CHAPTER **60**

Pharmacological Interventions for Alcohol Use Disorder

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CHAPTER OUTLINE

INTRODUCTION

There were over 140,000 deaths, attributable to excessive alcohol use, annually, from 2015 to 2019. Each year, there was a total of 3.6 million years of potential life lost due to these deaths[1] Most recent national statistics estimate that 14.5 million people, above the age of 12, meet criteria for alcohol use disorder (AUD) with less than 10% of them receiving any treatment.[2] The first medication to treat AUD, disulfiram, was approved in 1949 and yet, in 2020, less than 6% of individuals who received care for AUD were treated with a U.S. Food and Drug Administration (FDA) approved medication.[3] These data show substantial underutilization of these pharmacological interventions that have been shown to reduce return to use risk, improve retention in treatment, and reduce health care costs associated with AUD.[4] Medications used to treat substance use disorders, including AUD, have been shown to restore in part the upregulation of impulse and reward circuitry and down regulation of cognitive control, which occur with these disorders and lead to compulsive substance use despite negative consequences.[5] In this chapter, we selectively review the literature on the use of medications to reduce drinking or prevent return to use in those with alcohol use above recommended limits with a focus of the chapter on developments of current interest to the clinician or that are likely to yield important clinical advances in the future.

The first main approach to the use of medications in the treatment of individuals with AUD involves direct efforts to reduce or stop drinking behavior by producing adverse effects when alcohol is consumed or by modifying the neurotransmitter systems that mediate alcohol reinforcement. **Table 60-1** lists the four medications or formulations that use this approach and are approved by the FDA for the treatment of AUD. The table also shows the year of FDA approval, the presumed mechanism of action, and the approved dosage for each. The medications are discussed individually in the sections that follow. The second main approach to the treatment of AUD involves the treatment of persistent psychiatric symptoms, which aims to stop or reduce drinking by modifying the motivation to use alcohol to "self-medicate" such symptoms. Medications for which this rationale underlies their use in the treatment of AUD are discussed in the latter part of this chapter.

TABLE 60-1 Medications Approved by the U.S. Food and Drug Administration for the Treatment of Alcohol Dependence

Medication	Year Approved	Description
Disulfiram	1949	Aversive medication; after ingestion, alcohol consumption leads to a variety of aversive symptoms. Approved dosage is 250-500 mg/d.
Naltrexone	1994	Orally bioavailable opioid antagonist that decreases the reinforcing effects of alcohol. Most robust effects clinically are to reduce risk of heavy drinking. Approved dosage is 50 mg/d.
Acamprosate	2004	GABA receptor agonist and NMDA receptor modulator. Most robust effects clinically are to maintain abstinence. Approved dosage is 666 mg three times daily.
Long-acting naltrexone	2006	Injectable formulation that produces detectable plasma concentrations for 30 days. May help to improve adherence compared to oral formulation. Approved dosage is 380 mg/mo.

In guiding patients in choosing a medication to help them manage excessive alcohol use, clinicians must personalize treatment recommendations to fit with patient determined outcomes. For some patients, complete abstinence from alcohol will be the goal, while others may express desire to merely moderate their drinking. Both goals are

acceptable as many health outcomes improve significantly with the reduction of heavy drinking.[6]

MEDICATIONS USED TO REDUCE OR STOP DRINKING

Several neurotransmitter systems appear to influence the reinforcing or discriminative stimulus effects of ethanol: endogenous opioids; catecholamines, especially dopamine; serotonin (5-HT); and excitatory amino acids (eg, glutamate).[7,8] Although these systems function interactively to influence drinking behavior, many of the medications that have been employed to treat AUD affect neurotransmitter systems relatively selectively. Consequently, these systems are discussed individually here.

Opioidergic Agents

Naltrexone and, to a lesser extent, nalmefene, both of which are opioid antagonists with no intrinsic agonist properties, have been studied for the treatment of AUD. In 1984, naltrexone was approved by the FDA for the treatment of (pre-DSM-5) opioid dependence; in 1994, it was approved for the treatment of (pre-DSM-5) alcohol dependence. Nalmefene is approved in the United States as a parenteral formulation for the acute reversal of opioid effects. As we discuss these medications below, we'll be using the terms (from the DSM-5) AUD or (pre-DSM-5) alcohol dependence, depending on the terminology and diagnostic criteria used in the referenced studies.

Naltrexone

The approval by the FDA of naltrexone for alcohol dependence was based on the results of two single-site studies, which showed it to be efficacious in the prevention of return to heavy drinking.[9,10] In a 12-week trial in a sample of veterans with alcohol dependence, Volpicelli et al.[9] found naltrexone to be well tolerated and to result in significantly less craving for alcohol and fewer drinking days than placebo. Among patients who drank, naltrexone

also limited the progression from initial sampling of alcohol to return to heavy drinking, presumably because of their experiencing less euphoric effects of alcohol, suggesting that naltrexone blocked the endogenous opioid system's contribution to alcohol's "priming effect."[11]

The efficacy of combining naltrexone with either supportive or cognitive-behavioral therapy (CBT) in patients with alcohol dependence was studied by O'Malley et al.[10] This 12-week trial showed the medication to be well tolerated and to be superior to placebo in increasing the rate of abstinence and reducing the number of drinking days and return to use events and the severity of alcohol-related problems. There was an interaction effect of medication and therapy. The cumulative rate of abstinence was highest for patients treated with naltrexone and supportive therapy. However, for patients who drank, those who received naltrexone and coping skills therapy were least likely to return to heavy drinking.

Analysis of the potential mediating variables in these effects showed that naltrexone reduced craving for alcohol, alcohol's reinforcing properties, the experience of intoxication, and the chances of continued drinking following a brief period of drinking.[11] During a 6-month, posttreatment follow-up period, the effects of naltrexone diminished gradually over time, suggesting that patients may benefit from treatment with naltrexone for longer than 12 weeks.[12]

Many, but not all, subsequent studies of naltrexone have provided support for its use in alcohol treatment. The literature on naltrexone treatment of AUD has been reviewed in detail in a number of meta-analyses. The meta-analyses that included the largest number of studies[13],[14],[15] show a clear advantage for naltrexone over placebo on several drinking outcomes.

A network meta-analysis of 54 RCTs found naltrexone to be effective in reducing heavy drinking days and promoting abstinence when compared to placebo.[13]

A Cochrane systematic review included 50 RCTs investigating the effect of naltrexone versus placebo on drinking outcomes with (N = 7,793). They concluded that naltrexone reduced the risk of heavy drinking, drinking days, heavy drinking days, consumed amount of alcohol, and the alcohol

consumption biomarker, gamma-glutamyl transferase. Naltrexone was not found to effectively prevent return to any drinking.[14]

The meta-analysis of Jonas et al.[15] included 44 placebo-controlled trials of naltrexone (N = 2,347). The number needed to treat to prevent any return to any alcohol drinking was 20 and the number needed to treat to prevent return to heavy drinking was 12.

