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Review Article

Integrated Multidisciplinary Management of Alcohol-Associated Liver Disease

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Abstract

Alcohol-associated liver disease (ALD) is one of the most common liver diseases and indications for liver transplantation (LT). Alcohol use disorder (AUD), a frequent accompaniment in ALD patients, may also be associated with psychiatric comorbidities such as depression and anxiety. Identification of ALD at an earlier stage, and treatment of AUD may help prevent progression to advanced stage of ALD such as cirrhosis and alcoholic hepatitis. Screening for alcohol use and AUD treatment in ALD patients is often not performed due to several barriers at the level of patients, clinicians, and administrative levels. This review details the integrated multidisciplinary care model especially on the specific role of the hepatologist, psychiatrist, addiction counselor, and social worker in providing complete management for the dual pathology of liver disease and of AUD. Laboratory assessment, pharmacological and behavioral therapies, and recommended assessments for follow-up care by the respective specialists is outlined. We provide perspective along with the literature support, with the goal of providing team based comprehensive care of patients with ALD.

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Introduction

Alcohol-associated liver disease (ALD) is one of the most common liver diseases worldwide. There were over 2 million cases of alcohol-associated cirrhosis in 2017, which contributed to 48% of cirrhosis related hospitalizations and 27% of deaths, with over $23 billion spent on direct patient care in the US.[1,2] Alcoholic hepatitis (AH) contributes significantly to the ALD related disease burden, with a risk of up to 60–80% mortality in short-term at 90 days especially in those with severe forms of acute on chronic liver failure.[3,4] During the coronavirus 2019 (COVID-19) pandemic, over 60% of individuals increased alcohol consumption[5] with an accelerated increase in ALD related healthcare burden.[6–8] Further, this disease burden is increasing in young individuals including prevalence of alcohol use disorder (AUD), hospitalizations, liver transplant (LT) need, and patient mortality.[9–11]

Approximately 10–20% of patients with ALD develop cirrhosis, with the highest risk and progression of fibrosis in those with AH.[2,12] Patients with ALD present at an advanced spectrum of liver disease of cirrhosis, AH, and complications compared to liver diseases other than ALD.[13,14] Further, the progression of liver disease is much faster to more advanced forms and complications in ALD patients.[2] This becomes even more relevant given lack of effective medical therapies for ALD.[2,15] Although, LT is an effective destination therapy for ALD cirrhosis, only 4% of LT were reported to be performed for AH in the US from regions with most LT performed for this indication.[6] Due to lack of uniform objective criteria for candidate selection for early liver transplantation (eLT) in severe AH, it is used heterogeneously across providers and transplant centers,[6] with some centers not performing LT for AH and some centers performing up to 4% of all LT for a diagnosis of AH.

AUD and addiction to alcohol is a chronic relapsing condition characterized by inability to abstain, impairment in behavioral control, cravings, diminished recognition of problems with one's behaviors and interpersonal relationships, and a dysfunctional emotional response. A total of 10.2% of individuals ≥ 12 years old in the USA had a diagnosis of AUD in 2020.[5] Diagnosis of AUD is made using the Diagnostic Statistical Manual fifth edition (*DSM-5*) criteria, with at least two criteria met of 11 focusing on alcohol use in spite of harms or negative effects, craving, tolerance, or withdrawal. The number of positive criteria increases with severity, with 4–5 indicating moderate, and six or more criteria defines severe AUD.

Clearly, individuals with harmful alcohol use who are at risk of developing ALD should be identified early at any opportunity of medical encounters so that they can be engaged in focused counseling aiming to reduce alcohol use and pre-

Keywords: Alcohol; Cirrhosis; Liver transplant; Depression; Anxiety; Multidisciplinary.
Abbreviations: ALD, Alcohol-Associated Liver Disease; AH, Alcoholic Hepatitis; AUD, Alcohol Use Disorder; LT, Liver Transplant.
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Table 1. Barriers limiting implementation of managing alcohol use disorder and establishing integrated multidisciplinary care model in routine clinical practice

