Preventing drinking relapse in patients with alcoholic liver disease

Your role is essential in preventing, detecting, and co-managing alcoholic liver disease in inpatient and ambulatory settings

Alcohol use disorder (AUD) is a mosaic of psychiatric and medical symptoms. Alcoholic liver disease (ALD) in its acute and chronic forms is a common clinical consequence of long-standing AUD. Patients with ALD require specialized care from professionals in addiction, gastroenterology, and psychiatry. However, medical specialists treating ALD might not regularly consider medications to treat AUD because of their limited experience with the drugs or the lack of studies in patients with significant liver disease. Similarly, psychiatrists might be reticent to prescribe medications for AUD, fearing that liver disease will be made worse or that they will cause other medical complications. As a result, patients with ALD might not receive care that could help treat their AUD (Box, page 24).

Given the high worldwide prevalence and morbidity of ALD, general and subspecialized psychiatrists routinely evaluate patients with AUD in and out of the hospital. This article aims to equip a psychiatrist with:

- a practical understanding of the natural history and categorization of ALD
- basic skills to detect symptoms of ALD
- preparation to collaborate with medical colleagues in multidisciplinary management of co-occurring AUD and ALD
- a summary of the pharmacotherapeutics of AUD, with emphasis on patients with clinically apparent ALD.

continued
Categorization and clinical features

Alcoholic liver damage encompasses a spectrum of disorders, including alcoholic fatty liver, acute alcohol hepatitis (AH), and cirrhosis following varying durations and patterns of alcohol use. Manifestations of ALD vary from asymptomatic fatty liver with minimal liver enzyme elevation to severe acute AH with jaundice, coagulopathy, and high short-term mortality (Table 1, page 26). Symptoms seen in patients with AH include fever, abdominal pain, anorexia, jaundice, leukocytosis, and coagulopathy.3

Patients with chronic ALD often develop cirrhosis, persistent elevation of the serum aminotransferase level (even after prolonged alcohol abstinence), signs of portal hypertension (ascites, encephalopathy, variceal bleeding), and profound malnutrition. The survival of ALD patients with chronic liver failure is predicted in part by a Model for End-Stage Liver Disease (MELD) score that incorporates their serum total bilirubin level, creatinine level, and international normalized ratio. The MELD score, which ranges from 6 to 40, also is used to gauge the need for liver transplantation; most patients who have a MELD score >15 benefit from transplant. To definitively determine the severity of ALD, a liver biopsy is required but usually is not performed in clinical practice.

All patients who drink heavily or suffer with AUD are at risk of developing AH; women and binge drinkers are particularly vulnerable.4 Liver dysfunction and malnutrition in ALD patients compromise the immune system, increasing the risk of infection. Patients hospitalized with AH have a 10% to 30% risk of inpatient mortality; their 1- and 2-month post-discharge survival is 50% to 65%, largely determined by whether the patient can maintain sobriety.5 Psychiatrists’ contribution to ALD treatment therefore has the potential to save lives.

Screening and detection of ALD

Because of the high mortality associated with AH and cirrhosis, symptom recognition and collaborative medical and psychiatric management are critical (Table 2, page 29). A psychiatrist evaluating a jaundiced patient who continues to drink should arrange urgent medical evaluation. While gathering a history, mental health providers might hear a patient refer to symptoms of gastrointestinal bleeding (vomiting blood, bloody or dark stool), painful abdominal distension, fevers, or confusion that should prompt a referral to a gastroenterologist or the emergency department. Testing for urinary ethyl glucuronide—a direct metabolite of ethanol that can be detected for as long as 90 hours after ethanol ingestion—is useful in detecting alcohol use in the past 4 or 5 days.

Medical management of ALD

Corticosteroids are a mainstay in pharmacotherapy for severe AH. There is evidence for improved outcomes in patients with severe AH treated with prednisolone for 4 to 6 weeks.5 Prognostic models such as the Maddrey’s Discriminant Function, Lille Model, and the MELD score help determine the need for steroid use and identify high-risk patients. Patients with active infection
or bleeding are not a candidate for steroid treatment. An experienced gastroenterologist or hepatologist should initiate medical intervention after thorough evaluation.

