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Diagnosis and Pharmacotherapy of Alcohol Use Disorder
A Review

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IMPORTANCE Alcohol consumption is associated with 88 000 US deaths annually. Although routine screening for heavy alcohol use can identify patients with alcohol use disorder (AUD) and has been recommended, only 1 in 6 US adults report ever having been asked by a health professional about their drinking behavior. Alcohol use disorder, a problematic pattern of alcohol use accompanied by clinically significant impairment or distress, is present in up to 14% of US adults during a 1-year period, although only about 8% of affected individuals are treated in an alcohol treatment facility.

OBSERVATIONS Four medications are approved by the US Food and Drug Administration to treat AUD: disulfiram, naltrexone (oral and long-acting injectable formulations), and acamprosate. However, patients with AUD most commonly receive counseling. Medications are prescribed to less than 9% of patients who are likely to benefit from them, given evidence that they exert clinically meaningful effects and their inclusion in clinical practice guidelines as first-line treatments for moderate to severe AUD. Naltrexone, which can be given once daily, reduces the likelihood of a return to any drinking by 5% and binge-drinking risk by 10%. Randomized clinical trials also show that some medications approved for other indications, including seizure disorder (eg, topiramate), are efficacious in treating AUD. Currently, there is not sufficient evidence to support the use of pharmacogenetics to personalize AUD treatments.

CONCLUSIONS AND RELEVANCE Alcohol consumption is associated with a high rate of morbidity and mortality, and heavy alcohol use is the major risk factor for AUD. Simple, valid screening methods can be used to identify patients with heavy alcohol use, who can then be evaluated for the presence of an AUD. Patients receiving a diagnosis of the disorder should be given brief counseling and prescribed a first-line medication (eg, naltrexone) or referred for a more intensive psychosocial intervention.

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In 2016, 6.6% of the US adult population reported heavy alcohol use and 26.2% reported at least 1 episode of binge drinking (defined as 4 or more drinks in a day for women and 5 or more drinks in a day for men) during the preceding month (**Box 1**).[1] Between 2006 and 2010, the annual number of alcohol-associated deaths in the United States was approximately 88 000, or 9.8% of all US deaths.[2] In 2010, the estimated alcohol-related costs in the United States were $249 billion, 77% of which was attributable to binge drinking.[3] Regular binge drinking can lead to an alcohol use disorder (AUD), which is defined as a problematic pattern of alcohol use accompanied by clinically significant impairment or distress[4] (**Box 2**).

Worldwide, 5.9% of deaths (7.6% in men, 4.0% in women) are attributable to alcohol use. The leading causes of alcohol-associated deaths are cardiovascular disease and diabetes (33.4%), injuries (17.1%), gastrointestinal diseases (16.2%), and cancers (12.5%).[5] AUD may be accompanied by psychiatric disorders (eg, drug use disorders, major depressive and bipolar I disorders, specific phobias, antisocial and borderline personality disorders)[6] and by somatic and psychosocial problems (eg, liver disease; pancreatitis; cancer of the head, neck, liver, colon, and rectum; unintentional injuries; aggression; violence; suicide).[5,7] In a cross-sectional survey of 2979 individuals with AUD, 77% reported a moderate to severe psychiatric or somatic disorder. Individuals with both AUD and a psychiatric or somatic disorder had poorer associated health-related quality of life and lower work productivity than those with AUD only.[8]

This article reviews the diagnosis and pharmacologic treatment of AUD, including medications approved for AUD treatment by the US Food and Drug Administration (FDA) and those used off label. Psychosocial therapies, the most common modality of AUD treatment and typically provided to both the active and placebo groups in pharmacotherapy trials for AUD,[9] are briefly reviewed.

Box 1. Definitions of Binge Drinking, Standard Drinks, Heavy Alcohol Use, and Alcohol Use Disorder

Binge drinking: For male individuals, consumption of ≥5 standard drinks on the same occasion, and for female individuals, consumption of ≥4 standard drinks on the same occasion.
A standard drink consists of 0.6 oz of ethanol, which is contained in 12 oz of beer (ABV = 5%), 5 oz of wine (ABV = 12%), and 1.5 oz of spirits (ABV = 40%).

Heavy alcohol use: Binge drinking on 5 or more days in the past month.

Alcohol use disorder: Problematic pattern of alcohol use leading to clinically significant impairment or distress. Alcohol use disorder requires that ≥2 diagnostic criteria (Box 2) be met within a 12-month period. Mild equals 2-3 criteria; moderate, 4-6 criteria; and severe, 7-11 criteria.[1]

Abbreviation: ABV, alcohol by volume.

Methods

A literature review was conducted on July 1, 2017, and it was updated on June 15, 2018. To provide wide coverage of available studies, we searched PubMed (pharmacological treatment AND alcohol use disorder AND humans AND meta-analysis) for English-language meta-analyses of medication trials published since January 1, 2008. From these, we selected meta-analyses of multiple medications[10-12] and meta-analyses of individual medications.[13-18] In the absence of a meta-analysis focused on a specific medication's efficacy, we selected individual randomized clinical trials (RCTs), prioritizing multicenter RCTs[19] because they are more likely than single-site ones[20] to be representative of the medication's effects. To estimate the frequency of adverse events, we also prioritized meta-analyses[14,15,21,22] and, when none was available, selected multicenter RCTs.[23-25] Data presented in this article were obtained directly from published literature and not synthesized for the review.