Follow-up studies of patients treated with naltrexone or placebo for 12 weeks[12,16] or 4 months[17] have shown that the medication group differences are no longer significant at posttreatment follow-up. These findings suggest that treatment with naltrexone is warranted for longer than 4 months, though the optimal duration of treatment is unknown.

An alternate approach to the use of naltrexone based on its efficacy in reducing the risk of heavy drinking among patients who continue to drink was evaluated in a study that compared the effects of naltrexone 50 mg with those of placebo in an 8-week study of unhealthy drinking.[18] In this study, patients were randomly assigned to receive study medication either daily or for use targeted to situations identified by the patients as being high risk for heavy drinking (with the number of tablets available for use by patients in the targeted conditions decreasing over the course of the trial). Irrespective of whether they received naltrexone or placebo, patients who were trained and encouraged to use targeted treatment showed a reduced likelihood of any drinking. There was also a 19% reduction in the likelihood of heavy drinking with naltrexone treatment, suggesting that naltrexone may be useful in reducing heavy drinking, among patients who want to reduce their drinking to safe levels.

Targeted naltrexone was also used by Heinala et al.,[19] who compared it with placebo, paired with either coping skills or supportive therapy. During an initial 12 weeks of treatment, this study showed an advantage for naltrexone in preventing return to heavy drinking but only when combined with coping skills therapy. During a subsequent 20-week period, subjects were told to use the medication only when they craved alcohol (ie, targeted treatment). The beneficial effect of naltrexone on the risk of return to use was generally sustained during the period of targeted treatment. Based on these findings, it appears that targeted medication administration may be useful both for the initial treatment of unhealthy drinking and for maintenance of the beneficial effects of an initial period of daily naltrexone.

O'Malley et al.[20] conducted a sequence of randomized trials in which subjects with alcohol dependence were first treated with 10 weeks of open-label naltrexone 50 mg, combined with either CBT or primary care management (PCM; a less intensive, supportive approach). Treatment responders from the PCM group and from the CBT group continued in separate 24-week, placebo-controlled studies of maintenance naltrexone. No difference was observed with respect to persistent heavy drinking, with more than 80% of both groups having a positive outcome. However, the percentage of days abstinent declined more over time for the PCM group. In the follow-up studies, there was a greater maintenance response for naltrexone than placebo when combined with PCM, but the advantage for naltrexone did not reach significance when combined with CBT. These findings suggest that the beneficial effects of treatment with naltrexone can be maintained during an extended period using either a more intensive, skills-oriented treatment (ie, CBT) or a less intensive, supportive treatment combined with continued naltrexone administration.

Since naltrexone only targets certain aspects of AUD (ie, reduced alcohol reinforcement or cue-induced craving), there has been an interest in combining it with medications that might influence other signs/symptoms of AUD. Symptoms often seen after alcohol abstinence are difficulty sleeping, anxiety, irritability, decreased concentration, and depressed mood. This constellation of symptoms has been called protracted withdrawal. If not addressed, the symptoms of protracted withdrawal are thought to lead to return to alcohol use (ie, negative reinforcement). The anticonvulsant gabapentin may help reduce these symptoms. As such, naltrexone has been evaluated in combination with gabapentin to determine if the combination was superior to naltrexone alone and/or placebo in decreasing alcohol use.

Anton et al.[21] conducted a 16-week clinical trial of 150 subjects with alcohol dependence who were randomly assigned to naltrexone 50 mg/d alone for 16 weeks (N = 50), naltrexone 50 mg/d with gabapentin up to 1,200 mg/d for the first 6 weeks (N = 50), or double placebo (N = 50). All study patients received a combined behavioral intervention that combined CBT, motivation enhancement, and twelve-step facilitation techniques. The results indicated that during the first 6 weeks, when gabapentin was combined with naltrexone, the combination group had a longer interval to heavy drinking than did the naltrexone alone group (which was similar to

placebo), had fewer heavy drinking days than did the naltrexone alone group (which had more than did the placebo group), and had fewer drinks per drinking day than did the naltrexone alone group and the placebo group. The findings in the combination group faded over the remaining weeks of the study. There was some suggestion that the combination may work best in individuals who had previously experienced alcohol withdrawal. The investigators hypothesized that the lack of efficacy for naltrexone versus placebo may have been due to the robust psychosocial intervention.[17]

Poor adherence to oral naltrexone has been shown to reduce the potential benefits of the medication.[22] This generated interest in the development and evaluation of long-acting injectable formulations of the medication. The rationale behind this approach is that monthly, compared with daily, administration would improve medication adherence and that parenteral administration would increase bioavailability by avoiding first-pass metabolism.

Two dosage strengths of a second formulation were evaluated over 6 months of treatment in combination with a low-intensity psychosocial intervention in more than 600 individuals with AUD who received 6 monthly injections of either long-acting naltrexone (380 mg or 190 mg) or matching volumes of placebo.[23] Abstinence from alcohol was not required for study participation. The medication and the injections were well tolerated. Compared with placebo, treatment with the 380-mg naltrexone formulation reduced the event rate of heavy drinking by 25%, a statistically significant effect. The 17% reduction in the rate of heavy drinking produced by the 190-mg formulation did not reach statistical significance. Based on these findings, the FDA approved long-acting naltrexone for monthly administration at a dosage of 380 mg. Because the analysis also showed that the most robust effects of the medication were seen in patients who were abstinent (by choice) for at least a week before randomization, the package insert states that the medication should be used only in individuals with AUD who are abstinent at treatment initiation. However, abstinence should not be a requirement for initiating treatment with long-acting naltrexone, as patients can still experience reduction in heavy drinking days without requiring a lead in period of abstinence.[23,24]

In a meta-analysis of 7 RCTs (N =1,500) of adults with AUD receiving treatment in outpatient clinics, long-acting naltrexone was compared to

placebo in its effect on alcohol consumption. Long-acting naltrexone was found to significantly reduce drinking and heavy drinking days per month. Additionally, treatment duration of more than 3 months was found to be significantly associated with a reduction of heavy drinking days per month.[24]

Clinical Considerations in the Use of Naltrexone

The clinical use of naltrexone is relatively straightforward. The medication can be prescribed with or without psychosocial treatment. Liver function tests (LFTs) should be checked at baseline and within several weeks after initiating treatment. Prescribing should be avoided in the context of acute liver injury or severe impairment. Naltrexone can be started in patients with mild liver impairment, where liver function tests are no higher than 3 times the upper limit of normal range. Ongoing monitoring is required only if symptoms warrant it because the consistent effect of naltrexone in studies of AUD has been to decrease liver enzyme concentrations.

Oral naltrexone should be administered initially at a dosage of 25 mg/d to minimize adverse effects. The dosage can then be increased in 25-mg increments every 3 to 7 days to a maximum dosage of 150 mg/d using desire to drink or another symptom that the patient identifies as reflective of risk of return to heavy drinking. It should be noted, however, that there is no clear evidence that a higher dosage is more efficacious than is the FDA-approved dosage of 50 mg/d. Nausea and other gastrointestinal symptoms are most common early in treatment, as are neuropsychiatric symptoms (eg, headache, dizziness, lightheadedness, weakness), and are usually transient. Delaying or avoiding a dosage increase can be used to address more persistent adverse events. In a few patients flu-like symptoms occur, and the patient may not be willing to consider options other than discontinuation.