Liver transplantation. A select group of patients with refractory liver failure are considered for liver transplantation. Although transplant programs differ in their criteria for organ listing, many require patients to demonstrate at least 6 months of verified abstinence from alcohol and illicit drugs as well as adherence to a formal AUD treatment and rehabilitation plan. The patient’s psychological health and prognosis for sustained sobriety are central to candidacy for organ listing, which highlights the key role of psychiatrists.

Further considerations. Thiamine and folate often are given to patients with ALD. Abdominal imaging and screening for HIV and viral hepatitis—identified in 10% to 20% of ALD patients—is routine. Alcohol abstinence remains central to survival because relapse increases the risk of recurrent, severe liver disease. Regrettably, many physical symptoms of liver disease, such as portal hypertension, ascites, and jaundice, can take months to improve with abstinence.

Treating AUD in patients with ALD
Successful treatment is multifaceted and includes more than just medications. Initial management often includes addressing alcohol withdrawal in dependent patients.6

Behavioral interventions are effective and indispensable components in preventing relapse,7 including a written relapse prevention plan that formally outlines the patient’s commitment to change, identifies triggers, and outlines a discrete plan of action. Primary psychiatric pathology, including depression and anxiety, often are comorbid with AUD; concurrent treatment of these disorders could improve patient outcomes.8

Benzodiazepines often are used during acute alcohol withdrawal. They should not be used for relapse prevention in ALD because of their additive interactions with alcohol, cognitive and psychomotor side effects, and abuse potential.9,10 Many of these drugs are cleared by the liver and generally are not recommended for use in patients with ALD.

Other agents, further considerations. Drug trials in AUD largely have been conducted in small, heterogeneous populations and revealed modest and, at times, conflicting drug effect sizes.6,11,12 The placebo effect among the AUD population is pronounced.6,7,13 Despite these caveats, several agents have been studied and validated by the FDA to treat AUD. Additional agents with promising pilot data are being investigated. Table 37,10,11,13-43 (page 30) summarizes drugs used to treat AUD—those with and without FDA approval—with a focus on how they might be used in patients with ALD. Of note, several of these agents do not rely on the liver for metabolism or excretion.

There is no agreed-upon algorithm or safety profile to guide a prescriber’s decision making about drug or dosage choices when treating AUD in patients with ALD. Because liver function can vary among patients as well as during an individual patient’s disease course, treatment decisions should be made on a clinical, collaborative, and case-by-case basis.

That being said, the AUD treatment literature suggests that specific drugs might be more useful in patients with varying severity of disease and during different phases of recovery:

- **Acamprosate** has been found to be effective in supporting abstinence in sober patients.14,44
- **Naltrexone** has been shown to be useful in patients with severe alcohol cravings. By modulating alcohol’s rewarding effects, naltrexone also reduces heavy alcohol consumption in patients who are drinking.14,15,44
- **Disulfiram** generally is not recommended for use in patients with clinically apparent hepatic insufficiency, such as decompensated cirrhosis or preexisting jaundice.

Although alcohol abstinence remains the treatment goal and a requirement for liver transplant, providers must recognize that
### Table 1
Clinical and laboratory picture of alcoholic liver disease

<table>
<thead>
<tr>
<th>Disease phenotype</th>
<th>Clinical features</th>
</tr>
</thead>
</table>
| **Asymptomatic hepatic steatosis** (outpatient) | **Incidence:** 2% to 5% of U.S. adult population  
**Symptoms:** Often asymptomatic, well-nourished, occasional hepatomegaly/RUQ pain, impaired cognition, appear medically well  
**Risk factors:** Daily alcohol consumption >2 to 3 drinks/d, female sex  
**Prognosis:** Generally favorable and reversible with abstinence  
**Treatment:** Alcohol detoxification to sobriety, multivitamin, counseling, psychiatric medications to prevent relapse |
| **Alcoholic hepatitis syndrome** (hospitalized) | **Incidence:** 5 to 10 per 100,000  
**Symptoms:** Acute jaundice, nausea, abdominal pain, fever, encephalopathy  
**Risk factors:** Binge intake >4 weeks in chronic user, younger age, genetic polymorphisms  
**Prognosis:** 10% to 30% 1-month mortality; 50% 1-year mortality with abstinence; 90% mortality without abstinence  
**Treatment:**  
- Manage acute alcohol withdrawal  
- Thiamine, folate  
- Enteral nutrition  
- Steroids for 6 weeks in selected patients could improve short-term survival  
- Alcohol abstinence  
- Management of encephalopathy, bleeding, ascites  
- Not candidates for liver transplant at most centers |
| ** Decompensated alcoholic cirrhosis** (chronic liver failure) | **Incidence:** Unknown but 10% to 15% of patients with heavy alcohol use will develop cirrhosis  
**Symptoms:** Anorexia, weight loss, cachexia, ascites, muscle wasting/weakness  
**Risk factors:** Lifetime alcohol consumption exceeding 4 drinks/d over ≥10 years  
**Prognosis:** Determined by severity of portal HTN complications (variceal bleeding, ascites, encephalopathy). If MELD >20, then approximately 70% 1-year survival even with abstinence  
**Treatment:**  
- Thiamine, folate, and multivitamins  
- Medical management of ascites with diuretics  
- Lactulose/rifaximin for encephalopathy  
- Endoscopy for varices  
- Transplant in selected patients with favorable prognosis for long-term abstinence, favorable compliance |