When available, data are presented as percentages (eg, percentage abstinent) in the active and control treatment groups. For meta-analyses, which use standardized effects to combine results from multiple studies, we present the effect sizes. These include Cohen *d*, the difference between 2 means divided by the pooled standard deviation. Cohen *d* = 0.2 is a small effect size; 0.5, medium; and 0.8, large. Effects smaller than *d* = 0.2 are trivial, despite statistical significance. Hedges g is similar to Cohen *d* but uses pooled weighted standard deviations, which provide greater accuracy in estimating very small effect sizes.

Search Results

The PubMed search identified 81 articles published since 2008. From these, we selected 3 meta-analyses that covered multiple medications and were published in the past 5 years.[10-12] We also selected meta-analyses of 6 individual medications[13-18] and 2 RCTs of medications to treat AUD, a multicenter RCT,[19] and a single-site RCT.[20] To estimate the frequency of adverse events, we selected 4 meta-analyses[14,15,22,23] and 3 multicenter RCTs.[23-25]

Observations

Etiology and Neuropharmacology

Nearly 50% of AUD risk is heritable, ie, transmissible from parent to offspring, with the other 50% attributable to environmental factors.[26] A survey of more than 17 000 adult members of a health maintenance organization identified childhood and adolescent stressors, including verbal, physical, and sexual abuse and household instability (eg, physical violence directed at the mother; parental psychiatric illness, including substance use disorder; incarceration of household members), as environmental factors associated with AUD.[27] There was a strong, graded association between the number of stressors reported and the risk of AUD. There was also an interaction of stressors with a parental history of AUD, consistent with a model in which environmental factors augment a biological predisposition to AUD.[27]

The rewarding (pleasurable or stimulating) effects of alcohol are mediated by the release of dopamine in the mesolimbic dopamine system, which projects to the orbitofrontal and prefrontal cortices, areas of the brain that regulate motivation and cognitive control.[28] Alcohol also affects neurotransmitter systems involving γ-aminobutyric acid, endogenous opioids, glutamate, cannabinoids, norepinephrine, and serotonin,[29] as well as neuroendocrine systems, including the hypothalamic-pituitary-adrenal axis.[30] These systems interact with the mesolimbic dopamine reward system. Evidence of a neurobiological basis for alcohol-related reward underscores the potential utility of medications to reduce heavy alcohol use and treat AUD.

Clinical Presentation

In the United States, men are more likely to drink alcohol and to receive a diagnosis of an AUD than women. In 2016, 72.7% of men and 66.0% of women aged 18 years or older reported drinking in the past year, and 7.8% of men and 4.2% of women received an AUD diagnosis.[1] Native American individuals had the highest prevalence of AUD (9.2%), followed by non-Hispanic white individuals (5.9%), black (5.6%), Hispanic (5.1%), Pacific Islander (3.5%), and Asian (3.0%) individuals.[1] Alcohol use and the risk of AUD peak in younger adults, with those aged 21 through 25 years having the highest prevalence of past-year drinking (82.6%) and those aged 18 through 25 years having the highest prevalence of AUD (10.7%).[1] Marital status also influences AUD rates, which are highest among individuals who have never married, followed by those who are separated, divorced, or widowed, and finally those who are married or cohabiting.[6]

Patients with AUD often present in primary care or psychiatric outpatient settings, the emergency department, or to medical and surgical inpatient services. It is recommended that clinicians routinely screen all adults aged 18 years or older for unhealthy alcohol use based on a direct assessment of their level of drinking.[31]

Screening and Diagnosis

The diagnosis of AUD requires that at least 2 of the 11 *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria be present (Box 2). Despite the availability of valid screening methods for unhealthy alcohol use, in 2011, only 1 in 6 US adults and 1 in 4 persons who acknowledged binge drinking reported ever

having been asked by a health professional about their drinking.[32] Three methods to screen for heavy alcohol use have been recommended by the US Preventive Services Task Force[31]: the Alcohol Use Disorders Identification Test (AUDIT),[33] the AUDIT-C,[34] or a single question such as "How many times in the past year have you had 5 (for men) or 4 (for women) or more drinks in a day?"[31]

The AUDIT, a 10-item self-report instrument (https://pubs.niaaa.nih.gov/publications/Audit.pdf), asks about drinking and alcohol-related consequences during the preceding year.[33] AUDIT scores range from 0 to 40, with higher scores indicating greater likelihood of harmful drinking. The first 3 AUDIT items measure the quantity and frequency of alcohol consumption and comprise the AUDIT-C, with scores ranging from 0 to 12; higher scores indicate greater alcohol consumption.[34] A meta-analysis of 14 studies directly compared the performance of the AUDIT and AUDIT-C in screening for AUD in primary care, with no significant difference in accuracy between them.[35] For the AUDIT, the optimal cutoff score is greater than or equal to 4 (which yields sensitivity and specificity for detecting heavy alcohol use of 84%-85% and 77%-84%, respectively) or greater than or equal to 5 (sensitivity of 70%-92% and specificity of 73%-94%).[32] At a cutoff score of greater than or equal to 4, the AUDIT-C has a sensitivity of 74% to 76% and a specificity of 80% to 83%, and at greater than or equal to 3 its sensitivity is 74% to 88% and specificity 64% to 83%.[31] For the single-item questionnaire, greater than or equal to 1 binge-drinking day in the past year had a sensitivity of 82% to 87% and a specificity of 61% to 79%.[31] Although all 3 self-report screening approaches perform well in identifying binge drinking or heavy alcohol use, the single-item and 3-item AUDIT-C are briefer and more feasible for clinical use than the AUDIT.

