# Pharmacotherapy for Adults With Alcohol Use Disorder (AUD) in Outpatient Settings

## Focus of This Summary

This is a summary of a systematic review evaluating the evidence regarding the efficacy, comparative effectiveness, and adverse effects of medications in adults with alcohol use disorder (AUD). The systematic review included 167 articles reporting on 135 eligible studies published from January 1, 1970, to October 11, 2013. The full report, listing all studies, is available at *www.effectivehealthcare.ahrq.gov/alcohol-disorder.* This summary is provided to inform discussions with patients and/or caregivers of treatment options and to assist in decisionmaking along with consideration of a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines.

## Background

Alcohol misuse, or unhealthy alcohol use, includes the full spectrum: from drinking above recommended limits (i.e., risky or hazardous drinking) to AUD. Alcohol misuse is associated with numerous health and social problems and more than 85,000 deaths per year in the United States. In the past, disorders of alcohol use included alcohol abuse and alcohol dependence. However, in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), these categories are no longer distinguished, and in their place, DSM-5 identified AUD. The DSM-5 uses 11 criteria to define AUD (see Appendix 1 on page 3), the presence of 2 of which indicates AUD.

Common treatments for AUD include cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholics Anonymous®), and pharmacotherapy. These treatments are often used in combination with each other.

Two oral medications (naltrexone and acamprosate) and a long-acting injectable formulation of naltrexone have been approved by the FDA for the treatment of alcohol dependence in patients who are able to abstain from alcohol. Disulfiram has been approved as an aid in the management of selected patients who want to remain in a state of enforced sobriety so that supportive and psychotherapeutic treatment may be applied to best advantage. These medications were approved before publication of the DSM-5, which no longer has a separate category for alcohol dependence. Additional medications that have not been approved for the treatment of alcohol dependence or AUD have been used or studied as treatment for AUD. Guidelines from the Veterans Health Administration, the National Institute on Alcohol Abuse and Alcoholism, and the Substance Abuse and Mental Health Services Administration recommend that medications should be routinely considered in combination with a psychological intervention for people with alcohol dependence. However, many patients with AUD do not receive treatment, and medications for AUD are underutilized. It is estimated that fewer than 1 in 10 people who are treated for AUD receive medications.† Expanding awareness and access to medication-assisted treatment for AUD has the potential to improve health outcomes.

## Conclusions

There was moderate-strength evidence that acamprosate and oral naltrexone improve alcohol consumption outcomes for patients with AUD. Head-to-head trials have not consistently established the superiority of one medication over another. Evidence related to injectable naltrexone is currently limited. Evidence from randomized, placebo-controlled trials does not support the efficacy of disulfiram. Disulfiram may be recommended to individuals who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable or to individuals who prefer disulfiram and understand its risks.†† Most studies evaluated medications in combination with a psychosocial cointervention; the potential benefits of using the medications alone are less well established.

Evidence was insufficient to assess the effectiveness of medications in specific population subgroups (based on age, ethnicity, smoking status, comorbidities, or genotype). Evidence from randomized trials was insufficient to determine the effectiveness of AUD medications for improving health outcomes. Epidemiologic studies consistently related heavy alcohol consumption to an increased risk of serious health problems and suggest that improving alcohol consumption outcomes would likely result in improved health outcomes.

Several medications unapproved by the FDA have been studied and/or used to treat alcohol disorders, including antidepressants, anticonvulsants, antipsychotics, and anxiolytics. However, there is insufficient evidence for the effectiveness of most of these medications in patients with AUD. There was moderate-strength evidence for the efficacy of topiramate (i.e., unapproved use under the FDA label) in improving some consumption outcomes.

Factors that may guide medication choices include frequency of administration, dosing schedule or other barriers to adherence, potential adverse events, coexisting symptoms, and availability of treatments.

† Office of Applied Studies. Results From the 2013 National Survey on Drug Use and Health: Summary of National Findings. Section 7.3. Alcohol Use Treatment and Treatment Need. HHS Publication No. (SMA) 14-4863. Rockville, MD: Substance Abuse and Mental Health Services Administration; September 2014.