---

ALT: alanine transaminase; AST: aspartate transaminase; CBC: complete blood count; CTP: Child-Turcotte-Pugh score; HTN: hypertension; INR: international normalized ratio; MELD: Model for End-Stage Liver Disease; RUQ: right upper quadrant; WBC: white blood cell count

**Clinical Point**  
Psychiatric pathology, including depression and anxiety, often are comorbid with AUD; concurrent treatment could improve outcomes
Clinical Point

The patient’s psychological health and prognosis for sustained sobriety are central to candidacy for organ listing.
Table 2

Diagnosis and management of acute alcoholic hepatitis

<table>
<thead>
<tr>
<th>Lab tests</th>
<th>Medical therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum AST:ALT ratio of 2:1 (Variable albumin and total bilirubin)</td>
<td>Referral to gastroenterologist/hepatologist for evaluation</td>
</tr>
<tr>
<td>Basic metabolic panel (kidney injury common) and INR (often elevated)</td>
<td>Consider prednisolone or pentoxifylline</td>
</tr>
<tr>
<td>CBC: Frequent leukocytosis with neutrophilia</td>
<td>Candidates for treatment, including steroids: Recent jaundice, history of alcohol use disorder, no recent (&lt;15 days) GI hemorrhage, labs consistent with AH, prognostic scores, no infection</td>
</tr>
<tr>
<td>Toxicology: Positive blood alcohol level or urine ethyl glucuronide</td>
<td>Enteral nutrition for protein-calorie malnutrition</td>
</tr>
<tr>
<td>Abdominal ultrasonography (to exclude other causes of jaundice)</td>
<td>Vitamin supplementation (thiamine, folate)</td>
</tr>
<tr>
<td>Screen for HBV and HCV with HBsAg, anti-HBc, anti-HBs and anti-HCV, respectively</td>
<td>Consider pharmacologic treatment for AUD</td>
</tr>
<tr>
<td>Screen for infection (blood and urine cultures, ascitic fluid cultures, chest radiography)</td>
<td>Substance abuse treatment referral for AUD treatment</td>
</tr>
</tbody>
</table>

References


* urethyl glucuronide is a direct metabolite of ethanol that can be detected in urine for up to 90 hours

AH: alcoholic hepatitis; ALT: alanine transaminase; AST: aspartate transaminase; AUD: alcohol use disorder; GI: gastrointestinal; HBc: hepatitis B core antibodies; HBs: hepatitis B surface antibodies; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HCV: hepatitis C virus; INR: international normalized ratio
### Table 3