Patients who screen positive for binge drinking or heavy alcohol use should be queried to determine whether they meet diagnostic criteria for AUD (Box 2). The severity of AUD and the specific criteria exhibited can be used to determine the most appropriate treatment approaches. Although patients with mild AUD may benefit from medication, there is a limited amount of evidence on the topic. In view of this and because most RCTs have enrolled participants with moderate or severe AUD, a recent practice guideline[36] recommended pharmacotherapy only for patients with AUD that is moderate or severe. For a patient who reports alcohol withdrawal symptoms, the history and severity of withdrawal signs and symptoms should be assessed to determine whether pharmacotherapy is required to treat the withdrawal syndrome.

Box 2. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* Diagnosis of Alcohol Use Disorder

Alcohol use disorder is a problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least 2 of the following, occurring within a 12-mo period:

1. Alcohol is often taken in larger amounts or over a longer period than was intended.
2. There is a 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 reduced because of alcohol use.
8. Recurrent alcohol use in situations in which it is physically hazardous.
9. Alcohol use is continued despite knowledge pf 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 desired effects
    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 (refer to criteria A and B of the criteria set for alcohol withdrawal)
    b. Alcohol (or closely related substance, such as benzodiazepine) taken to relieve or avoid withdrawal symptoms

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Treatment

Despite the high prevalence, mortality, and economic costs of AUD, in 2015, only 8.3% of the 15.8 million adults who reported needing treatment for an alcohol problem received specialty alcohol treatment.[37] Common sources of help for people with an AUD are 12-step groups (eg, Alcoholics Anonymous) and outpatient treatment by medical or nonmedical health care practitioners. Alcohol-specific psychosocial treatment has strong favorable effects on drinking outcomes. In a study of 482 alcohol-dependent adults for whom treatment was primarily psychosocial,[38] the 30-day abstinence rates 1 year after the initial assessment were 57% for the treatment sample (n = 371) and 12% for a comparison group (n = 111) identified from the general population (odds ratio = 14.67; 95% CI, 6.45-33.38). The proportion of individuals without binge drinking, psychosocial problems, or alcohol dependence symptoms was 40% in the treated group and 23% in the untreated group (odds ratio = 7.30; 95% CI, 3.49-15.30).[38]

Medications for treating AUD are underprescribed. In one study of retail outlets in the United States for 2002 through August 2007, less than 9% of patients who needed treatment for an AUD received a single prescription of any of the 4 medications approved by the FDA to treat AUD.[39] Systematic efforts in the Veterans Health Administration to increase the use of medication-assisted treatment for AUD yielded a prescription rate of only 3.4%.[40]

Patients with an AUD often have co-occurring psychiatric disorders,[6] although psychiatric symptoms (eg, depressed mood) often diminish or resolve with a reduction in heavy alcohol use or abstinence from alcohol.[41] Persistent symptoms even with abstinence may require pharmacologic treatment. When psychiatric symptoms persist despite a substantial reduction or cessation in drinking, the optimal approach is to continue alcohol pharmacotherapy and add a specific psychiatric medication. One example that illustrates the potential utility of combining medications to treat a co-occurring AUD and psychiatric disorder is a study that randomly assigned 170 depressed patients with AUD to treatment

Table 1. Food and Drug Administration–Approved Medications for Treating Alcohol Use Disorder

	Medication[a]			
	Disulfiram	Naltrexone	Long-Acting Injectable Naltrexone	Acamprosate
Indication	Management of selected chronic alcohol patients who want to remain in a state of enforced sobriety	Treatment of alcohol dependence	Treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting	Maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent
Dosage	FDA-approved dosage: 250-500 mg/d orally Dosage used in clinical trials: 125-500 mg/d	FDA-approved dosage: 50 mg/d orally Dosage used in clinical trials: 50-100 mg/d, with an initial dosage of 25-50 mg/d	FDA-approved dosage: 380 mg/mo intramuscularly Dosage used in clinical trials: 190 mg or 380 mg/mo	FDA-approved dosage: 1998 mg/d orally Dosage used in clinical trials: 1000-3000 mg/d
Effect size(s)	A meta-analysis of 22 studies (N = 2414)[13] showed an association of disulfiram with sustained abstinence from alcohol compared to control conditions only in open-label studies (Hedges g = 0.70, 95% CI, 0.46 to 0.93); there was not a significant association in blinded trials (Hedges g = 0.01, 95% CI, −0.29 to 0.32).[b] Disulfiram was associated with a better response than control conditions when medication adherence was supervised (N = 13 studies; Hedges g = 0.82, 95% CI, 0.59 to 1.05), but not when it was unsupervised (N = 9 studies; Hedges g = 0.26, 95% CI, −0.02 to 0.53).[13]	A meta-analysis (N = 16 studies and 2347 patients) showed a risk decrease (RD) for a return to any drinking associated with naltrexone 50 mg/d (RD = −0.05 (95% CI, −0.10 to −0.002); number needed to treat (NNT) = 20]. Naltrexone was also associated with reduced risk of binge drinking [19 studies; N = 2875; RD = −0.09 (95% CI, −0.13 to −0.04); NNT = 12).[11]	In the only placebo-controlled trial of long-acting naltrexone, the median monthly number of binge drinking days declined by 13.3 in the placebo group (to 6.0/mo), 14.8 in the 190-mg group (to 4.5/mo), and 16.2 in the 380-mg group (to 3.1/mo).[20]	In a meta-analysis of 16 studies (N = 4827),[11] acamprosate treatment was associated with a greater reduction in the risk of drinking among abstinent patients [RD = −0.09 (95% CI, −0.14 to −0.04); NNT = 12], but no reduction in the likelihood of binge drinking.
Most common adverse effects	Moderate or severe drowsiness occurred in 8% of patients treated with disulfiram 250 mg.[37] More severe adverse events associated with disulfiram (hepatitis, neuropathy, optic neuritis, psychosis, and confusional states) are rare.[48]	Somnolence (29.5%), nausea (25.8%), vomiting (16.9%), decreased appetite (17.7%), abdominal pain (15.9%), insomnia (16.4%), and dizziness (11.9%)[14]	Same adverse events as oral naltrexone and also injection site reactions	The only adverse event that was more common with acamprosate than placebo was diarrhea (24.9%).[15]
Clinical notes	Because the disulfiram-ethanol interaction can present as an emergency, use of disulfiram to reduce drinking, rather than sustain abstinence, is not advised.	Naltrexone can block the effects of opioid analgesics and precipitate withdrawal in a patient physically dependent on opioids.	Naltrexone can block the effects of opioid analgesics and precipitate withdrawal in a patient physically dependent on opioids.	Not metabolized; can be used in patients with hepatic disease.