Long-acting naltrexone is only available as a 380-mg dose, which should be administered as a deep intramuscular injection in the upper, outer quadrant of the gluteal muscle of the buttock every 4 weeks. With repeated administrations, the injection should be alternated to the side contralateral to the immediately preceding injection. The medication is approved for use in patients who are abstinent from alcohol and who are also receiving psychosocial treatment. The precise length of the period of abstinence is not specified, and there is no evidence of any risk of consuming alcohol with

naltrexone. Adverse effects with this formulation are similar to those of the oral medication, though pain and inflammation at the injection site may also occur. Local interventions, such as warm compresses, and nonsteroidal anti-inflammatory medications can be used to treat such injection site reactions.

Nalmefene

Nalmefene has also been evaluated as a treatment for AUD. As with naltrexone, nalmefene is an opioid antagonist without agonist properties. Nalmefene's affinity for the μ- and κ-opioid receptors is similar to that of naltrexone, though its affinity for the δ-opioid receptor is greater than that of naltrexone.[25] A pilot study of nalmefene 40 mg/d showed it to be superior to both 10 mg/d of the medication and placebo in the prevention of return to heavy drinking in patients with alcohol dependence.[26] A subsequent study showed no difference between nalmefene 20 or 80 mg/d. However, when combined, the nalmefene-treated subjects reported significantly less heavy drinking than did the placebo group.[27] A 12-week, multisite, dose-ranging study compared placebo with 5, 20, or 40 mg of nalmefene in a sample of recently abstinent outpatients with alcohol dependence.[28] In this study, all subjects showed a reduction in self-reported heavy drinking days and on biological measures of drinking, with no difference between the active medication and placebo groups on these measures. Targeted nalmefene (where subjects were encouraged to use 10 to 40 mg of the medication when they believed drinking to be imminent) was combined with a minimal psychosocial intervention in a multicenter, placebo-controlled, randomized trial.[29] Nalmefene was superior to placebo in reducing heavy drinking days, very heavy drinking days, and drinks per drinking day and in increasing abstinent days. Further, after 28 weeks of treatment, when a subgroup of nalmefene-treated subjects was randomized to a withdrawal extension, patients assigned to receive placebo were more likely to return to heavier drinking. Nalmefene was approved for reduction of alcohol use by the European Medicines Agency in 2013 at a dosage of 18 mg/d as needed when the patient perceives a risk of alcohol consumption.

SUMMARY

There is an abundance of evidence demonstrating the efficacy of opioid antagonists (particularly naltrexone) for the treatment of AUD. These are safe medications that can be used to assist patients in achieving complete abstinence from alcohol or reduction in heavy drinking days. Naltrexone can be used as targeted treatment, on days with potential increased risk of drinking, if patients are having difficulty with daily adherence or with tolerating it. Patients who have a family history of AUD, early age of drinking onset, or who have co-occurring use of substances other than alcohol, may have a better clinical response to naltrexone.[30] Long-acting naltrexone should be considered when adherence to medication is challenging. Treatment with it can be initiated even if patients are not abstinent, and outcomes are likely to improve with longer duration of treatment.

Acamprosate

Acamprosate (calcium acetyl homotaurinate) is an amino acid derivative that increases gamma-aminobutyric acid (GABA) neurotransmission and has complex effects on excitatory amino acid (ie, glutamate) neurotransmission, which is most likely the effect that is important for its therapeutic effects in AUD. Acamprosate was first shown in a single-site study to be twice as effective as placebo in reducing the rate at which patients with alcohol dependence returned to drinking.[31] The medication has been studied extensively in Europe, and three of the European studies provided the basis for the approval of acamprosate by the FDA for clinical use in the United States.[32]

A meta-analysis of 35 RCTs investigating acamprosate's utility in treating AUD concluded that it was effective in reducing heavy drinking as well as promoting abstinence from alcohol.[13] A meta-analysis of continuous abstinence showed also significant advantage for acamprosate over placebo, and although the effects were modest, they increased progressively as treatment duration increased from 3 to 6 and then to 12 months.[33]

In a study that has implications for the use of acamprosate in combination with disulfiram, a multicenter trial was conducted in which patients were randomly assigned to receive acamprosate or placebo, with stratification for those who voluntarily were using disulfiram. Acamprosate

was found to be superior to placebo on measures of total abstinence and on cumulative abstinent days.[34] The group treated with acamprosate and disulfiram showed a significantly greater percentage of abstinent days than did any of the other three groups. However, because the design was not fully randomized, more rigorous studies of this combination therapy are needed to evaluate the validity of these findings.

Studies in more than 4,000 patients in Europe provided evidence of a beneficial effect of acamprosate in the prevention of return to drinking and in the reduction of drinking in those who return to use. However, two multicenter trials conducted in the United States, the first being a multicenter trial of two active dosages of acamprosate[35] and the second being the COMBINE (Combining Medications and Behavioral Interventions for Alcoholism) study,[17] the largest alcohol treatment trial to date (described in the following section), failed to show an advantage of acamprosate over placebo on an intent-to-treat basis. This raises the question of the factors that distinguish alcohol pharmacotherapy trials in Europe from those in the United States. Differences in features of study design (eg, European studies required a lengthier period of abstinence) and of the samples studied (eg, European subjects drank more heavily) may explain these discrepant findings.

Clinical Considerations in the Use of Acamprosate

Acamprosate is FDA approved at a dosage of 1,998 mg/d (ie, two 333-mg capsules three times per day) in patients who are abstinent from alcohol and receiving psychosocial treatment. The most common adverse effects of the drug are generally mild and transient and include gastrointestinal (eg, diarrhea, bloating) and dermatological (eg, pruritus) complaints. In contrast to disulfiram and naltrexone, which are metabolized in the liver, acamprosate is excreted unmetabolized, so that renal function is the rate-limiting factor in the drug's elimination. Evaluation of renal function prior to initiation of the drug is warranted, particularly in individuals who have a history or are otherwise at risk of renal disease and in the elderly.

Studies Comparing Acamprosate With Naltrexone and the Two Medications Combined

Two placebo-controlled studies have directly compared treatment with acamprosate, naltrexone, and acamprosate and naltrexone combined. In the first study, a 12-week trial in 160 patients, all three active medication groups (naltrexone, acamprosate, and the two medications combined) were significantly more efficacious than was placebo.[36] In that study, although the rate of return to use of participants in the combined medication group was significantly lower than that in either the placebo or acamprosate groups, it was not statistically better than naltrexone alone.