Barrier	Possible solution
Clinician level barriers	
Clinician training	Hepatology training curriculum, ECHO model
Time for screening for AUD	Education, AUDIT-C shorter version
Patient level barriers	
Awareness and lack of insight	Education and Brief Intervention
Lack of accepting diagnosis and/or treatment	Nonjudgmental approach, avoid stigma
Too sick for treatment	Digital monitoring and telemedicine
System and administration level barriers	
Financial and insurance	Funding and social work support
Resources and manpower	Collaborative billing models
Protocol in monitoring	Protocol on biomarkers use and alcohol relapse definition

AUD, Alcohol Use Disorder.

vent development of cirrhosis and its complications.[16] In a retrospective cohort study using the Danish database, 5% of women and 6% of men developed cirrhosis during a follow-up between 1998 and 2002. The majority of individuals who developed cirrhosis had one or more medical encounters during their follow-up, with missed opportunities to identify those with exposure to harmful alcohol use, and prevent advanced ALD. Controlling the risk factor of cessation of alcohol use is also the single most important determinant of liver related readmission to the hospital and long-term patient survival in patients with AUD and decompensated cirrhosis and those with AH.[17–19] In prospective studies, among patients who survived an episode of severe AH, the risk of long-term mortality was over two-fold higher in those reducing their alcohol intake below the recommended harmful limits compared with those completely abstaining from alcohol use.[17,20] It clearly remains to be seen if there is a safe limit of alcohol use that can be allowed in these patients with advanced liver disease. Although complete abstinence is ideal, but is difficult to achieve in a majority of these patients.[21] Further, AUD treatment including behavioral and/or pharmacological therapies are rarely used in ALD patients including those with cirrhosis.[18,19,22,23] For example, in a retrospective cohort of over 35,682 veterans with ALD cirrhosis and a diagnosis of AUD, only less than 14% were treated for the AUD within 6 months from diagnosis, with only 0.4% receiving some pharmacotherapy.[22]

Barriers to AUD treatment

Patients with liver disease aggravated by alcohol suffer from a dual pathology of AUD and liver disease. Educating patients with ALD and AUD on the need for complete abstinence is not enough and may require management by hepatology specialists for liver disease and by an addiction team for managing the dual pathology. That is preferably achieved within an integrated multidisciplinary care model.[23,24] This care model has shown to reduce alcohol relapse both within and outside LT settings.[19,25–27] However, the implementation of such models in clinical practice is challenging.[22–24] Although national and international organizations have proposed integrated care models to manage ALD patients,[4,28] widespread adoption of these recommendations is poor.[22] Barriers at the level of patients, clinicians, and systems may be encountered in treating patients with ALD and AUD (Table 1).[23,24,29]

Integrated multidisciplinary care model

Several disciplines working in an integrated team has been proposed as a model to for comprehensive care for the dual pathology of AUD and of ALD.[24,26,30] An integrated care model overcomes several but not all of the barriers limiting AUD treatment in ALD patients. Specifically, an integrated care model is successful in overcoming the barrier of insufficient physician training to treat AUD, and increasing the comfort level of hepatologists in addressing AUD and of addiction team in prescribing medications in ALD patients.[24] However, this model may not completely overcome stigma attached to the diagnosis of ALD[26] and uncertainty on where to seek treatment, described by Szerman et al.[30] as the "wrong door syndrome." Moreover, organizational and logistical barriers because of limited resources allocated to mental health and addiction care limit the establishment and implementation of an ideal integrated care model and overcoming siloed practices of the two different specialties.[24,26] Hepatologists, psychiatrists, addiction counselors, and social workers see patients at the same location under the same roof in an ideal integrated multidisciplinary care model, with a goal of providing comprehensive patient care to manage both AUD as well as liver disease. AUD treatment in an integrated care model compared with siloed treatment of AUD and of ALD results in reduced risk of relapse to alcohol with improved liver related outcomes, especially among LT recipients. For example, in a recent systematic review, pooled data from six studies on 649 LT recipients, AUD treatment using an integrated care model reduced alcohol relapse by 44% and patient mortality by 71% with and odds ratios (ORs) and 95% confidence intervals (CIs) of 0.56 (0.36–0.87) and 0.29 (0.08–0.99).[20]