**Medications used to treat alcohol use disorder: Indications, mechanism of action, and use**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indications and use</th>
<th>Dosing</th>
<th>Metabolism (M)/excretion (E)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naltrexone&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reduce reinforcing aspects of alcohol, drinking cues, and heavy drinking&lt;sup&gt;13-17&lt;/sup&gt;</td>
<td>50 mg/d&lt;sup&gt;15,18&lt;/sup&gt; or 100 mg/d orally,&lt;sup&gt;7&lt;/sup&gt; 380 mg subcutaneous once monthly&lt;sup&gt;18&lt;/sup&gt;</td>
<td>M: Hepatic&lt;sup&gt;18&lt;/sup&gt; E: Mostly renal, fecal 2% to 3%&lt;sup&gt;15,18&lt;/sup&gt;</td>
<td>Opioid receptor antagonist&lt;sup&gt;7,15,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Disulfiram&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Promotion of alcohol abstinence&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Commonly 250 mg/d but has been used in higher and lower dosages&lt;sup&gt;13,23,24&lt;/sup&gt;</td>
<td>M: Hepatic&lt;sup&gt;24&lt;/sup&gt; E: Renal 70% to 76%, fecal 20%, lung 20% to 30%&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Primarily psychological—anticipation of disulfiram-ethanol reaction (tachycardia, flushing, nausea, vomiting) Blocks aldehyde dehydrogenase resulting in accumulation of acetaldehyde&lt;sup&gt;25&lt;/sup&gt;</td>
</tr>
<tr>
<td>Acamprosate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Promotion of abstinence by reducing cravings&lt;sup&gt;14,19&lt;/sup&gt;</td>
<td>666 mg, 3 times daily&lt;sup&gt;27&lt;/sup&gt;; 3 g/d orally&lt;sup&gt;7&lt;/sup&gt;</td>
<td>M: None&lt;sup&gt;27&lt;/sup&gt; E: Renal&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Antagonist at the NMDA receptor although mechanism of action is not fully understood&lt;sup&gt;17,19&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Promotion of abstinence in patients with protracted alcohol withdrawal, reduction of alcohol craving&lt;sup&gt;10,16&lt;/sup&gt;</td>
<td>600 to 1,800 mg/d&lt;sup&gt;10,16,28,29&lt;/sup&gt;</td>
<td>M: None&lt;sup&gt;30&lt;/sup&gt; E: Renal 75%, fecal 25%&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Modulates GABA deficits (via action at pre-synaptic calcium channels) and glutamate excess&lt;sup&gt;16,29&lt;/sup&gt;</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Promotion of abstinence, reduction in alcohol reinforcement, reduce heavy drinking and cravings, reduction in total drinking days&lt;sup&gt;11,31&lt;/sup&gt;</td>
<td>75 to 400 mg/d&lt;sup&gt;11,31-33&lt;/sup&gt;</td>
<td>M: Not extensively metabolized&lt;sup&gt;34&lt;/sup&gt; E: Renal&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Decreases dopamine activity after alcohol use through enhancement of GABA action, some glutamate antagonism&lt;sup&gt;11,31,32,35&lt;/sup&gt;</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Reduction in alcohol craving and consumption,&lt;sup&gt;1&lt;/sup&gt; promotion of abstinence&lt;sup&gt;27&lt;/sup&gt;</td>
<td>30 to 60 mg/d in 3 divided doses&lt;sup&gt;38&lt;/sup&gt;</td>
<td>M: Liver, limited&lt;sup&gt;38&lt;/sup&gt; E: Renal&lt;sup&gt;38&lt;/sup&gt;</td>
<td>GABA-B receptor agonist mediating reinforcing effects of alcohol through action in ventral tegmental area&lt;sup&gt;37&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>FDA-approved for treatment of AUD  
ALT: alanine transaminase; AUD: alcohol use disorder; GABA: \( \gamma \)-aminobutyric acid; NMDA: N-methyl-D-aspartate
### Medications used to treat alcohol use disorder: Indications, mechanism