The COMBINE study, a 4-month, multicenter, placebo-controlled study conducted at 11 sites in the United States, compared naltrexone, acamprosate, and their combination in a sample of nearly 1,400 abstinent individuals with alcohol-dependence. The design of the study was complex, insofar as two different behavioral interventions (medical management or an intensive behavioral treatment) were combined with naltrexone (100 mg/d), acamprosate (3 g/d), naltrexone and acamprosate, or placebo, so that eight groups received study medication. Further, to evaluate the effects of placebo treatment, a ninth group, which received an intensive behavioral treatment but no medication, was also included. Overall, when receiving treatment, subjects significantly increased the percentage of abstinent days. Groups receiving naltrexone and medical management; intensive behavioral treatment, medical management, and placebo; and naltrexone, intensive behavioral treatment, and medical management had a significantly greater percentage of days abstinent than the group receiving placebo and medical management. Naltrexone also reduced the risk of heavy drinking days in the group receiving medical management but not intensive psychotherapy. In addition to showing a modest advantage for the use of either naltrexone or intensive behavioral treatment, it is noteworthy that the study failed to show an advantage for acamprosate over placebo, either alone or when added to naltrexone, on any of the drinking outcomes. The study also showed evidence of a placebo response among individuals receiving the intensive behavioral intervention, in that those who received neither an active nor a

placebo medication showed significantly less improvement than those who were treated with placebo.

Alcohol-Sensitizing Agents

Alcohol-sensitizing agents alter the body's response to alcohol, thereby making its ingestion unpleasant or toxic. Disulfiram is the only alcohol-sensitizing medication approved in the United States for the treatment of AUD and that is used clinically. Consequently, we focus on that agent here.

Disulfiram inhibits the enzyme aldehyde dehydrogenase, which catalyzes the oxidation of acetaldehyde to acetic acid. The ingestion of alcohol while this enzyme is inhibited elevates the blood acetaldehyde concentration, resulting in the disulfiram-ethanol reaction (DER). Symptoms and signs of the DER include warmness and flushing of the skin, especially that of the upper chest and face; increased heart rate; palpitations; and decreased blood pressure. They may also include nausea, vomiting, shortness of breath, sweating, dizziness, blurred vision, and confusion. Most DERs are self-limited, lasting about 30 minutes. Occasionally, the DER may be severe, with marked tachycardia, hypotension, or bradycardia; rarely, it may result in cardiovascular collapse, congestive failure, and convulsions. The intensity of the DER varies both with the dose of disulfiram and the volume of alcohol ingested. It should be noted that some patients may show a complete absence of a DER while others may have a severe reaction even with small quantities of alcohol.[37] Although severe reactions are usually associated with high doses of disulfiram (over 500 mg/d), combined with more than 2 oz of alcohol, deaths have occurred with lower dosage and after a single drink.[38,39]

The largest and most methodologically sound study of disulfiram was a multicenter trial conducted by the Veterans Administration Cooperative Studies Group. In that 1-year study, more than 600 male patients with alcohol dependence were randomly assigned to receive either 1 mg of disulfiram per day, 250 mg/d or an inactive placebo.[40] Patients assigned to the two disulfiram groups were told they were receiving the medication, but neither patients nor staff knew the dosage. Results showed that greater adherence with the medication regimen (in all three groups) was associated with a greater likelihood of complete abstinence. Among patients who

resumed drinking, those in the group receiving 250 mg of disulfiram reported significantly fewer drinking days than did patients in either of the other two groups. Based on these findings, it appears that disulfiram may be helpful in reducing the frequency of drinking in men who continue to drink, though given the large number of statistical analyses, it is possible that this finding arose by chance. Similarly, a systematic review of 11 randomized controlled trials (N = 1,527) concluded that supervised administration of disulfiram improved short-term abstinence, prolonged days until return to drinking, and reduced the number of drinking days.[41]

In taking these results into consideration, and given disulfiram's aversive mechanism of action, this medication will likely be most clinically effective in a patient whose goal is complete abstinence from alcohol and who agrees to supervised treatment.[42] Specific behavioral efforts to enhance adherence to disulfiram (as well as other medications for the treatment of alcohol use disorder) include contracting with the patient and a significant other to work together to ensure adherence and the provision to the patient of incentives, regular reminders and other information, and behavioral training and social support.[43]

During shared decision-making with the patient on selecting disulfiram, clinicians should make patients aware of the potential hazards of the medication. This includes recommending avoidance of over-the-counter preparations that contain alcohol (eg, mouthwash) and substances that can interact with disulfiram and the potential for a DER to be precipitated by alcohol used in food preparation. Patients should also do a patch test for any topical products that may contain alcohol (eg, sanitizer, perfume). The administration of disulfiram to anyone who does not agree to use it, does not seek to be abstinent from alcohol, has not attained at least 48 hours of abstinence prior to first administration, or has any psychological or medical contraindications is not recommended. Given its potential to produce serious adverse effects when combined with alcohol, disulfiram cannot be recommended for use as part of a moderation approach to alcohol treatment.

Pharmacology and Clinical Use of Disulfiram

Disulfiram is administered and is almost completely absorbed orally. Because it binds irreversibly to aldehyde dehydrogenase, renewed enzyme

activity requires the synthesis of new enzyme, so that the potential exists for a DER to occur at least 2 weeks from the last ingestion of disulfiram. Consequently, alcohol should be avoided during this period.

Disulfiram commonly produces a variety of adverse effects, including drowsiness, lethargy, and fatigue.[44] Although more serious adverse effects, such as optic neuritis, peripheral neuropathy, and hepatotoxicity occur rarely, patients treated with disulfiram should be monitored regularly for visual changes and symptoms of peripheral neuropathy and the medication should be discontinued if they appear. Further, the patient's liver enzymes should be monitored every 3 months to identify hepatotoxic effects, which may also warrant discontinuation of the medication. Psychiatric effects of disulfiram, though uncommon and probably occur only at higher dosages of the drug, may occur due to disulfiram's inhibition of a variety of enzymes in addition to aldehyde dehydrogenase. For example, disulfiram inhibits dopamine beta-hydroxylase, which increases dopamine concentrations, which in turn can exacerbate psychotic symptoms in patients with schizophrenia and rarely result in psychotic or depressive symptoms among individuals without a psychotic disorder. Such symptoms should also lead to the discontinuation of the medication.

There is a correlation between the risk of most adverse effects and dosage, although the risk of hepatic injury does not appear to be related to dose. This concern about dosage-related adverse events has resulted in the daily dosage prescribed in the United States being limited to 250 to 500 mg/d.

GABAergic Agents

There is growing interest in the use of GABAergic medications for the treatment of AUD, although currently none are FDA approved for this indication. Although these medications have different mechanisms of action, it is likely that they exert beneficial effects in AUD through their actions as glutamate antagonists and GABA agonists, helping to normalize the abnormal activity in these neurotransmitter systems seen following chronic heavy drinking. Medications in this group include topiramate, gabapentin, pregabalin, and baclofen.