Assessment of liver disease

It should be recognized that patents with AUD may have liver disease with causes other than alcohol, such as nonalcoholic fatty liver disease caused by metabolic syndrome and obesity, chronic viral (hepatitis B, hepatitis C, or human immunodeficiency virus) infections, and other rare diseases including alpha-1 antitrypsin deficiency, autoimmune diseases, and drug induced liver injury.[31] A thorough assessment of liver disease (Fig. 1) other than diagnosis of the underlying liver disease includes determination of liver fibrosis in those without cirrhosis, complications of liver disease in those with cirrhosis (ascites, hepatic encephalopathy, var-

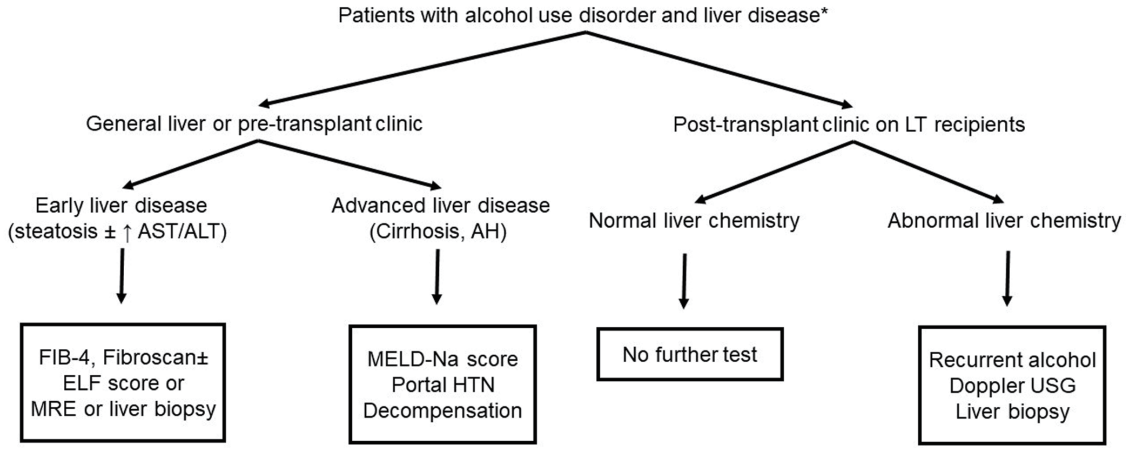

Fig. 1. Assessment by liver specialist on patients with alcohol use disorder and liver disease. Decompensation includes one or more of ascites, hepatic encephalopathy, variceal bleeding, hepatocellular carcinoma; enhanced liver fibrosis (ELF) score incorporating an algorithm using special laboratory evaluation for serum hyaluronic acid, tissue inhibitor of metalloproteinase, and procollagen III amino terminal peptide. AH, alcoholic hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4 score (patient's age, AST, ALT, platelet count); HTN, hypertension; LT, liver transplant; MRE, magnetic resonance elastography; MELD-Na, model for end-stage liver disease-sodium score (algorithm including serum total bilirubin, serum creatinine, institutional normalized ratio, and serum sodium); USG, ultrasonography.

ices, and portal hypertension, malnutrition, and hepatocellular carcinoma), model for end-stage liver disease score, need for LT, graft function as evaluated with liver chemistry in LT recipients, and if abnormal further evaluation that may include a doppler ultrasound examination for hepatic vasculature, cholangiogram for biliary abnormalities, serological work-up for opportunistic infections, and a liver biopsy for acute or chronic rejection. Use of noninvasive serological and radiological markers for fibrosis assessment is limited by overestimation of fibrosis in patients who are actively drinking alcohol. In these patients, liver stiffness and fibrosis assessment should be adjusted for serum bilirubin and AST values or tests repeated after at least 2 weeks of abstinence.[32] The sequence and extent of these tests varies from patient to patient depending on clinical scenario, availability, and provider / patient choice. It is recommended to provide an adequate nutrition intake for cirrhosis patients with 30–35 kcal/kg/d and 1.0–1.5 gm/k/d protein intake, with vegetable and not animal sources of protein, especially in patients with hepatic encephalopathy.[33] Patients are advised to take small frequent meals and include a nighttime snack before going to bed to maintain nutritional status and avoid muscle loss.[33] It is recommended to include a dietician as a part of the multidisciplinary care model, especially for patients who are unable to take adequate nutrition. For patients with a caloric intake below 21.5 kcal/k/d, nutritional supplementation should be used, preferably by the enteral route.[34]