Abbreviations: FDA, Food and Drug Administration; NNT, number needed to treat; RD, risk decrease.

[a] None of these medications has psychotropic effects or abuse potential.

[b] Hedges g: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect.

with sertraline (200 mg/d [n = 40]), naltrexone (100 mg/d [n = 49]), sertraline plus naltrexone (n = 42), or double placebo (n = 39) for 14 weeks. The combined treatment group had a significantly higher abstinence rate (53.7%) and longer time before relapsing to heavy alcohol use (median = 98 days) than the other 3 groups (naltrexone, 21.3% and 29 days, respectively; sertraline, 27.5% and 23 days, respectively; and placebo, 23.1% and 26 days, respectively). The naltrexone-only, sertraline-only, and placebo groups did not differ from one another.[42] In combining medications, the potential for drug-drug interactions should be considered.[43]

Although the traditional goal of treating AUD is abstinence from alcohol, treatments that reduce drinking without requiring abstinence are more attractive to many patients and can lead to a substantial reduction in alcohol-related problems.[44] In a secondary analysis[45] of participants in the largest alcohol pharmacotherapy trial to date, the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence study,[46] patients' scores on a measure of alcohol-related problems increased (worsened) directly with the number of binge-drinking days that they reported. Findings such as these led the FDA to accept the goal of no binge drinking as an alternative to abstinence in AUD treatment trials.[47] Nonetheless, in the study, although the no-binge-drinking group had better longer-term outcomes than the group with some binge drinking, the group that was abstinent had the best outcomes.[46]

FDA-Approved Medications for Treating AUD

Disulfiram, first approved for treating AUD in 1949, inhibits aldehyde dehydrogenase, which metabolizes acetaldehyde, a toxic metabolite of alcohol (**Table 1**). Inhibiting the enzyme rapidly increases the concentration of acetaldehyde and produces a disulfiram-ethanol reaction, characterized by nausea, flushing, vomiting, sweating, hypotension, palpitations, and (rarely) serious reactions, including cardiovascular collapse. Although these effects are well recognized, their frequency is not documented in the literature. The presumed effectiveness of disulfiram is based

on the patient's fear of these adverse effects, not a direct pharmacologic action.

A meta-analysis of 22 RCTs (N = 2414 participants) compared the success rate of disulfiram and controls, with success defined as one of the following: total abstinence, percentage of abstinent days, mean days of alcohol use, likelihood of no relapse, longer time to first heavy drinking day, or 3 or more weeks of consecutive abstinence. Disulfiram was associated with a higher success rate than control conditions only in open-label studies (Hedges g = 0.70; 95% CI, 0.46-0.93), with no statistically significant association in blinded trials (Hedges g = 0.01; 95% CI, 0.29-0.32).[13] Although overall the lack of evidence from controlled, blinded trials does not support the use of disulfiram for treating AUD, in the meta-analysis the supervised ingestion of the drug to ensure adherence was associated with a significantly better outcome (Hedges g = 0.82; 95% CI, 0.59-1.05) than unsupervised treatment (N = 9 studies; Hedges g = 0.26; 95% CI, −0.02 to 0.53).[13]

In a multicenter trial of disulfiram (N = 605 male veterans), the only adverse event that was significantly more frequent in the group that received disulfiram at 250 mg/d, other than events related to the disulfiram-ethanol interaction, was drowsiness, which was moderate or severe in 8% of patients treated with that dosage.[23] More severe adverse events associated with disulfiram include hepatitis, neuropathy, optic neuritis, psychosis, and confusional states, which are rare, although their frequency is not documented in the literature.[48] Because the disulfiram-ethanol interaction can present as an emergency, use of disulfiram to reduce drinking, rather than sustain abstinence, is not advised.