†† National Institute for Health and Care Excellence. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. NICE Guideline No. CG115. *www.nice.org.uk/guidance/CG115/chapter/1-Guidance#interventions-for-alcohol-misuse*. Published February 2011. Accessed July 16, 2014.

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## Clinical Bottom Line

**Table 1: Summary of Findings and Strength of Evidence for the Efficacy of Medications Used To Treat AUD Versus Placebo**

*(Note: Studies assessed in this review typically included psychosocial cointerventions; effect sizes reflect the added benefits of medications beyond those of psychosocial cointerventions.)*

| Medication | Outcome | N Studies[a] | N Subjects | Finding | Effect Size (95% CI) | NNT[b] | SOE |
|---|---|---|---|---|---|---|---|
| **Acamprosate vs. placebo** | Return to any drinking | 16 | 4,847 | Reduced by acamprosate | RD: -0.09 (-0.14 to -0.04) | 12 | ●●○ |
| | Return to heavy drinking | 7 | 2,496 | No difference | RD: -0.01 (-0.04 to 0.03) | NA | ●●○ |
| | Percentage of drinking days | 13 | 4,485 | Reduced by acamprosate | WMD: -8.8 (-12.8 to -4.8) | NA | ●●○ |
| **Disulfiram vs. placebo** | Return to any drinking | 2 | 492 | No difference | RD: -0.04 (-0.11 to 0.03) | NA | ●○○ |
| **Naltrexone 50 mg oral vs. placebo** | Return to any drinking | 16 | 2,347 | Reduced by naltrexone | RD: -0.05 (-0.10 to -0.00) | 20 | ●●○ |
| | Return to heavy drinking | 19 | 2,875 | Reduced by naltrexone | RD: -0.09 (-0.13 to -0.04) | 12 | ●●○ |
| | Percentage of drinking days | 15 | 1,992 | Reduced by naltrexone | WMD: -5.4 (-7.5 to -3.2) | NA | ●●○ |
| | Percentage of heavy drinking days | 6 | 521 | Reduced by naltrexone | WMD: -4.1 (-7.6 to -0.61) | NA | ●●○ |
| **Naltrexone injection vs. placebo** | Return to any drinking | 2 | 939 | No difference | RD: -0.04 (-0.10 to 0.03) | NA | ●○○ |
| | Return to heavy drinking | 2 | 615 | No difference | RD: -0.01 (-0.14 to 0.13) | NA | ●○○ |
| | Percentage of heavy drinking days | 2 | 926 | Reduced by naltrexone | WMD: -4.6 (-8.5 to -0.56) | NA | ●○○ |
| **Topiramate[c] vs. placebo** | Percentage of drinking days | 2 | 521 | Reduced by topiramate | WMD: -8.5 (-15.9 to -1.1) | NA | ●●○ |
| | Percentage of heavy drinking days | 2 | 521 | Reduced by topiramate | WMD: -11.5 (-18.3 to -4.8) | NA | ●●○ |
| | Number of drinks per drinking day | 2 | 521 | Reduced by topiramate | WMD: -1.1 (-1.7 to -0.4) | NA | ●●○ |
| **Other drugs[c]** | The evidence is insufficient to determine the efficacy of other medications because of inconsistency, imprecision, or lack of sufficient studies in the literature (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, paroxetine, quetiapine, varenicline, viloxazine). | | | | | | |

CI = confidence interval; N = number; NA = not applicable; NNT = number needed to treat; RD = risk difference; SOE = strength of evidence; WMD = weighted mean difference.

[a] This column only includes studies rated as having a low or medium risk of bias that were included in the main analysis; these numbers do not include studies rated as having a high or unclear risk of bias that were included in sensitivity analyses.

[b] In the NNT column, NA indicates that the risk difference (95-percent confidence interval) was not statistically significant and that an NNT was not calculated or that the effect measure was not one that allows direct calculation of an NNT (e.g., weighted mean difference).

[c] Medications that have not been approved by the FDA for the treatment of alcohol dependence, alcohol abuse, or AUD.