Assessment of AUD

The addiction counselor determines the severity of AUD (Fig. 2), identifies barriers that may impact access to treatment and assesses motivation to change, and assists in making recommendations on the level of care needed (see later section on behavioral therapies), recovery specific resources, and relapse prevention planning.[35] Biomarkers may be used to complement self-reported alcohol use for better accuracy in determining active ongoing alcohol consumption.[36] Several biomarkers measure direct damage of end organs from alcohol like aspartate amino transferase, alanine amino transferase, carbohydrate deficient transferrin, gamma-glutamyl transpeptidase, mean corpuscular volume, or products of alcohol metabolism like ethyl glucuronide, ethyl sulfate, and phosphatidylethanol. The first group of biomarkers related to end-organ damage are limited by low sensitivity and specificity. Of the biomarkers measuring alcohol metabolites, phosphatidylethanol is used most often in clinical practice as it is most accurate, not confounded by endogenous alcohol exposure, and can detect alcohol use within the previous up to 3 weeks from the last drink.[36,37]

If an addiction counselor is unavailable, a social worker can fill in this role, which is mainly to assess the biological, psychological, and social assessment of the patient to provide a holistic approach to patient care, and improve patient outcomes.[5] The social worker emphasizes the importance of self-determination and assists patients to develop meaningful goals that support their overall health. Additionally, the addiction counselor provides resources to empower and guide patients to overcome barriers and achieve these goals.[38]

Assessment of psychiatric status and comorbidities

The psychiatric assessment begins with the Patient Health Questionnaire-9 to assess depression and the Generalized Anxiety Disorder-7 questionnaire to assess anxiety (Supplementary Tables 1 and 2). The psychiatrist also complements addiction counselors and social workers to provide clarification on the diagnosis and treatment of AUD and of other recreational substance use, monitor alcohol use on follow-up as the diagnosis of AUD is often evolving, provide pharmacotherapy for AUD and for psychiatric comorbidities (see later section on pharmacotherapies), and identify post-acute withdrawal syndrome, which can overlap with psychiatric comorbidities (depression, anxiety, insomnia), and can last from months for up to 2 years after the cessation of alcohol.[39]

Management of AUD

This can be achieved by behavioral and/or pharmacological therapies.

Behavioral Therapies

These therapies are effective in motivating patients to change their behavior, and virtual options may allow easier access for individuals seeking help. Person-centered approaches