Naltrexone is a nonselective antagonist of μ-, κ-, and δ-opioid receptors that was initially approved to treat opioid dependence. By reducing mesolimbic opioidergic activity and thereby modulating the dopamine-mediated rewarding effects of alcohol, it reduces alcohol consumption. Two initial 12-week RCTs in which naltrexone 50 mg/d or placebo was initiated after patients achieved a period of abstinence led to the FDA's approval of that dosage for treating alcohol dependence.[49,50] A meta-analysis supports naltrexone's efficacy in reducing both the risk of relapse to any drinking (16 studies; N = 2347; risk decrease = −0.05; 95% CI, −0.10 to −0.002; number needed to treat = 20) and a return to binge drinking (19 studies; N = 2875; risk decrease = −0.09; 95% CI, −0.13 to −0.04; number needed to treat = 12).[11] Both associations, although statistically significant, are modest in magnitude, which has limited the use of naltrexone for treating AUD.[39]

Two dose levels (190 and 380 mg/mo) of a long-acting, injectable formulation of naltrexone that was developed to increase medication adherence and bioavailability were compared with placebo in a multicenter RCT of 624 participants.[19] The median number of binge-drinking days during the pretreatment period was 19.3 days/mo, which during the 24-week treatment period declined to 6.0 days/mo in the placebo group, 4.5 days/mo in the 190-mg group, and 3.1 days/mo in the 380-mg group. The decrease in the 380-mg group was significantly greater than in the placebo group,[19] leading to its approval by the FDA for treating patients with AUD who are able to abstain from alcohol in an outpatient setting before treatment initiation. In a pilot study, 23 male veterans received a 30-day prescription of oral naltrexone 50 mg and 22 received a single 380-mg intramuscular injection of naltrexone before discharge.[51] The likelihood of no binge drinking increased in both groups, from 13.6% during pretreatment to 75.0% at 45 days posttreatment in the oral naltrexone group and from 13.6% to 77.8% in the long-acting naltrexone group. The study's short duration and small sample size did not allow an adequate test of the difference between the 2 formulations.

Common adverse effects of oral naltrexone (vs placebo) include somnolence (29.5% vs 17.8%), nausea (25.8% vs 16.3%), vomiting (16.9% vs 10.4%), decreased appetite (17.7% vs 11.8%), abdominal pain (15.9% vs 7.5%), insomnia (16.4% vs 13.4%), and dizziness (11.9% vs 6.2%).[14] The drug blocks the therapeutic effects of opioid analgesics and can precipitate opioid withdrawal in a patient who is physically dependent on opioids. Long-acting naltrexone can cause the same adverse events as oral naltrexone and also injection-site reactions.[19]

Acamprosate modulates glutamatergic neurotransmission, which may underlie its efficacy in treating AUD. The FDA-approved daily dosage of the drug is 1998 mg. A meta-analysis concluded that acamprosate treatment was associated with a greater reduction than placebo in the risk of drinking among abstinent patients (16 studies; N = 4847; risk decrease = −0.09; 95% CI, −0.14 to −0.04; number needed to treat = 12) but no reduction in the likelihood of binge drinking.[11] The drug is FDA approved to sustain abstinence in patients with AUD who are abstinent at treatment initiation. Acamprosate does not interact with other psychotropic agents and is well tolerated. Of 38 adverse events considered, the only one that occurred more frequently with acamprosate than placebo was diarrhea (24.9% vs 13.9%).[15]

Non–FDA-Approved Medications for Treating AUD

Nalmefene is a μ- and δ-opioid receptor antagonist and a κ-opioid receptor partial agonist (**Table 2**). Findings from 3 multicenter trials conducted in Europe, in which patients were instructed to use the medication as needed (ie, when they were tempted to drink alcohol), led to nalmefene's approval in the European Union to reduce alcohol consumption in patients with alcohol dependence, including men who consume ethanol at more than 60 g/d (approximately 4 standard drinks) or women who consume more than 40 g/d (approximately 3 standard drinks) (see Box 1 for the definition of a standard drink). In a meta-analysis of 5 RCTs (N = 2567),[16] nalmefene treatment was associated with a reduction of 1.65 more binge-drinking days per month (95% CI, 0.89 to 2.41) than placebo at 6 months and 1.60 more binge-drinking days per month (95% CI, 0.35 to 2.85) at 1 year. Nalmefene was also associated with a greater reduction in total alcohol consumption (standardized mean difference [a measure of effect size] = −0.20 [95% CI, 0.10 to 0.30], a small effect) at 6 months.[16]

The evidence supporting the registration of nalmefene has been criticized because the evidence of efficacy was limited to a subgroup of patients defined retrospectively, the outcome measures and sensitivity analyses were not defined a priori, and the drug was compared only with a placebo, rather than to an active comparator such as naltrexone.[54]

The adverse events reported most commonly with nalmefene (vs placebo) were nausea (22.1% vs 5.9%), dizziness (18.2% vs 5.0%), insomnia (13.4% vs 5.4%), headache (12.3% vs 8.3%), vomiting (8.7% vs 2.3%), fatigue (8.3% vs 4.6%), and somnolence (5.2% vs 2.9%).[21]

Baclofen, a γ-aminobutyric acid–B receptor agonist, is FDA approved to reduce spasticity associated with neurologic disorders.

Table 2. Non–Food and Drug Administration–Approved Medications for Treating Alcohol Use Disorder