**Table 2: Comparative Effectiveness and Strength of Evidence for Acamprosate and Naltrexone as Treatment for AUD**

| Medication | Outcome | N Studies[a] | N Subjects | Finding | Strength of Evidence |
|---|---|---|---|---|---|
| **Acamprosate vs. naltrexone** | Return to any drinking | 3 | 800 | Not significant[a] | ●●○ |
| | Return to heavy drinking | 4 | 1,141 | Not significant[a] | ●●○ |
| | Percentage of drinking days | 2 | 720 | Not significant[a] | ●○○ |

[a] The 95-percent confidence interval was not statistically significant.

**Strength of Evidence Scale***

| | | |
|---|---|---|
| High: | ●●● | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate: | ●●○ | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| Low: | ●○○ | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. |
| Insufficient: | ○○○ | Evidence either is unavailable or does not permit a conclusion. |

* Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. May 2010;63(5):513-23. PMID: 19595577.

## Clinical Bottom Line *(Continued)*

**Table 3: Mechanism of Action of Medications Used in the Treatment of AUD and Their Adverse Effects**

| Medication | Adult Dosing | Mechanism of Action | Common Adverse Effects | Contraindications |
|---|---|---|---|---|
| **Acamprosate** | Oral: 666 mg (two 333-mg tablets) 3 times per day | Modulates hyperactive glutamatergic N-methyl-D-aspartate receptors | Anxiety<br>Diarrhea<br>Vomiting | Severe renal impairment[a] |
| **Naltrexone** | Oral: 50 to 100 mg per day<br>Intramuscular: 380 mg per month | Opioid antagonist that competitively binds to opioid receptors and blocks the effects of endogenous opioids such as β-endorphin<br>Decreases the craving for alcohol | Dizziness<br>Nausea<br>Vomiting | Liver failure<br>Acute hepatitis and precautions for other hepatic disease |
| **Disulfiram** | Oral: 250 to 500 mg per day | Expectation or experience of an adverse response to alcohol consumption<br>Inhibits ALDH2, causing accumulation of acetaldehyde during alcohol consumption, which, in turn, produces various adverse effects such as nausea, dizziness, flushing, and changes in heart rate and blood pressure | Drowsiness<br>Metallic or garlic taste in mouth | Severe myocardial diseases<br>Psychoses<br>Liver failure<br>Hypersensitivity to thiuram derivatives |
| **Topiramate[b,c]** | Oral: 25 to 400 mg per day | Blocks voltage-dependent sodium channels, augments the activity of the neurotransmitter γ-aminobutyrate, antagonizes certain subtypes of the glutamate receptor, and inhibits the carbonic anhydrase enzyme | Paresthesia<br>Anorexia<br>Dizziness<br>Somnolence<br>Psychomotor slowing<br>Abnormal vision<br>Fever | None |

[a] Dose adjustment for moderate renal impairment.

[b] This medication has not been approved by the FDA for the treatment of alcohol dependence, alcohol abuse, or AUD.

ALDH2 = aldehyde dehydrogenase 2

[c] The prescribing information sheet for topiramate lists warnings for several serious adverse effects. These include warnings for acute myopia and secondary angle closure glaucoma, suicidal behavior and ideation, and fetal toxicity. Clinicians are advised to refer to the prescribing information sheet for additional information on adverse effects.

## Other Findings of the Review

- The studies included in this review mainly focused on drinking-related outcomes. Evidence from randomized trials was insufficient to permit a conclusion that treatment with acamprosate or naltrexone leads to improved health outcomes (e.g., mortality, quality of life, function, and accidents). However, evidence from epidemiologic literature consistently related heavy alcohol consumption to an increased risk of serious health problems such as cancer, liver cirrhosis, chronic pancreatitis, coronary heart disease, stroke, depression, fetal alcohol syndrome, and violence. Such epidemiologic evidence would suggest that improving alcohol consumption outcomes likely results in improved health outcomes.
- Evidence related to the effectiveness of medications for treating patients with AUD in primary care settings was more limited, as fewer studies were conducted in these settings. This finding should not be interpreted to mean that medications cannot be used to treat AUD in primary care settings, but rather only that evidence regarding benefits and harms of the medications in these settings was limited. Some studies included in this review that were conducted in non–primary care settings used a "primary-care model" or used interventions that may be adaptable for delivery in primary care.