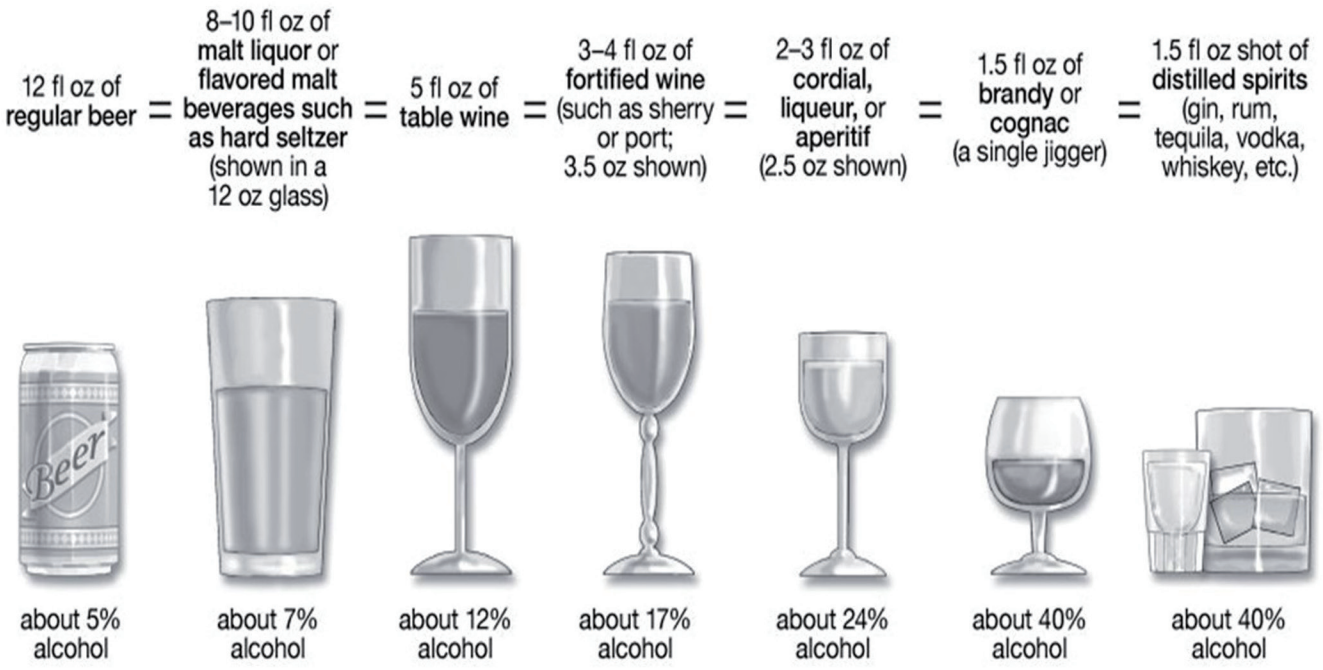

Fig. 2. Definition of an alcohol-containing drink. Source: https://www.niaaa.nih.gov/sites/default/files/standard-Drink-June2022.jpeg.

are used to formulate an approach that the individual can carry out successfully. Facilitated by licensed professionals, evidenced-based therapies such as cognitive behavioral therapy, which helps patients identify and modify behavior by adjusting their thought patterns and motivational interviewing, that utilizes techniques to help patients gain motivation by resolving their ambivalences about changing behavior have been shown to be effective.[40,41] Therapies can be delivered in the form of group, individual and family therapy with the goal to control alcohol use and transition the patients into self-management of their addiction.[40]

The determination of level of care requires comprehensive evaluation of AUD using the American Society of Addiction Medicine criteria developed in the 1980s by an interdisciplinary group. This includes an assessment of six dimensions, with each of these dimensions scaled for severity from 1 to 4 (Table 2). The total severity score determines the level of care recommendation, and ongoing assessment helps transition the patient on the continuum of care (Table 3).[42,43]

Outpatient treatment

Outpatient treatments include individual therapy and/or group therapy. Individual therapy is appropriate for individuals that are stable in their recovery or can also be given as an adjunct to group therapy. It provides a confidential space to the participant to focus on individual areas of concerns. Group therapy including education, skill building, cognitive restructuring, and interpersonal processing focuses on identifying and processing the underlying factors that contributed to addiction. It is an effective modality due to its advantages of peer support, reducing isolation, observing the success of others, structure, accountability, and feedback.[40] Recovery community groups are popular, as they are offered at no cost to attend have an accommodating time schedule, offer autonomy in deciding the amount of information to share, and

Table 2. Assessing alcohol use disorder on six dimensions as per American Society of Addiction Medicine (ASAM) criteria

Dimension	Assessment
1. Acute intoxication and/or withdrawal potential	Significant risk of severe withdrawal symptoms or seizures
2. Biomedical conditions and complications	Any acute or chronic medical illness that might interfere with the current treatment
3. Emotional, behavioral, or cognitive conditions and complications	Any psychiatric issues, including behavioral or emotional problems that might impede the treatment process
4. Readiness to change	Patient's openness to treatment, acceptance of addiction, readiness for change, and motivation for compliance
5. Relapse, continued use or problem potential	Patient's ability to cope with cravings, comprehension of triggers, and ability to abstain
6. Recovering/living environment	Current living situation, adequacy of social support network, and financial resources