	Medication			
	Nalmefene	Baclofen	Gabapentin	Topiramate
Indication(s)	United States: Complete or partial reversal of opioid drug effects European Union: Help reduce alcohol consumption in adults with alcohol dependence who consume >60 g (≈4 drinks) per day (men) or >40 g (≈3 drinks/ day) (women).	Alleviation of signs and symptoms of spasticity resulting from multiple sclerosis	Management of postherpetic neuralgia in adults and adjunctive therapy in the treatment of partial seizures in patients age 3 and older.	Monotherapy for partial onset or primary generalized tonic-clonic seizures, adjunctive therapy for partial onset seizures or primary generalized tonic-clonic seizures and seizures associated with Lennox-Gastaut syndrome; migraine prophylaxis; weight loss and chronic weight management (in combination with phentermine)
Dosage	Approved dosage for AUD (in the European Union): 18 mg/d (as needed) Dosage in clinical trials for AUD: 5-80 mg/d in 1 dose or 2 divided doses	Dosage in clinical trials for AUD: 30-180 mg/d in up to 4 divided doses	Dosage in clinical trials for AUD: 600-1800 mg/d in 3 divided doses	Dosage in clinical trials for AUD: 75-300 mg/d in 2 divided doses
Effect size(s)	In a meta-analysis of 5 RCTs (N = 2567),[16] nalmefene treatment was associated with a reduction in binge drinking of 1.65 d (95% CI, 0.89 to 2.41) more per month at 6 mo and by 1.60 d more per month (95% CI, 0.35 to 2.85) at 1 y, and with a reduction in total alcohol consumption of 20% (95% CI, 0.10 to 0.30) at 6 mo.	In a meta-analysis of 13 RCTs (N = 1492),[17] baclofen was associated with a significantly greater time to first lapse to drinking [SMD = 0.42 (95% CI, 0.19 to 0.64)] and a greater likelihood of abstinence during treatment [odds ratio = 1.93 (95% CI, 1.17 to 3.17)], with no greater difference at a higher dosage (>60 mg/d). Persons who drank very heavily at study entry had a greater association of abstinence with baclofen.	Of 3 peer-reviewed, placebo-controlled RCTs (total N = 231), the largest (N = 150) showed that gabapentin resulted in a rate of abstinence of 11.1% (95% CI, 5.2 to 22.2) in the 900-mg/d group and 17.0% (95% CI, 8.9 to 30.1) in the 1800-mg/d group, compared with 4.1% (95% CI, 1.1 to 13.7) for placebo. The rate of no binge drinking was 22.5% (95% CI, 13.6 to 37.2) in the placebo group, 29.6% (95% CI, 19.1 to 42.8) in the gabapentin 900 mg/d group, and 44.7% (95% CI, 31.4 to 58.8) in the 1800 mg/d group.[20] Preliminary findings from a multi-center trial of enacarbil ER (N = 346)[52] showed no treatment effect on the primary outcome measure, percent of subjects with no binge drinking (28.3% vs 21.5% for placebo) or any other drinking measures.	In a meta-analysis of 7 RCTs (N = 1125), there were small-to-medium effects of topiramate on abstinent days (Hedges g = 0.468)[a] and binge drinking days (Hedges' g = 0.406).[18]
Most common adverse effects	Nausea (22.1%), dizziness (18.2%), insomnia (13.4%), headache (12.3%), vomiting (8.7%), fatigue (8.3%), somnolence (5.2%)[21]	With low-dose treatment (30 mg/d): drowsiness (39.1%), dizziness (26.4%), headache (25.3%), confusion (23.0%), muscle stiffness (16.1%), excessive perspiration (14.9%), itching/pruritus (14.9%), abnormal muscle movements (13.8%), numbness (12.6%), slurred speech (10.3%)[24]	Dizziness (19.1%), somnolence (14.1%), ataxia or gait disorder (14.0%), peripheral edema (6.6%)[22]	Paresthesia (50.8%), dysgeusia (23.0%), anorexia (19.7%), difficulty with concentration/ attention (14.8%), nervousness (14.2%), dizziness (11.5%), pruritis (10.4%).[25] Transient mental slowing and modest reductions in verbal fluency and working memory are generally dose related.[53]
Clinical notes	Not approved in the United States for treating AUD	Temporary recommendation in France for use in the management of alcohol dependence at a maximum recommended dosage of 80 mg/d	Potential bias due to high rate of treatment non-completion in the largest trial.[53] Additional studies needed to validate medication effects.	To reduce risk/severity of adverse effects, begin treatment at 25-50 mg/d, with 25-50 mg/d increases at weekly intervals. Contraindicated in patients with a predisposition or history of metabolic acidosis, renal calculi, and secondary angle closure glaucoma.

Abbreviations: AUD, alcohol use disorder; RCT, randomized clinical trial.

[a] Hedges g: 0.2 = small effect, 0.5 = medium effect, and 0.8 = large effect.

In 2014, it was given a temporary recommendation in France for treating alcohol dependence. A recent meta-analysis on outcome data from 13 RCTs (total N = 1492)[17] showed that baclofen was associated with a significantly greater time to first lapse to drinking (standardized mean difference = 0.42; 95% CI, 0.19 to 0.64), a greater likelihood of abstinence during treatment (odds ratio = 1.93; 95% CI, 1.17 to 3.17), and a nonsignificantly greater percentage of days abstinent (standardized mean difference = 0.21; 95% CI, −0.24 to 0.66) than placebo. There was also a significant difference based on dosage: studies of baclofen at less than 60 mg/d showed the drug to be associated with a longer time to a first lapse in drinking (standardized mean difference = 0.57; 95% CI, 0.30 to 0.84), whereas those that used greater than 60 mg/d did not (standardized mean difference = 0.12; 95% CI, −0.07 to

0.28).[17] Finally, higher daily alcohol use at baseline was associated with a larger baclofen treatment effect.[17] In summary, baclofen was associated with delay in return to drinking and with sustained abstinence, particularly in individuals who at baseline drank very heavily, with no added benefit at a dosage greater than 60 mg/d.