Topiramate

Topiramate was initially studied in a single-site, 12-week, placebo-controlled trial, with the dosage gradually increased over 8 weeks to a maximum of 300 mg/d. Topiramate-treated patients showed significantly greater reductions than did placebo-treated patients in drinks per day, drinks per drinking day, drinking days, heavy drinking days, and γ-glutamyl transpeptidase levels.[45] Based on these findings, a subsequent multicenter study was conducted,[46] which showed many of the same effects on drinking as the single-site study, though topiramate was not as well tolerated as it was in the initial trial. The authors interpreted these findings to reflect the more rapid dose titration (to a maximum of 300 mg/d, but over 6 weeks). Topiramate's effect on the above reported drinking outcomes was also reported in a meta-analysis of 7 RCTs (N = 1,125).[47] A subsequent network meta-analysis of 12 RCTs concluded that topiramate had a moderate effect size for abstinence though it was not significantly better than oral naltrexone or acamprosate. It was also twice as likely as placebo to cause significant adverse effects leading to discontinuation.[13] The most common adverse effect of topiramate compared to placebo is numbness and tingling (which is secondary to the commonly observed metabolic acidosis produced by the antagonism by topiramate of carbonic anhydrase), with other common side effects including a change in the sense of taste, tiredness/sleepiness, fatigue, dizziness, loss of appetite, nausea, diarrhea, weight decrease, and difficulty concentrating, with memory, and in word finding. Of clinical concern also are suicidal thoughts or actions, which have been reported uncommonly but at a frequency greater than that seen with placebo treatment. Other adverse effects of topiramate that are less likely to occur but potentially serious are renal calculi and acute secondary glaucoma. Topiramate is also category D in pregnancy and is associated with oral clefts in exposed infants.

These findings provide clear support for the efficacy of this anticonvulsant for the treatment of AUD and suggest that the use of topiramate for this purpose should include a slowly increasing dosage. Additional research focusing on the optimal rate of dosage increase and the minimal dosage that is efficacious in AUD is warranted. In regard to precision medicine, a randomized, controlled, double-blind trial of

topiramate 200 mg/d versus placebo showed a robust effect of topiramate on number of heavy drinking days, but in a subsample of Americans of European descent, this effect was accounted for almost entirely by a single nucleotide polymorphism in the gene coding for one of the subunits of the kainate type of glutamate receptor.[48] This finding requires replication in a larger prospective study before it would be clinically applicable.

Gabapentin and Pregabalin

Gabapentin is FDA approved for the adjunctive treatment of partial seizures and postherpetic neuralgia. It is a structural analog of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) and is hypothesized to work via blocking voltage-dependent calcium channels and modulating excitatory neurotransmitter release.[49] Its off-label use to treat AUD was initially demonstrated in three randomized clinical trials (N = 231) concluding that gabapentin reduced heavy drinking, increased abstinence, improved sleep, and reduced acute/protracted withdrawal syndromes.[50,51] A dose-related effect on abstinence rate, no heavy drinking, cravings, mood and sleep was found. These effects were more pronounced in the gabapentin 1,800-mg group (abstinence: NNT = 8; no heavy drinking: NNT = 5).[52] A subsequent multicenter RCT of (N = 346) patients with AUD used an extended-release formulation, gabapentin enacarbil and found no significant difference compared to placebo in any outcomes; percent of no heavy drinking days, subjects abstinent, days abstinent, heavy drinking days, drinks per week, drinks per drinking day, alcohol craving, alcohol-related consequences, sleep problems, smoking, and depression/anxiety symptoms.[53] The use of gabapentin's prodrug in this trial and differences in pharmacokinetics may explain this outcome. A meta-analysis of 7 RCTs, including the above negative study, reported on gabapentin's effect on 6 AUD treatment-related outcomes; complete abstinence, relapse to heavy drinking, percent days abstinent, percent heavy drinking days, drinks per day, and gamma-glutamyl transferase (GGT) concentration. It concluded that, despite effect sizes trending favorably for gabapentin over placebo, only reduction in percent of heavy drinking days was significant, highlighting a need to more clearly define gabapentin's role in AUD treatment.[54] This role may include treating patients with AUD who are also experiencing withdrawal symptoms as exemplified in a RCT of (N = 96) patients with AUD, who

also met criteria for alcohol withdrawal, randomized to receive gabapentin (1,200 mg/d) versus placebo.[55] The gabapentin arm was found to have fewer heavy drinking days (NNT = 5.4) and more total abstinence (NNT = 6.2). These effects were even more pronounced in the high alcohol withdrawal group (N = 45) in terms of heavy drinking days (NNT = 3.1) and total abstinence (NNT = 2.7). The group with low alcohol withdrawal showed no difference between gabapentin and placebo on these outcomes.

Pregabalin is structurally similar to gabapentin and exerts its effect via similar action at voltage-gated calcium channels. Pregabalin is thought to have some pharmacokinetic and pharmacodynamic advantages over gabapentin, including more binding affinity at its target, more potency, more bioavailability, and better absorption.[56] Pregabalin has been studied for treatment of AUD as well. A 3-month double-blind RCT compared pregabalin 150 mg to placebo in (N = 100) patients with AUD. Pregabalin was found to be superior in treatment retention, reducing total alcohol consumption, reducing heavy drinking days, and increasing abstinent days. Pregabalin did not differ from placebo in terms of its effect on cravings, depression, anxiety, or GGT activity.[57] Similar outcomes were reported in an open-label, 8-week long, study of (N = 18) participants with AUD, who were titrated to 600 mg/d. However, 80% of participants reported adverse events with 11% dropping out.[58] Since this was not an RCT, more studies are needed to determine the optimal dose of pregabalin for AUD, but these results suggest lower doses will likely be better tolerated while maintaining effectiveness.

Baclofen

This GABA-B receptor agonist has been approved as an antispasmodic for more than 30 years and has recently been studied as a treatment for AUD, although is not FDA approved for such treatment. In a small trial, Addolorato et al.[59] randomly assigned recently abstinent individuals with alcohol dependence to receive up to 30 mg/d of the medication or placebo divided into three daily doses. The medication was well tolerated, and the baclofen-treated group was more likely to remain abstinent over the 1-month treatment period (also showing a greater number of cumulative abstinence days) than was the placebo group. Another study by these

investigators[60] evaluated the efficacy of baclofen in a sample of 84 patients with alcohol dependence with liver cirrhosis. Baclofen-treated patients were significantly more likely than placebo-treated patients to maintain abstinence (71% versus 29%), with a concomitant doubling of abstinence days in the baclofen group. The medication was well tolerated, and the baclofen group showed a nonsignificant lower rate of study dropout than did the placebo group (14% versus 31%). Subsequent studies have shown contradictory findings. A flexible dosing double-blind randomized trial with 56 participants found significantly higher total abstinence rates and abstinence duration among participant who received active medication (mean dose in the active baclofen group = 180 mg [SD = 86.9]/day).[61] However, a larger multicenter randomized, double-blind trial with 151 participants compared a high-dose baclofen group (mean = 93.6 [SD = 40.3]/day) to 30 mg/d and placebo groups and saw no differences between groups in any measure of alcohol use while also noting frequent adverse events in the high-dose group.[62] Another multicenter randomized, double-blind trial among 180 U.S. military veterans similarly found no effect of baclofen 30 mg/d compared to placebo on any alcohol use outcomes.[63]

A Cochrane review of 12 RCTs concluded that there was no significant difference between baclofen and placebo with regards to AUD treatment outcomes.[64] Since baclofen has demonstrated safety and efficacy in reducing drinking in patients with alcohol-related liver disease,[60],[65] there has been continued interest in delineating moderators of its potential benefit in treating AUD. An RCT of (N = 120) participants with AUD, randomized to receive baclofen 30mg or 90mg or placebo, showed that baclofen reduced heavy drinking days (–13.6 days) and increased abstinent days (+12.9 days) over the 16-week trial period; 90 mg showed greater efficacy. However, they also found a moderating effect of sex, with men benefitting from and tolerating 90 mg, while women benefited only from 30 mg and did not tolerate 90 mg.[66]

Taken together, current evidence suggests that higher doses of baclofen may result in positive outcomes in treatment of AUD and that it can be a potential treatment in patients with alcohol-related liver disease.