Table 3. Level of care continuum as per American Society of Addiction Medicine

Level of treatment	Description
I: Outpatient treatment	Organized nonresidential services or office practices with designated addiction treatment personnel who provide professionally directed evaluation, treatment, and recovery services to addicted patients. The services are provided in regularly scheduled sessions of usually fewer than 9 h per week.
II: Intensive outpatient and partial hospitalization treatment	An organized service with designated addiction personnel provides a planned treatment regimen consisting of regularly scheduled sessions of at least 9 h per week within a structured program. This level of care affords patients the opportunity to interact with the real-world environment while still benefiting from a programmatically structured therapeutic milieu.
III: Medically monitored inpatient (residential) treatment	Offered in permanent facilities with inpatient beds, includes a planned regimen of round-the-clock professionally directed evaluation, care, and treatment for addicted patients provided by designated addiction personnel. The treatment is specific to addiction and does not require the full resources of an acute care general hospital.
IV: Medically managed inpatient treatment	Designated addiction professionals provide a round-the-clock planned regimen of medically directed evaluation, care, and treatment for addicted patients in an acute care inpatient setting. A multidisciplinary staff and the full resources of a general hospital are available to provide treatment for patients with severe acute problems necessitating primary medical and nursing services. Treatment is specific to addiction, although the available support services allow concurrent treatment of coexisting acute biomedical and emotional conditions.

are offered either in-person or virtually.[44] Alcoholics Anonymous, founded in 1935, is the most well-known recovery community group which has continued to grow to a global level.[45] Additional support groups have been developed over the years with varying philosophies to recovery which offers diverse treatment opportunities for patients.[40]

Intensive outpatient treatment

Intensive outpatient treatment is a highly utilized treatment program, and is offered by 46% of treatment facilities in the US.[46] It can be administered as the primary treatment, a step down from residential treatment, or a step up from a less intensive treatment. Benefits include flexible timing, developing and practicing recovery skills, and incorporating community support to help with transition into self-management.[46,47]

Inpatient treatment

Inpatient treatment in an acute care setting is supplemented by the facilities of the hospital itself to manage associated medical issues. This is the best example of integrated multidisciplinary comprehensive care of patients by professionals for the medical and addiction issues in an acute care setting (Table 3). Completing inpatient therapy is usually transitioned to outpatient treatment sessions.

Pharmacological therapy

Therapies for AUD

We recommend a clear discussion with patients that medications are not the sole treatment for their AUD, and behavioral treatments are the cornerstone which provides accountability, structure, and a support network. This network in particular not only assists with ongoing recovery efforts, but tends to have a positive and lasting impact on patient mental health. There are three FDA-approved medications for AUD; naltrexone, acamprosate, and disulfiram. Data on these drugs for AUD in ALD patients are limited, as randomized controlled trials in AUD typically exclude patients with ALD because AUD treatments are rarely used in ALD patients. On clinicaltrials.gov there is a study in which 12 patients with ALD were given acamprosate to evaluate its safety in the context of liver disease (https://clinicaltrials.gov/ct2/show/results/NCT04287920). As acamprosate has no hepatic metabolism, it is considered to be safe for use in ALD patients. However, caution should be taken in those with renal impairment as advanced ALD patients with decompensated cirrhosis and AH may have renal dysfunction due to hepatorenal syndrome, with this agent not recommended in patients with creatinine clearance below 30 mL/min. Disulfiram and naltrexone carry a risk for hepatotoxicity especially if administered to patients with liver disease. There are no studies of disulfiram specific to ALD patients. However, there is a recent retrospective study published in 2022 of 100 patients prescribed naltrexone with concurrent ALD; it evaluated hepatic safety by monitoring liver enzyme changes during naltrexone treatment and follow-up. The results were an overall decrease in AST and ALT, indicating safety in patients with liver disease, including those with compensated cirrhosis.[48] The study is promising in that, if replicated, it may significantly alter clinical practice for the better; however, the study does call for more safety data for those with decompensated cirrhosis. More often, off-label treatments for AUD are used in ALD patients which include varenicline, topiramate, gabapentin, baclofen and ondansetron (Table 4).[26,27,49]