Although baclofen treatment is associated with abstinence, it has not been associated with improvement on other drinking outcomes, such as binge drinking and the percentage of abstinent days. Baclofen is also associated with adverse effects, including sedation (reported by 46.5% of high-dose baclofen patients compared with 24.5% of placebo patients).[55] In a low-dose baclofen study (30 mg/d),[24] the common adverse events observed more frequently with baclofen than placebo were drowsiness (39.1% vs 32.6%), dizziness (26.4% vs 22.8%), headache (25.3% vs 19.6%), confusion (23.0% vs 15.2%), muscle stiffness (16.1% vs 12.0%), excessive perspiration (14.9% vs 10.9%), itching or pruritus (14.9% vs 9.8%), abnormal muscle movements (13.8% vs 9.8%), numbness (12.6% vs 1.0%), and slurred speech (10.3% vs 4.3%).

Gabapentin is FDA approved to treat epilepsy and neuropathic pain. To our knowledge, there are no published meta-analyses of gabapentin for treating AUD, with the only peer-reviewed findings coming from 3 placebo-controlled, RCTs (total N = 231 patients).[56] The largest of these trials (N = 150) compared gabapentin 900 or 1800 mg/d with placebo for 12 weeks and showed a higher rate of abstinence in the low- and high-dose gabapentin groups (11.1% [95% CI, 5.2% to 22.2%] and 17.0% [95% CI, 8.9% to 30.1%], respectively) than placebo (4.1%; 95% CI, 1.1% to 13.7%). The placebo group had a lower rate of no binge drinking (22.5%; 95% CI, 13.6% to 37.2%) than the groups receiving gabapentin at either 900 mg/d (29.6%; 95% CI, 19.1% to 42.8%) or 1800 mg/d (44.7%; 95% CI, 31.4% to 58.8%).[20] However, this study had a high dropout rate (43%), which could have biased the findings. Preliminary findings from a multicenter trial of enacarbil ER, a prodrug formulation, in 346 patients with moderate or severe AUD[52] showed no effect of gabapentin on either the primary outcome measure, percentage of subjects with no binge-drinking days (28.3 vs 21.5 for gabapentin and placebo, respectively), or any other drinking measure.

The most common adverse events associated with gabapentin treatment compared with placebo are dizziness (19.1% vs 6.6%), somnolence (14.1% vs 5.2%), ataxia or gait disorder (14.0% vs 2.2%), and peripheral edema (6.6% vs 1.5%).[22] A systematic review showed that approximately 1% of the general population misused gabapentin for recreational purposes, self-medication, or intentional self-harm, either alone or in combination with other substances (including alcohol).[53]

Topiramate is FDA approved to treat seizure disorder, prevent migraine, and facilitate weight loss (in combination with phentermine). A meta-analysis of the medication's effects in AUD, which included 7 RCTs (total N = 1125), showed that topiramate was associated with a greater number of abstinent days (Hedges g = 0.468) and lower binge-drinking frequency (Hedges g = 0.406) than placebo.[18]

Blodgett et al[18] compared effect sizes for topiramate and naltrexone from 3 randomized trials (1 placebo-controlled and 2 open-label studies) that directly compared the 2 medications. Topiramate was associated with a significantly greater reduction than naltrexone on an aggregate measure of binge drinking (Hedges g = 0.284; *P* = .04), although not on an aggregate measure of abstinence (Hedges g = 0.149; *P* = .30). However, a recent meta-analysis comparing the associations of nalmefene, naltrexone, acamprosate, baclofen, and topiramate with reduced drinking in 6036 patients[57] concluded that there was no high-grade evidence supporting the use of these medications to control drinking. Ascertaining the relative efficacy of medications to treat AUD will require large, high-quality, RCTs that compare these and other medications directly.

The adverse effects that were significantly more common with topiramate than with placebo were paresthesia (50.8% vs 10.6%), dysgeusia (23.0% vs 4.8%), anorexia (19.7% vs 6.9%), difficulty with concentration or attention (14.8% vs 3.2%), nervousness (14.2% vs 7.5%), dizziness (11.5% vs 5.3%), and pruritus (10.4% vs 1.1%).[25] A more detailed analysis of the transient cognitive impairment caused by topiramate showed that it includes mental slowing and modest reductions in verbal fluency and working memory, which are generally dose related.[58]

Developments in the Pharmacogenetics of AUD

In the past decade, advances in human genetics have led to the identification of genetic polymorphisms that may predict individual responses to medications for treating AUD.[59] Although initial pharmacogenetic findings for some medications have shown promise for this use, prospective data have either failed to confirm the effects or are not available. Therefore, the use of pharmacogenetics is not recommended in treating AUD.

Clinical Practice Guidelines

A recent practice guideline published by the American Psychiatric Association[36] recommended that the FDA-approved drugs disulfiram, naltrexone, and acamprosate be offered to patients with moderate to severe AUD. The data reviewed here support the use of naltrexone to reduce the risk of binge drinking and acamprosate to maintain abstinence, although in 2 US multicenter studies acamprosate was no better than placebo on any alcohol-related outcomes.[11] The use of disulfiram appears justified only when its administration is supervised to ensure adherence. The American Psychiatric Association guideline also suggests that gabapentin or topiramate be offered to patients who prefer one of these drugs or who are intolerant of or have not responded to the FDA-approved medications.[36]

The small number of patients studied, the high rate of loss to follow-up, and the fact that gabapentin can be used by patients, particularly those with a substance use disorder, to achieve intoxication argue against its use as a first-line treatment for AUD. A meta-analysis of topiramate's efficacy showed clinically significant associations with improvements on multiple alcohol-related outcomes.[18] Consistent with that evidence, topiramate, disulfiram, acamprosate, and naltrexone are recommended as appropriate first-line treatments in the practice guideline published by the Department of Veterans Affairs/Department of Defense.[60] Even before the publication of the practice guideline, the use of topiramate to treat AUD doubled in the Veterans Affairs Health System in a 3-year period.[61]