Serotonergic Agents

Ondansetron

Ondansetron is a 5-HT receptor antagonist approved for the treatment of chemotherapy-induced and postoperative nausea. Using a subtyping approach, Johnson et al.[67] found that ondansetron selectively reduced drinking among patients with early onset of unhealthy drinking (ie, before age 25; early-onset patients with alcohol dependence). Specifically, ondansetron was superior to placebo on the proportion of days abstinent and on the intensity of alcohol intake. In contrast, late-onset patients with alcohol dependence showed effects of ondansetron on drinking behavior that were comparable to those of placebo. In a subsequent 8-week, open-label study of ondansetron, early-onset patients with alcohol dependence had a significantly greater decrease in drinks per day, drinks per drinking day, and alcohol-related problems than did late-onset patients with alcohol dependence.[68] Furthermore, a prospective double-blind trial of ondansetron in which participants were randomized based upon polymorphisms in the gene coding for the serotonin transporter showed a positive response in participants with the polymorphisms.[69] A retrospective analysis of the same data showed that polymorphisms in the genes coding for serotonin 5-HT3 receptor subtypes also predicted outcome.[70]

Psychedelics

There has been re-ignited interest in the use of psychedelics in a variety of psychiatric and substance use disorders. Certain serotonergic psychedelics have evidence of variable strength investigating their potential benefit in treating AUD. A small open label trial in (N = 10) participants with AUD that combined 2 doses of psilocybin with a 12-session psychosocial intervention found that percent drinking days and heavy drinking days were significantly reduced, as compared to prior to treatment. These improvements were sustained throughout the 36-week follow-up period. It was also noted to reduce drinking consequences, cravings, self-efficacy, and mood with no notable adverse effects.[71] A larger randomized, double-blind trial (N = 95) used a similar design with diphenhydramine as the control condition, 12 psychotherapy sessions and two medication sessions at 4 and 8 weeks. Compared to control, psilocybin treatment reduced percent of heavy drinking days and mean daily alcohol consumption over the 32 study

weeks.[72] A meta-analysis of 6 RCTs (N = 536), investigating lysergic acid diethylamide's (LSD) use in AUD treatment, found a single dose of LSD to have a beneficial effect on unhealthy alcohol use (NNT = 6) until 6 months post treatment. It was also found to increase total abstinence (NNT = 7) after a single dose until 3 months posttreatment.[73]

More modern-day trials and replication studies are needed to evaluate whether there is a clearer role for serotonergic agents in the treatment of heavy drinking or AUD in individuals differentiated by AUD subtype or genotype.

Alpha Adrenergic Antagonists

There is growing interest in targeting autonomic and stress response systems in AUD treatment, using adrenergic antagonists, such as prazosin and doxazosin. A randomized, double-blind, controlled trial of (N = 40) participants with AUD, compared prazosin 16 mg/d with placebo. Participants were exposed to cues related to stress, alcohol, and relaxation. Alcohol cravings, anxiety, heart rate, and ACTH levels were checked at baseline and after the cues. Prazosin reduced stress and cue-induced alcohol cravings as well as alcohol and stress cue-induced anxiety. It lowered basal cortisol and ACTH levels as well. This effect was only observed in those without a lifetime anxiety disorder.[74] This normalization of autonomic stress response may improve alcohol cravings and drinking outcomes. This was highlighted in a two-part study where patients with AUD, with varying degrees of alcohol withdrawal, initially underwent functional magnetic resonance imaging then were randomized to a 12-week trial, comparing prazosin to placebo, with regards to their effects on neural circuit stress response and subsequent heavy drinking outcomes. Part 1 of the study identified greater disruption in response to stress and alcohol cues in the medial prefrontal cortex and striatum in patients with high alcohol withdrawal symptoms, with a subsequent increase in heavy drinking days. In part 2, prazosin reversed this identified stress response, when compared with placebo, in turn leading to fewer drinking days during the 12-week treatment period.[75] Another RCT on (N = 90) participants with AUD compared prazosin 16 mg/d (divided in TID dosing) to placebo with regards to effect on number of drinks per week, number of drinking days per week,

and number of heavy drinking days per week. Participants with PTSD were excluded in order to isolate prazosin's effect on AUD. Eighty participants were able to complete the dose titration period. Prazosin decreased the number of heavy drinking days and the number of drinks per week, more rapidly than placebo, over the 12-week trial period. Prazosin had no effect on the number of drinking days per week.[76]

Another study of (N = 36) participants with AUD, that also excluded PTSD, found no difference between prazosin and placebo in reduction of drinking. However, in a post-hoc analyses, prazosin was found to increase the rate of reduction in the number of drinks per week in a subgroup of participants who were able to adhere to and tolerate the medication, A larger effect was also observed in participants with higher baseline diastolic blood pressure.[77] An additional 12-week, double-blind RCT of prazosin versus placebo (N = 100) found that in the subset of participants with high levels of alcohol withdrawal, participants treated with prazosin had significantly fewer drinking days and heavy drinking days than did those treated with placebo, but this effect was not observed among the subset with low alcohol withdrawal.[78]

Thus, tolerability concerns may be contributing to this variation in study outcomes, or, as with gabapentin as described above, prazosin may be most efficacious among individuals with high levels of alcohol withdrawal.

Doxazosin differs from prazosin with its longer half-life, allowing for once-a-day dosing and improved adherence, slower onset of action, and lower risk of hypotensive side effects. In a double-blind RCT of (N = 41) participants with AUD, 16 mg/d of doxazosin did not differ from placebo in its effect on drinks per week and heavy drinking days per week. However, family history was found to be a moderator of effect with doxazosin reducing drinking in participants with a high family history density of AUD.[79] Further analyses from this study found higher baseline diastolic blood pressure predicted a significant effect of doxazosin in reducing heavy drinking days and drinks per week.[80]

These studies support the hypothesis of potential benefit from alpha antagonists in treating AUD and warrant more research. Investigating precision medicine approaches such as baseline stress reactivity, blood pressure, and family history and potential genetic markers mediating

response, may enhance our understanding of the role of these agents in AUD treatment.

