Alcohol consumption is responsible for three million deaths annually, representing about 5% of all deaths worldwide. Alcohol use disorder (AUD), a common consequence of excessive alcohol consumption, often leads to the development of chronic liver disease (CLD), which is marked by gradual destruction of liver tissue over time and includes liver fibrosis and cirrhosis. The diagnosis of AUD is based on criteria set by the Fifth Edition of the *Diagnostic and Statistical Manual of Mental Disorders*, and the term AUD has replaced “alcohol abuse” and “alcohol dependence.” To identify high-risk drinking and possible AUD in the outpatient setting, providers can use various screening methods. Factors associated with risk for heavy drinking relapse include AUD severity, social factors, psychiatric comorbidities, and treatment compliance and motivation.

AUD is not only limited to those with alcohol-related liver disease (ALD), but can be present in other causes of CLD such as nonalcoholic steatohepatitis. In United States and in Europe, AUD affects about 10% of the general population. AUD has also been increasing in prevalence despite the World Health Organization’s efforts to tackle the disorder. The National Epidemiology Survey on Alcohol indicated that the 12-month prevalence of alcohol use, high-risk drinking, and AUD were on the rise across all sociodemographic groups in the United States. Also, although the US Preventive Services Task Force has increased the awareness of AUD screening, there are limited management options for those with AUD and CLD. This review will discuss the general approach to AUD in CLD, including pharmacological and psychosocial interventions, and its future direction.

**MANAGEMENT OF AUD**

A multidisciplinary approach with pharmacological and psychosocial support is the most effective strategy for...
the management of AUD; focus is on reducing alcohol intake, promoting long-term abstinence, and preventing relapse.11

Pharmacological Interventions

Medications that have received US Food and Drug Administration (FDA) approval for the management of AUD, but not in patients with CLD, are acamprosate,12 disulfiram,13 and naltrexone14,15 (Table 1). All but acamprosate are metabolized by the liver and/or have the possibility of leading to liver toxicity; therefore, investigations in randomized controlled trials in patients with CLD have been limited. Naltrexone, a pure opioid antagonist, helps modify the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption and reduce the incidence of relapse to heavy drinking.16,17 Pharmacological interventions yet to be approved by the FDA for general use in AUD include baclofen, gabapentin, nalmefene, and topiramate (Table 1). Of the medications listed, only disulfiram carries a black box warning: it is never to be administered to a patient who is intoxicated or unable to consent.

Baclofen, an anticonvulsant medication, is the only drug in its class that has been studied in randomized controlled trial settings and has been shown to be effective compared with placebo in reducing alcohol intake and increasing abstinence rate among patients with AUD and CLD.18-20 It is currently approved for AUD in the European Union, but it has not received FDA approval for use in patients with AUD and CLD. Moreover, the efficacy of baclofen in patients with AUD has been contested, most notably with the Cochrane Database of Systematic Reviews concluding that there was no difference between baclofen and placebo in achieving and maintaining abstinence or reducing alcohol consumption in the 12 randomized controlled trials studied, 11 of which compared baclofen with placebo and 1 of which compared baclofen with acamprosate.21

Nalmefene, a mu-opioid antagonist and partial kappa agonist, may have an advantage over naltrexone22,23; however, more studies are warranted. It is currently approved for AUD in the European Union, but is not available in the United States. Ondansetron is an antiemetic that showed reduction in alcohol use in a randomized controlled trial in

