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

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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.[1] 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,[2] 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

Alcoholic liver disease

Clinical Point

A psychiatrist evaluating a jaundiced patient who continues to drink should arrange urgent medical evaluation

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Box

Key points about treating liver disease in patients with alcoholism

Collaborative management of medical, substance-related, and psychiatric symptoms of ALD offers medical and psychiatric benefits
Psychiatrists are essential for successful monitoring and treatment of ALD. They should be knowledgeable about its signs and symptoms
In ALD, there is a role for AUD pharmacotherapy despite the risk of adverse effects
More research is needed to describe (1) the efficacy of AUD pharmacotherapy for preventing relapse in this population, (2) how these medications can be effectively and safely used in ALD patients, and (3) what care coordination strategies can make best use of multidisciplinary management of patients with comorbid ALD and AUD

ALD: alcoholic liver disease; AUD: alcohol use disorder

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 28***). 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 3***[1,7,10,11,13-43] (***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

Clinical Point

Alcohol abstinence remains central to survival because relapse increases the risk of recurrent, severe liver disease

Alcoholic liver disease

Clinical Point

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

Table 1

Clinical and laboratory picture of alcoholic liver disease

Disease phenotype	Clinical features
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

some patients might not be able to maintain long-term sobriety. Therefore, harm reduction models are important companions to abstinence-only models of AUD treatment.[45] The array of behavioral, pharmacological, and philosophical approaches to AUD treatment underlines the need for an individualized approach to relapse prevention.

Collaboration between medicine and psychiatry

When AUD and ALD are comorbid, psychiatrists might worry about making the patient's medical condition worse by prescribing additional psychoactive medications—particularly ones that are cleared by the liver. Remember that AUD confers a substantial mortality rate that is more than 3 times that of the general population, along with severe medical[46] and psychosocial[31] effects. Although prescribers must remain vigilant for adverse drug effects, medications easily can be blamed for what might be the natural progression and symptoms of AUD in patients with ALD.[26] This erroneous conclusion can lead to premature medication discontinuation and undertreatment of AUD.

In the end, keeping the patient sober and mentally well might be more beneficial than eliminating the burden of any medication side effects. Collaborative medical and psychiatric management of ALD patients can ensure that clinicians properly weigh the risks, benefits, and duration of treatment unique to each patient.

Starting AUD treatment promptly after alcohol relapse is essential and entails a multidisciplinary effort between medicine and psychiatry, both in and out of the hospital. Because the relapsing, ill ALD patient most often will be admitted to a medical specialist, AUD might not receive enough attention during the medical admission. Psychiatrists can help in initiating AUD treatment in the acute medical setting, which has been shown to improve the outpatient course.[6] For medically stable ALD patients admitted for inpatient psychiatric care or presenting a clinic, the mental health clinician should be aware of key laboratory and physical exam findings.

continued

Clinical Point

The patient's psychological health and prognosis for sustained sobriety are central to candidacy for organ listing

Objective laboratory and prognostic markers

Labs:
- Serum AST and ALT may be mildly elevated or >2:1 ratio
- CBC shows mild macrocytosis without anemia
- Urine ethyl glucuronide to verify alcohol use in past 5 days
- Normal albumin, bilirubin, and INR

Imaging: Increased hepatic steatosis on CT and MRI might be seen

Biopsy: Variable amount of steatosis with mild inflammation and pericellular fibrosis

Prognosis: Might improve/resolve with abstinence or lead to progressive liver damage/fibrosis with continued alcohol use

Labs:
- Serum AST:ALT > 2:1 often seen but both <1,000 IU/mL
- Urinary ethyl glucuronide to verify alcohol use in past 3 to 5 days
- CBC: Moderate to severe macrocytosis with anemia, frequent thrombocytopenia, leukocytosis with left shift if severe
- Moderate to severely elevated bilirubin and INR, low albumin always seen

Imaging: Hepatic steatosis in CT or MRI +/- hepatosplenomegaly, +/- ascites and venous collaterals

Biopsy: Steatosis with neutrophilic inflammation, cirrhosis in 40% to 60%

Prognosis: Discriminant function ≥32 has 30% to 50% mortality at 1 month

Labs:
- Serum AST and ALT often normal or minimally elevated
- CBC: Moderate to severe macrocytosis with anemia, low WBC and platelets because of portal HTN
- Bilirubin and INR may only be mildly elevated; low albumin
- CTP score ranges from 5 to 15
- 1 to 3 points for albumin, bilirubin, INR, and ascites and encephalopathy
- CTP A = 5 to 6 points
- CTP B = 7 to 9 points
- CTP C ≥10 points

Imaging: Small shrunken, nodular liver with ascites, collaterals, and splenomegaly