Combining Psychosocial Treatments With Alcohol Treatment Medications

Psychosocial interventions have been shown to be efficacious in treating heavy alcohol use or AUD.[9] These include brief interventions,

motivational enhancement therapy, cognitive behavioral therapy, behavioral approaches, family therapies, and 12-step facilitation (to approximate the 12-step treatment in a study environment).[9] Of these, brief interventions, which are commonly 15 to 20 minutes long, are most feasible in medical settings. When more intensive psychosocial therapy is needed (eg, cognitive behavioral therapy), it may be most feasible for a therapist trained in the specific method to provide it in concert with a medical practitioner who can prescribe an alcohol treatment medication. A recent meta-analysis of 34 studies (N = 15 197)[62] showed that participants who received a brief psychosocial intervention consumed 20 g (95% CI, 12 to 28 g), or approximately 1.5 standard drinks (Box 1), less per day than those in a minimal or no-intervention comparison group after 1 year. However, there was little difference between groups on the frequency of drinking or binge-drinking days. The studies largely excluded individuals with an AUD and did not study counseling with medication.

Most clinical trials of alcohol treatment medications provide patients with a standardized psychosocial treatment to enhance their retention and treatment adherence.[9] Studies of medications to reduce drinking or maintain abstinence have included a wide range of psychosocial treatments. Although combining psychosocial and pharmacologic treatments for AUD could be more efficacious than either treatment alone, few studies have examined the effect of varying the intensity of the psychosocial treatment. Therefore, definitive recommendations on the optimal combinations are not possible. The Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence study[46] compared 4 months of treatment with naltrexone, acamprosate, or their combination with placebo in 1383 patients. All groups received either medical management, a low-intensity behavioral treatment designed for use in primary-care settings, or a combined behavioral intervention, a more intensive treatment delivered by licensed behavioral health specialists. Group assignments were randomized for both the medication (which was administered double blind) and behavioral treatments (for which raters were blinded). During the 4-month treatment period, 68.2% of naltrexone-treated patients had greater than or equal to 1 binge-drinking day compared with 71.4% of placebo patients (P = .02). When naltrexone treatment was combined with medical management, naltrexone-treated patients were abstinent on 80.6% of days compared with 75.1% in the placebo group (P = .009). Although the combined behavioral intervention was more efficacious than medical management, it did not enhance medication efficacy.[46] Thus, providing AUD patients with a brief psychosocial intervention and a first-line alcohol treatment medication or referring them for specialized psychotherapy can help them to reduce both the frequency with which they drink and their risk of binge drinking.

Recommended Approach to Treatment

Patients receiving a diagnosis of an AUD should be advised to substantially reduce or stop their alcohol use. Although recent guidelines on moderate drinking recommend that men consume no more than 2 drinks per day and women 1 drink per day, with no binge drinking,[63] a meta-analysis of nearly 600 000 participants showed a positive curvilinear association with alcohol consumption level, with increased all-cause mortality risk beginning at 100 g (ie, 7 standard drinks) per week, irrespective of sex.[64]

Together with brief counseling, a first-line medication such as oral naltrexone is well tolerated. It can be initiated at a once-daily dosage of 25 mg and increased to 50 mg after 3 days and 100 mg after 7 days.[46] Studies have not directly compared the effects of requiring abstinence before initiation of a medication to treat AUD. Although there is evidence that a longer period of abstinence prior to initiating treatment with long-acting naltrexone may result in better treatment outcomes,[65] studies of naltrexone[66] and topiramate[25,67] that did not require abstinence before treatment have shown the active medication's superiority to placebo treatment.

Patients whose drinking does not respond to this approach or who seek or would benefit from more intensive counseling can be referred to a behavioral specialist while continuing the medication. A similar referral can be provided to patients who choose not to use a medication. If naltrexone is determined to be ineffective after a month of treatment, treatment with an alternative drug, such as topiramate, can be initiated at a dosage of 25 mg daily, with a gradual increase during 5 to 6 weeks to 100 mg twice daily.[67]

Prognosis

Because AUD has a chronic, relapsing course, ongoing clinical management is required. In the absence of empirical data to guide the optimal duration of treatment, pharmacotherapy is recommended for at least 6 months, at which point its usefulness can be reevaluated. If deemed clinically necessary, the medication can be continued indefinitely.

Limitations

This review has some limitations. First, the literature on medications to treat AUD is limited. Except for naltrexone and acamprosate, the number of RCTs testing the efficacy of medications for AUD is inadequate to draw definitive conclusions. Second, randomized trials have not evaluated the optimal duration of treatment for any medication. Third, randomized trials have not evaluated use of a stepped approach or combination therapy for a patient with a partial or nonresponse to treatment. Fourth, this review is based largely on meta-analyses, and although they provide the broadest coverage of the literature, the outcomes used to evaluate therapies differ across studies (eg, number needed to treat, different measures of effect size), making comparisons across medications difficult and limiting their clinical applicability.

Conclusions

Validated screening methods are available to identify patients with heavy alcohol use. Patients who meet criteria for an AUD should be prescribed brief counseling and naltrexone as initial therapy or referred for a more intensive psychosocial intervention. With continued monitoring of the patient's drinking, the treatment can be altered by increasing the intensity or type of psychosocial treatment and adding or substituting another first-line medication to ensure the best outcomes. Additional research is needed to identify more efficacious medications and to define the optimal duration, sequence, and combination of therapies to guide the treatment of AUD.

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