**Appendix 1: Criteria Used To Define AUD in the DSM-5 (2013)****

1. Alcohol is taken in larger amounts or over a longer period than intended.
2. Persistent desire or unsuccessful efforts to cut down or control alcohol use.
3. A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects.
4. Craving or a strong desire or urge to use alcohol.
5. Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol.
7. Important social, occupational, or recreational activities are given up or curtailed because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol.
10. Tolerance, as defined by either of the following:
    a. A need for markedly increased amounts of alcohol to achieve intoxication or the desired effect.
    b. A markedly diminished effect with continued use of the same amount of alcohol.
11. Withdrawal, as manifested by either of the following:
    a. The characteristic withdrawal syndrome for alcohol.
    b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

** The presence of at least 2 of the 11 criteria listed indicates an AUD. The severity of the AUD is defined as follows: ***mild*** = the presence of two to three symptoms; ***moderate*** = the presence of four to five symptoms; ***severe*** = the presence of six or more symptoms.

## Gaps in Knowledge and Limitations of the Evidence Base

Several gaps and limitations were identified in the evidence base reviewed for this report:

- AUD as a clinical entity is new terminology that was introduced in the DSM-5. Using DSM-5 terminology, most participants in the included studies likely had moderate to severe AUD. Thus, applicability of the findings of this review to people with mild AUD is uncertain.
- No head-to-head studies of oral naltrexone and injectable naltrexone were found.
- It is unclear if patients need to stop drinking before starting medications in order to benefit from them. In most studies, patients abstained for at least 3 days before starting medication. However, a few studies showed improvement in consumption outcomes in people who were currently drinking.
- The psychosocial cointerventions used in the included studies were heterogeneous. Therefore, conclusions about the effects of medications when used in combination with specific psychosocial interventions are not permitted.
- The potential benefits of using the medications alone (without a psychosocial cointervention) are unknown. The studies typically evaluated the use of medications along with psychosocial cointerventions.
- Only a few studies reported information about suicide, suicidal ideation, or self-harmful behaviors.
- Little evidence was available to determine whether naltrexone can be used for people with various liver conditions. Oral naltrexone is currently contraindicated for patients with acute hepatitis or liver failure.
- The cause for the variability in patient response to medications is not clear from the included studies.

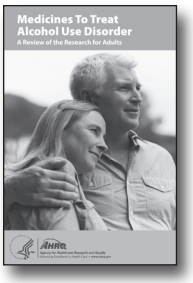
## Source

The information in this summary is based on *Pharmacotherapy for Adults With Alcohol-Use Disorders in Outpatient Settings*, Comparative Effectiveness Review No. 134, prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2012-00008-I for the Agency for Healthcare Research and Quality, May 2014. Available at *www.effectivehealthcare.ahrq.gov/alcohol-disorder.* This summary was prepared by the John M. Eisenberg Center for Clinical Decisions and Communications Science at Baylor College of Medicine, Houston, TX.

## What To Discuss With Your Patients and/or Their Caregivers

- The medications currently available for treating AUD and why a particular medication might be suitable for the patient
- Information on how the medications work to treat AUD
- The formulation of the medications (oral vs. injectable)
- The dose and frequency of the medications
- The duration of treatment with the medications
- The importance of having psychosocial cointerventions along with taking the medications
- Evidence related to the efficacy and relative effectiveness of the various medications for AUD
- Evidence related to the adverse effects associated with the medications for AUD
- The importance of adherence to medications for them to work
- The importance of attending followup appointments with you and other health care providers

## Companion Resource for Patients




*Medicines To Treat Alcohol Use Disorder: A Review of the Research for Adults* is a free companion to this clinician research summary. It can help patients and their caregivers talk with their health care professionals about the various medications that are available for treating AUD.

## Ordering Information

For electronic copies of *Medicines To Treat Alcohol Use Disorder: A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit *www.effectivehealthcare.ahrq.gov/alcohol-disorder*. To order free print copies of the patient summary, call the AHRQ Publications Clearinghouse at 800-358-9295.

## Additional Resources

Additional resources on AUD for clinicians, social workers, and other health care professionals are offered by the National Institute on Alcohol Abuse and Alcoholism and are available at *www.niaaa.nih.gov/publications/clinical-guides-and-manuals.*

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