Biopsy: Cirrhosis with minimal steatosis/inflammation

Prognosis: MELD score predicts mortality at 3 months:
- <9 = ~2% mortality
- 10 to 19 = 6% mortality
- 20 to 29 = 20% mortality
- 30 to 39 = 53% mortality
- >40 = 71% mortality

Alcoholic liver disease

Clinical Point

Harm reduction models are important companions to abstinence-only models of AUD treatment

Table 2

Diagnosis and management of acute alcoholic hepatitis

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

[a]Urine ethyl 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

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Alcoholic liver disease

Clinical Point

Keeping the patient sober and mentally well might be more beneficial than eliminating the burden of medication side effects

Table 3

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

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

[a]FDA-approved for treatment of AUD

ALT: alanine transaminase: AUD: alcohol use disorder; GABA: γ-aminobutyric acid; NMDA: *N*-methyl-D-aspartate

Advanced liver disease	Other medication features
Dose modification: Not required in patients with mild to moderate hepatic impairment[18,20] **Hepatotoxicity:** Hepatotoxicity in <5% at doses 7-times recommended daily dose[15]; use of naltrexone injection in patients with severe hepatic impairment has not been studied[18]; most transaminase elevations during therapy are mild, self-limited, and resolve with continued therapy[21] **Other toxicities:** Nervousness, restlessness, nausea, headache, anxiety, depression, vomiting, diarrhea, somnolence[7,13,15]	• Concomitant opioids are contraindicated[18] • Opioid-free period of 7 to 10 days is required[18] • Used in the treatment of cholestasis-related pruritis[22] • Injectable form can boost adherence and bypass hepatic first-pass metabolism
Dose modification: Associated with hepatotoxicity and should be used cautiously, if at all, in hepatic insufficiency[24] **Hepatotoxicity:** Dose-dependent, rapid-onset hepatitis (leukocyte infiltration, high aminotransferases—ALT predominant) in <1% with onset often 1 to 2 months after drug initiation[25] **Other toxicities:** Nausea, abdominal pain[13]; rarely psychosis, confusion, peripheral neuropathy, optic neuritis[26]	• Drug's effect size increased with close supervision of disulfiram compliance and patient awareness of drug's effect[23] • Preexisting liver pathology predisposes to bad outcomes in disulfiram-induced hepatitis[25] • Immediate drug discontinuation after jaundice appears reduces morbidity and mortality[24] • Small amounts of alcohol in over-the-counter drugs or household items can trigger symptoms
Dose modification: None[27] **Hepatotoxicity:** None[27] **Other toxicities:** Diarrhea, abdominal discomfort, anxiety[7,19]	• Reduces "negative cravings" (negative feelings arising in the absence of alcohol)[19]
Dose modification: None[30] **Hepatotoxicity:** None[30] **Other toxicities:** Somnolence, dizziness, headache, indigestion, myalgias, altered mental status, insomnia[10,28,29]	• No adverse interactions with alcohol[16] • Additive efficacy when used with naltrexone[16] • Might be helpful for treating comorbid insomnia,[16,28,29] mood and anxiety[10,29] • Withdrawal symptoms if stopped abruptly
Dose modification: Clearance may be reduced in hepatic insuffiency[34] **Hepatotoxicity:** None **Other toxicities:** Paresthesias, numbness, cognitive impairment, headache, dizziness, psychomotor slowing, weight loss, nausea/vomiting, somnolence[11,31-33]	• May be particularly useful in patients who also abuse stimulants[36] • Can improve mood during abstinence[32] • Low dosages might be effective (75 mg/d)[32] • Useful in addressing impulsivity[32]
Dose modification: None[38] **Hepatotoxicity:** Has not been linked to any clinically significant liver injury, including encephalopathy and hyperammonemia[39,40] **Other toxicities:** Drowsiness, weakness, fatigue, myalgia[37]	• Potential increased efficacy with higher doses[1] • Improves abstinence and some liver function tests in hepatitis C patients[41] • No inherent pleasurable or reinforcing properties[37] • Withdrawal when stopped abruptly • Overdose has been documented in alcohol-dependent patients[42] • Might reduce comorbid anxiety[43]

Clinical Point

Because an ill ALD patient often will be admitted to a medical specialist, AUD might not receive enough attention during the medical admission

continued

Alcoholic liver disease

Related Resources

- Khan A, Tansel A, White DL, et al. Efficacy of psychosocial interventions in inducing and maintaining alcohol abstinence in patients with chronic liver disease: a systematic review [published online August 6, 2015]. Clin Gastroenterol Hepatol. doi: 10.1016/j.cgh.2015.07.047.
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Drug Brand Names

Acamprosate • Campral
Baclofen • Lioresal
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

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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.