Other Agents

Varenicline

Research is ongoing to identify new treatment targets for management of AUD. Varenicline, a partial agonist of α4β2 nicotinic acetylcholine receptors and full agonist of α7 nicotinic acetylcholine receptors, is FDA approved for helping people to stop smoking. Given its central action in the ventral tegmental area, it may affect dopamine activity, which, in turn, could explain its potential utility in AUD treatment. A meta-analysis of ten studies (N = 731) found varenicline to significantly decrease cravings for alcohol, but it had no significant effect on other drinking outcomes.[81] In an RCT of (N = 200) participants with AUD, varenicline was found to reduce both alcohol consumption and cravings.[82] Its investigators explored potential moderators of response to varenicline and suggested it may be more effective in patients with less severe AUD (ie, patients with less alcohol-related consequences), of older age (>45 years), longer drinking time (>28 years), who preferred a goal of nonabstinence, and those who reduced their cigarette consumption due to treatment with varenicline.[83]

N-acetylcysteine

N-acetylcysteine (NAC) is a derivative of the amino acid *l*-cysteine. It is FDA approved for its hepatoprotective use in acetaminophen overdose and as a mucolytic. There is growing interest in its utility in treating substance use disorders as it has been shown to modulate glutamate transmission, which has been implicated in craving and withdrawal states. It has shown promise in treating cocaine, cannabis, opioid, and nicotine use disorders.[84] Its effect on alcohol consumption was observed in an RCT with (N = 302) participants randomized to treatment with NAC (600 mg BID) or placebo for cannabis use disorder. Compared to placebo, the NAC group had increased odds of abstinence, fewer drinks per week, and fewer drinking days per week. This was not correlated to changes in cannabis

consumption.[85] These findings highlight the need to investigate the effect of NAC on alcohol use further in studies focused on AUD.

MEDICATIONS TO TREAT CO-OCCURRING PSYCHIATRIC SYMPTOMS OR DISORDERS IN PATIENTS WITH ALCOHOL USE DISORDER

Although most patients with AUD report a reduction in mood or anxiety symptoms following acute withdrawal, for some these symptoms may persist for months. Even among patients without substantial symptoms of alcohol withdrawal, persistent, low-level mood or anxiety symptoms may develop, a condition that has been called "postacute withdrawal." In a substantial minority of patients, these symptoms may reflect diagnosable psychiatric disorders. Although medications (eg, serotonin reuptake inhibitors) are often prescribed during the post withdrawal period in hopes of relieving these symptoms, there is no good evidence that the treatment of persistent or subacute withdrawal symptoms that do not meet diagnostic criteria for a co-occurring psychiatric disorder results in better outcome in patients with AUD.

Many of the early studies of the efficacy of medications to treat mood disturbances targeted symptoms of depression and anxiety in unselected groups of patients with AUD after withdrawal. These and other methodological limitations in these studies make the failure to demonstrate an advantage over control conditions through reductions in either psychiatric symptoms or drinking behavior difficult to interpret.[86] Community studies have shown high rates of co-occurrence of psychiatric disorders in individuals with AUD.[87,88] Further, the majority of such individuals who seek treatment meet lifetime criteria for one or more psychiatric disorders in addition to AUD, most commonly mood disorders,

other substance use disorders, antisocial personality disorder, and anxiety disorders.[74],[75]

Antidepressants, benzodiazepines, and other anxiolytics, antipsychotics, and lithium have been used to treat anxiety and depression in the post withdrawal state. Although, in general, the indications for use of these medications in patients with AUD are similar to those for patients with psychiatric illness who do not have AUD, careful differential diagnosis is warranted to identify patients for whom the symptoms can be ascribed to substance use. Further, the choice of medications should take into account the increased potential for adverse effects when prescribed to individuals who are actively drinking heavily. Adverse effects can result from pharmacodynamic interactions with medical disorders that commonly occur in the course of AUD, as well as from pharmacokinetic interactions with medications prescribed to treat these disorders.[89]

Antidepressant Treatment of Unipolar Depression and Alcohol Use Disorder

Most of the studies in a meta-analysis that included 14 prospective, parallel-group, double-blind, randomized, placebo-controlled trials of antidepressants for a co-occurring substance use disorder and unipolar depression focused on alcohol dependence.[90] Eight studies (six of which were in patients with alcohol dependence) showed a significant or near-significant advantage for the active medication over placebo in reducing symptoms of depression. The pooled effect size on the standardized difference between means on the Hamilton Depression Rating Scale was 0.38 (95% CI 0.18 to 0.58), a small to moderate effect. Studies with a placebo response rate of more than 25% showed no advantage for the active medication, whereas those with a smaller placebo response rate yielded effects in the moderate to large range. Allowing a week of abstinence to transpire before making a diagnosis of depression predicted a better antidepressant response. In contrast, a larger proportion of women in the study sample, the use of serotonin reuptake inhibitors (versus tricyclic or other antidepressants), and a concurrent psychosocial intervention were associated with a poorer medication response. Studies that showed a moderate effect of the medication on depression scores also showed

moderate reductions in substance use, whereas smaller effects on depressive symptoms were associated with no beneficial effects on substance use.

Subsequent to this analysis, there have been studies of pharmacotherapy for co-occurring alcohol dependence and depression. A multicenter trial compared sertraline versus placebo in 328 patients with co-occurring major depressive disorder and alcohol dependence.[91] After a 1-week, single-blind, placebo lead-in period, patients were randomly assigned to receive 10 weeks of treatment with sertraline or placebo. Randomization was stratified, based on whether initially elevated depression scores declined with abstinence from heavy drinking. Both depressive symptoms and alcohol consumption decreased substantially over time in both groups, with no reliable medication group differences on depressive symptoms or drinking behavior in either group. The high placebo response rate may have contributed to the null findings.

An elegant clinical trial randomly assigned participants with co-occurring major depression and alcohol dependence, in double-blind fashion, to one of four treatment conditions: (1) sertraline 200 mg/d (N = 40), (2) naltrexone 100 mg/d (N = 49), (3) the combination of sertraline 200 mg/d and naltrexone 100 mg/d (N = 42), and (4) double placebo (N = 39). Over 14 weeks, the combination treatment group had a significantly higher abstinence rate and a significantly longer mean time to relapse to heavy drinking than did the other three groups. The combination group also had higher, though not statistically significantly higher, rates of depression remission with fewer serious adverse events than did the other three groups. The findings from this study, absent any contraindications, encourage the combination of naltrexone and sertraline for the treatment of patients with co-occurring AUD and depression.[92] If patients already had a therapeutic trial of sertraline and found it ineffective or intolerable, it is reasonable to consider an alternative antidepressant.