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**TABLE 1. FDA-APPROVED AND OFF-LABEL MEDICATIONS FOR AUD**

<table>
<thead>
<tr>
<th>Name</th>
<th>Dosage</th>
<th>Dosage in Clinical Trials for AUD</th>
<th>FDA-Approved for CLD?</th>
<th>Particular Cautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA-Approved Medications for AUD</strong></td>
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<tr>
<td>Acamprosate12</td>
<td>Oral: 666 mg three times daily</td>
<td>1000-3000 mg daily</td>
<td>No</td>
<td>• Reduce dosage in patients with renal impairment</td>
</tr>
<tr>
<td>Disulfiram13</td>
<td>Oral: 250-500 mg daily</td>
<td>125-500 mg daily</td>
<td>No</td>
<td>• Do not administer until the patient has abstained from alcohol for at least 12 hours • Black box warning • Do not start therapy until the patient is opioid-free for at least 1 week</td>
</tr>
<tr>
<td>Naltrexone12,14,15</td>
<td>Oral: 50 mg daily; IM: 380 mg once every 4 weeks</td>
<td>Oral: initial dose of 25-50 mg daily, then 50-100 mg daily for maintenance; IM: 190-380 mg monthly</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td><strong>Off-Label Medications for AUD</strong></td>
<td></td>
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<tr>
<td>Baclofen33,34</td>
<td>5 mg three times daily; increase dose every 3-5 days based on tolerance. Maximum: 15 mg three times a day</td>
<td>30-180 mg daily in up to four divided doses</td>
<td>No</td>
<td>• Approved in the European Union for AUD • Can lower the seizure threshold • Taper slowly (5-10 mg/week) to reduce risk for withdrawal symptoms</td>
</tr>
<tr>
<td>Gabapentin35</td>
<td>Oral: 300 mg daily; increase in 300-mg increments every 2 days up to a target dose of 600 mg three times daily</td>
<td>600-1800 mg daily in three divided doses</td>
<td>No</td>
<td>• Can be misused for recreational purposes, self-medication, or intentional self-harm26</td>
</tr>
<tr>
<td>Topiramate37</td>
<td>Oral: 25-50 mg daily with 25-50 mg daily increases at weekly intervals</td>
<td>75-300 mg daily in two divided doses</td>
<td>No</td>
<td>• Do not use in patients with metabolic acidosis, kidney stones, or secondary angle closure glaucoma</td>
</tr>
<tr>
<td>Nalmefene23,38</td>
<td>Oral: 18 mg daily as needed</td>
<td>20 or 80 mg daily</td>
<td>No</td>
<td>• Approved in the European Union for AUD • Not available in the United States</td>
</tr>
</tbody>
</table>
2000,24 but subsequent studies supporting its use in AUD have been lacking. Another potential medication for AUD that needs further studies is varenicline, an FDA-approved medication for smoking cessation. It was found to attenuate dopamine release in combined nicotine and ethanol administration in animal studies25-27 and reduce heavy drinking in men, but not in women, who also smoked cigarettes.28 Lastly, cannabinoids have shown attenuation of cue-elicited and stress-elicited alcohol seeking in animal models29; however, no human studies are available at this time.

Psychosocial Interventions

Various psychosocial therapies are used for AUD, and one of the few available randomized controlled trials comparing different counseling methods supported the use of motivational enhancement therapy.30 In those who screen positive for AUD, primary care providers should implement interventions focused on motivational enhancement and cognitive behavioral therapy, together with options for referral to specialists. Patients with AUD should be seen by psychologists and/or psychiatrists, particularly those with a background in addiction medicine, if available. Data regarding these interventions for AUD are limited, but some suggest a benefit in older men and patients with high-risk AUD drinking behavior patterns.31

Policy Interventions

On a societal level, there has been a push by the World Health Organization to tackle AUD through policy changes, mainly through promoting community action, regulating availability of alcohol, restricting marketing of alcohol, monitoring pricing changes, and addressing illicit production.1 Price availability and marketing are the best tactics to manage alcohol consumption on a societal level.32

NEXT STEPS

The European Association for the Study of the Liver and the American Association for the Study of Liver Diseases recently identified unmet needs and areas for future studies related to ALD.32 For the management of AUD, many of the pharmacotherapies approved have yet to be studied in patients with both AUD and CLD. In addition, well-conducted studies can better assess the efficacy of psychosocial interventions in this patient population. Currently, there are many potential providers involved in the care of patients with AUD and CLD, which often leads to fragmentation of care. Thus, it is critical to empower primary care physicians who can effectively integrate the multidisciplinary management of AUD through timely screenings and referrals for appropriate interventions by psychiatrists, therapists, and hepatologists.

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