmacotherapies for the treatment of AUD for improving consumption and general health outcomes.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	AUD is highly prevalent in the United States.[57] According to the SAMHSA's 2019 National Survey on Drug Use and Health, 14.1 million Americans aged 18 years and older had AUD in 2019.[51] An estimated 95,000 Americans die from alcohol-related causes annually, making alcohol the third-leading preventable cause of death in the United States after smoking and poor diet combined with physical inactivity.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the United States population or for a vulnerable population	Yes. The APA Practice Guideline for the Pharmacological Treatment of Patients with AUD[1] was published in 2018 and is based on evidence from the AHRQ systematic review from 2014[2]. An updated systematic review would help inform clinical practice and updating evidence recommendations through AHRQ's ongoing "EvidenceNOW: Managing Unhealthy Alcohol Use" Initiative."[54]
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. According to the CDC's most recent 2019 Alcohol Public Health report,[58] the cost of excessive alcohol use in the United States reached $249 billion in 2010. According to the report, 72% of this total cost was due to losses in workplace productivity, 11% was due to healthcare expenditures to treat problems caused by excessive drinking, and 15% attributable to law enforcement and other criminal justice expenses.
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes. A recent high-quality systematic or other evidence review that comprehensively evaluates all 31 pharmacotherapies of interest for the treatment of AUD is not available.
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes. The APA Practice Guideline for the Pharmacological Treatment of Patients with AUD[1] was published in 2018 and is based on a 2014 AHRQ evidence review. New pharmacologic treatments for AUD emerged since however there

	are no systematic reviews evaluating their effectiveness.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes. Pharmacological management of AUD remains highly variable with limited evidence-based guidance available regarding the benefits and harms of newer pharmacotherapies and variability in the effectiveness of these pharmacotherapies based on patient demographics, genetic characteristics, and comorbidities.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	We reviewed the entire primary literature search yield of 1,791 titles and abstracts and found the following: KQ1(a) – 10 primary studies[9-18] KQ1(b) – 3 primary studies[19-21] KQ2(a) – 5 primary studies[9, 10, 16-18] KQ2(b) – no primary studies KQ3(a) – 10 primary studies[9-11, 13-15, 17, 18, 22] KQ3(b) – 3 primary studies[19-21] KQ4 – 1 primary study[23] KQ5 – 22 primary studies[20, 22, 24-43] KQ6 – 6 primary studies[24, 29, 44-46] The estimated size of an updated systematic review for this topic is medium to large.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes. An updated systematic review on the topic would influence practice. Clinicians and policymakers are interested in implementing and using evidence on AUD treatment given the rise of alcohol consumption by adults in the last year during the COVID pandemic[59].
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes. AHRQ would use this review to inform their work including the EvidenceNOW Unhealth Alcohol Use Initiative and the Integration Academy. In addition, the APA has expressed interest in using an updated review when it updates its guideline on treatment for AUD[54].

Abbreviations: AHRQ =Agency for Healthcare Research and Quality; APA = American Psychiatric Association; AUD= alcohol use disorder; CDC = Centers for Disease Control and Prevention; KQ = Key Question; SAMHSA=Substance Abuse and Mental Health Services Administration.

Appendix C. Topic Nomination

0958 Updating Pharmacotherapy for Adults with Alcohol Use Disorders in Outpatient Settings

A topic nomination was submitted on the EHC website:

Submitted on Monday, July 19, 2021 - 11:36

==Topic Suggestion==

1. What is the decision or change you are facing or struggling with where a summary of theevidence would be helpful?
What medications are effective in reducing alcohol consumption and/or cravings in individuals with alcohol use disorder? We are interested in this topic because the current EPC review was completed in 2014.

2. Why are you struggling with this issue?
While there are 3 FDA approved medications for alcohol use disorder, only 1 of the 3 is widelyused because the other 2 are impractical to use (i.e. acamprosate is dosed 3 times a day with a total of 6 different tabs and disulfiram has been shown to have poor compliance). As such, onlynaltrexone (which is FDA-approved for alcohol use disorder) is widely used of the three but many patients may have contraindications to this medication. Many medications (such as gabapentin and topiramate) are being used "off-label" by clinicians in an attempt to treat the growing number of individuals with alcohol use disorder but the evidence around these medications has not been examined systematically. The recent COVID-19 pandemic has exacerbated the proportion of individuals struggling with unhealthy alcohol use and alcohol usedisorder.

Clinically, I struggle with how to best treat alcohol use disorder when naltrexone is contraindicated or poorly tolerated by patients. Frequently, I am left with using a medication with uncertain evidence in an attempt to offer the patient some treatment for alcohol use disorder. From an AHRQ perspective, an updated evidence synthesis would be very helpful forthe ongoing Evidence-Now: Managing Unhealthy Alcohol Use Initiative

3. What do you want to see changed? How will you know that your issue is improving or has been addressed? I would like to see an updated evidence synthesis examining the effectiveness ofthe various medications being used to treat alcohol use disorder. An updated evidence synthesis could also draw more awareness of the usefulness of medications for alcohol use disorder (current uptake by clinicians is quite low). I will know the issue has been addressed and/or is improving when higher proportions of patients with alcohol use disorder are being treated with medications and alcohol use disorder rates are decreasing.

4. When do you need the evidence report?
Friday, 09/30/2022

5. What will you do with the evidence report?

The evidence report will inform clinical practice and could inform the ongoing Evidence-Now:Managing Unhealthy Alcohol Use Initiative. They will also be used by addiction medicine organizations to inform practice guidelines.

==(Optional) About You==
What is your role or perspective? Primary care physician, addiction medicine specialist, AHRQprogram official for Evidence-Now: Managing Unhealthy Alcohol Use Initiative

If you are you making a suggestion on behalf of an organization, please state the name of theorganization: N/A

May we contact you if we have questions about your nomination?
YesFirst and Last Name: Sebastian Tong
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The results of this submission may be viewed at:
https://effectivehealthcare.ahrq.gov/node/16119/submission/20798