In summary, there is evidence that most episodes of post withdrawal depression will remit without specific treatment if abstinence from alcohol is maintained for a period of days or weeks.[93],[94] Starting new medications during this period should be minimized given this transient nature of substance induced depression. This will avoid the risks and confounding effects of polypharmacy. However, depression that persists a month out from last alcohol use requires a careful assessment for a separate but co-

occurring depressive disorder that may warrant treatment; including psychotherapy, medication, or both. Serotonin reuptake inhibitors and other antidepressants approved after the tricyclic antidepressants have become the first-line treatment of depression because they have a favorable adverse event profile. These medications have significantly less of the anticholinergic, hypotensive, or sedative effects of the tricyclic antidepressants, nor do they, with the possible exception of citalopram, have the adverse cardiovascular effects, which in overdose can be lethal. However, serotonin reuptake inhibitors can exacerbate the tremor, anxiety, and insomnia often experienced by patients with physiological dependence on alcohol who have been recently withdrawn from alcohol and may slightly increase the risk of gastrointestinal bleeding (particularly in combination with nonsteroidal anti-inflammatory drugs or aspirin).

Mood Stabilizer Treatment of Bipolar Disorder and Alcohol Use Disorder

Bipolar disorder co-occurs commonly with AUD. The presence of comorbid AUD is associated with an increased rate of mixed or dysphoric mania and rapid cycling, as well as greater bipolar symptom severity, suicidality, and aggression.[95] However, controlled trials of medication to treat these co-occurring disorders are difficult to conduct. A placebo-controlled trial of divalproex sodium in bipolar patients with alcohol dependence taking lithium showed that the drug significantly decreased the proportion of heavy drinking days (corroborated by a decrease in the concentration of gamma-glutamyl transpeptidase), whereas manic and depressive symptoms improved equally in both groups.[96]

Treatment of Co-occurring Anxiety Disorders and Alcohol Use Disorder

Benzodiazepines and Other Anxiolytics

Benzodiazepines are widely used and generally considered to be acceptable treatment for acute alcohol withdrawal. The relative merits of the use of

benzodiazepines in patients with alcohol and other substance use disorders during the post withdrawal period for the management of anxiety or insomnia have been debated in the medical literature.[97,98]

Early return to use, which commonly disrupts alcohol rehabilitation, can result from protracted withdrawal-related symptoms (eg, anxiety, depression, insomnia). This highlights the importance of addressing these symptoms in early abstinence to prevent relapse.

Short-term use of benzodiazepines to address anxiety must be weighed against the risk both of overdose, unhealthy use including addiction, physical dependence, and diversion on benzodiazepines. Although these medications alone are comparatively safe, even in overdose, their combination with other brain depressants (including alcohol) can be lethal. Although there is little doubt that individuals with AUD are more vulnerable to develop physical dependence on the benzodiazepines than is the average person, the potential for developing a sedative hypnotic use disorder may be lower than is generally believed.[99,100] However, physiological dependence on both alcohol and benzodiazepines may increase depressive symptoms,[93] and co-occurring alcohol and benzodiazepine use disorders may be more difficult to treat than is AUD alone.[101]

Buspirone, a nonbenzodiazepine anxiolytic, exerts its effects largely via its partial agonist activity at serotonergic auto receptors. Although comparable in efficacy to diazepam in the relief of anxiety and associated depression in outpatients with moderate-to-severe anxiety,[102,103] buspirone is less sedating than is diazepam or clorazepate, does not interact with alcohol to impair psychomotor skills, and does not have substance use disorder liability.[104,105] This pharmacological profile makes buspirone more suitable than benzodiazepines to treat anxiety symptoms among patients with alcohol dependence. In contrast to benzodiazepines, however, buspirone does not have acute anxiolytic effects, is not useful in the treatment of alcohol withdrawal, and is not useful for treating the insomnia that is commonly reported by patients with AUD during acute and protracted withdrawal.

Results from three of four placebo-controlled, double-blind trials of buspirone to treat anxiety symptoms among patients with AUD have shown

the drug to be superior to placebo in increasing treatment retention and reducing anxiety symptoms and measures of drinking.[106,107] Although buspirone appears to be useful in the treatment of anxiety symptoms in patients with AUD, it has not been possible to identify clinical features that differentiate individuals for whom buspirone may be most efficacious from those who are not responsive to the medication.

UTILIZATION OF PHARMACOTHERAPY IN THE TREATMENT OF ALCOHOL USE DISORDER

Despite data suggesting efficacy, the use of medications that have been FDA approved for treatment of AUD remains very limited. The lack of robust utilization can be found in large organizations such as the Veterans Health Administration as well as other public and private entities.[108,109] This limited use is evident even in clinicians who have been trained to treat AUD—addiction physicians. A survey of nearly 1,400 members of the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry[110] showed that they prescribed disulfiram to only 9% of their patients with alcohol dependence, and naltrexone was prescribed only slightly more frequently (ie, to 13% of patients). In contrast, antidepressants were prescribed to 44% of patients with AUD. Although nearly all these physicians had heard of disulfiram and naltrexone, their self-reported level of knowledge of these medications was much lower than that for antidepressants and benzodiazepines. Additionally, primary care physicians, who represent the clinicians most likely to diagnose AUD, were found to be unfamiliar with approved pharmacotherapies.[111] Clearly, additional education is needed to improve awareness among treatment professionals as well as patients.

SUMMARY AND CONCLUSIONS

As evidence has accumulated showing that a growing number of medications are efficacious for the treatment of AUD, the therapeutic options available to physicians in treating these patients have increased. Because all three medications that are FDA approved for the treatment of AUD have demonstrated efficacy in some patients, these medications should be considered a first-line treatment in patients with AUD. They can be used in combination with behavioral treatment, depending on availability and patient preference. Given limited data on how to choose which of the efficacious medications is appropriate for any given patient, the choice can be made collaboratively with the patient.

The treatment of psychiatric symptoms that co-occur with AUD, which can augment efforts at addressing alcohol use that is above recommended limits, has been studied in some detail. However, the literature remains mixed with respect to the efficacy of specific interventions. Anxiolytics, such as buspirone, and antidepressants with benign side effect profiles, such as serotonin reuptake inhibitors, may reduce alcohol intake and warrant careful evaluation in the treatment of anxious and depressed patients with AUD. However, even if medications that are prescribed to patients with AUD with persistent co-occurring mood and anxiety symptoms, they will not necessarily reduce alcohol consumption after moderate to severe AUD develops. This is likely to hold true even if pathological mood states were important in the initiation of heavy drinking.[68,112] That is, the neuroadaptive changes and the complex learning that characterize AUD[113] are not likely to resolve because one major contributing factor is brought under control. The challenge for practitioners treating AUD is to combine efficacious medications with empirically based psychological interventions and self-help group participation for those patients willing and able to incorporate these elements into their treatment.

The use of medications in patients who are actively participating in self-help groups may be particularly challenging. Although members of abstinence-oriented groups such as Alcoholics Anonymous may be willing to work with physicians when they prescribe disulfiram, the use of which is supportive of their goal of total abstinence, they may be less supportive of other medications that aim to reduce drinking and its associated medical, psychological, and social harm. Nonetheless, clinicians should support

patients, as allowing patients to choose their treatment goals increases their odds of success.[114]

Future research should investigate the safety and efficacy of medications to treat AUD, with adequate statistical power, in women, in different ethnic/racial groups, and in adolescent and geriatric samples.

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