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indications and use</th>
<th>Other medication features</th>
</tr>
</thead>
</table>
| Disulfiram | Alternates metabolism of acetaldehyde to acetic acid. | - Concomitant opioids are contraindicated<sup>18</sup>  
- Used in the treatment of cholestasis-related pruritus<sup>22</sup>  
- Injectable form can boost adherence and bypass hepatic first-pass metabolism |
| Naltrexone | A partial opioid receptor antagonist. | - Drug’s effect size increased with close supervision of disulfiram compliance and patient awareness of drug’s effect<sup>23</sup>  
- Preexisting liver pathology predisposes to bad outcomes in disulfiram-induced hepatitis<sup>25</sup>  
- Immediate drug discontinuation after jaundice appears reduces morbidity and mortality<sup>24</sup>  
- Small amounts of alcohol in over-the-counter drugs or household items can trigger symptoms |
| Baclofen | Acts as a γ-aminobutyric acid (GABA) B receptor agonist mediating some glutamate activity after alcohol use and promoting alcohol craving. | - No adverse interactions with alcohol<sup>16</sup>  
- Additive efficacy when used with naltrexone<sup>16</sup>  
- Might be helpful for treating comorbid insomnia<sup>16,23,29</sup> mood and anxiety<sup>12,29</sup>  
- Withdrawal symptoms if stopped abruptly |
| Topiramate | Acts as a GABA-B receptor agonist. | - May be particularly useful in patients who also abuse stimulants<sup>26</sup>  
- Can improve mood during abstinence<sup>32</sup>  
- Low dosages might be effective (75 mg/d)<sup>32</sup>  
- Useful in addressing impulsivity<sup>32</sup> |
| Acamprosate | Acts as an NMDA receptor antagonist. | - Potential increased efficacy with higher doses<sup>3</sup>  
- Improves abstinence and some liver function tests in hepatitis C patients<sup>41</sup>  
- No inherent pleasurable or reinforcing properties<sup>17</sup>  
- Withdrawal when stopped abruptly  
- Overdose has been documented in alcohol-dependent patients<sup>42</sup>  
- Might reduce comorbid anxiety<sup>43</sup> |

### Advance liver disease

- **Dose modification:** Not required in patients with mild to moderate hepatic impairment<sup>14,20</sup>
- **Hepatotoxicity:** Hepatotoxicity in <5% at doses 7-times recommended daily dose<sup>15</sup>; use of naltrexone injection in patients with severe hepatic impairment has not been studied<sup>16</sup>; most transaminase elevations during therapy are mild, self-limited, and resolve with continued therapy<sup>21</sup>
- **Other toxicities:** Nervousness, restlessness, nausea, headache, anxiety, depression, vomiting, diarrhea, somnolence<sup>7,13,15</sup>

### Other medication features

- Reduces “negative cravings” (negative feelings arising in the absence of alcohol)<sup>19</sup>
- Dosing
  - **Dose modification:** Associated with hepatotoxicity and should be used cautiously, if at all, in hepatic insufficiency<sup>24</sup>
  - **Hepatotoxicity:** Dose-dependent, rapid-onset hepatitis (leukocyte infiltration, high aminotransferases—ALT predominant) in <1% with onset often 1 to 2 months after drug initiation<sup>25</sup>
  - **Other toxicities:** Nausea, abdominal pain<sup>15</sup>; rarely psychosis, confusion, peripheral neuropathy, optic neuritis<sup>26</sup>

- Dose modification: None<sup>27</sup>
- Hepatotoxicity: None<sup>27</sup>
- Other toxicities: Diarrhea, abdominal discomfort, anxiety<sup>7,19</sup>

- Dose modification: None<sup>30</sup>
- Hepatotoxicity: None<sup>30</sup>
- Other toxicities: Somnolence, dizziness, headache, indigestion, myalgia, altered mental status, insomnia<sup>10,38,29</sup>

- Dose modification: Clearance may be reduced in hepatic insufficiency<sup>24</sup>
- Hepatotoxicity: None
- Other toxicities: Paresthesias, numbness, cognitive impairment, headache, dizziness, psychomotor slowing, weight loss, nausea/vomiting, somnolence<sup>11,31,33</sup>

- Dose modification: None<sup>48</sup>
- Hepatotoxicity: Has not been linked to any clinically significant liver injury, including encephalopathy and hyperammonemia<sup>28,40</sup>
- Other toxicities: Drowsiness, weakness, fatigue, myalgia<sup>37</sup>
Related Resources


Drug Brand Names

Acamprosate - Campral
Baclofen - Liorenal
Disulfiram - Antabuse
Gabapentin - Neurontin
Naltrexone - Revia, Vivitrol
Pentoxifylline - Trental
Prednisolone - Prelone
Rifaximin - Xifaxan
Topiramate - Topamax

Clinical Point

For medically stable ALD patients, the mental health clinician should be aware of key laboratory and physical exam findings.

Bottom Line

Patients with alcoholic liver disease (ALD) require collaborative care from specialists in addiction, gastroenterology, and psychiatry. Psychiatrists have a role in identifying signs of ALD, prescribing medication to treat alcohol use disorder, and encouraging abstinence. There is some evidence supporting specific medications for varying severity of disease and different phases of recovery. Pharmacotherapy decisions should be made case by case.