Though baclofen is not FDA approved for AUD, there is some data to support its use. A randomized controlled trial demonstrated the efficacy and safety of baclofen in patients with AUD and cirrhosis. In this study on 84 patients with alcohol-associated cirrhosis (42 assigned to placebo), abstinence was higher in the baclofen arm (71 vs. 29%, $p < 0.05$). There was also improvement in liver function including serum albumin and international normalized ratio.[50] A *post hoc* analysis of this study explored baclofen's effect in a subgroup of 24 patients (12 received placebo) with concomitant hepatitis C virus infection.[51]

Therapies for concomitant psychiatric comorbidities

It is crucial that providers managing ALD patients recognize coexisting associated psychiatric comorbidities like depression, anxiety, and insomnia.[26] For example, AUD as many as 50% of patients may have psychiatric comorbidities and 5–10% use recreational substances other than nicotine or marijuana.[52,53] Similar to management of AUD, there are

Table 4. Pharmacological therapies for AUD

Drug	Mechanism of action	Accepted dose range	AUD patients with hepatic impairment	Target outcome	Notes:
FDA-approved medications for AUD					
Naltrexone	Mu opioid receptor antagonist	50 mg orally daily 380 mg monthly intramuscular	Use with caution, regular monitoring and limit in advanced liver disease	Achieve and maintain abstinence and reduce drinking	Start at 25 mg orally with food, and increase to 50 mg dose if needed and tolerated.
Acamprosate	Modulates glutamate activity, NMDA receptor agonist	666 mg orally three times a day	No hepatic metabolism	Achieve and maintain abstinence	Number of pills, three times a day dosing and flatus may limit compliance.
Disulfiram	Inhibits aldehyde dehydrogenase	250–500 mg orally daily	Hepatically metabolized; caution or avoid use	Achieve and maintain abstinence	Caution in patients with history of psychosis.
Off-label treatments for AUD					
Varenicline	Nicotinic acetylcholine receptor agonist	Up to 1 mg orally twice daily	Safe, minimal hepatic metabolism	Reduce drinking (particularly useful for smokers)	EAGLES trial removed black box warning for serious neuropsychiatric events such as suicidality. Can cause vivid dreams.
Topiramate	Inhibits glutamate and increases GABA activity	Up to 300 mg/d orally in divided doses (lower doses better tolerated)	Partial hepatic metabolism by glucuronidation	Achieve abstinence reduce drinking, and craving outcomes	Dose dependent cognitive side effects may mimic hepatic encephalopathy. Consider lower dosing + psychotherapy.
Gabapentin	Modulates GABA-ergic transmission	Typically 900 mg orally twice daily; may need higher doses up to 1,200 mg three times a day	No hepatic metabolism	Achieve abstinence and reduce drinking	Caution with comorbid opioid use disorder, risk for misuse or abuse.
Baclofen	$GABA_B$ agonist	Typically 10–20 mg orally three times a day, not to exceed 80 mg per day	Safe, minimal hepatic metabolism	Achieve and maintain abstinence	Mixed results with higher dosing (upwards of 200 mg per day), and optimal dose remains debatable.
Ondansetron	5-HT3 receptor antagonist	1–16 mcg/kg twice daily	Overall safe, but caution due to reports of liver toxicity	Achieve abstinence and reduce drinking	Particularly useful in combination with naltrexone. Unclear clinical relevance of proposed dosing.

AUD, Alcohol Use Disorder; FDA, Food and Drug Administration; NMDA, N-methyl-D-aspartate.

Table 5. Pharmacotherapies for management of coexistent psychosomatic comorbidities in patients with alcohol use disorder (AUD)

Class	Acceptable in hepatic impairment	Generally avoid or notable clinical concerns
SSRI	Sertraline – generally safe, consider decreased dose with hepatic impairment, large dose range 25–200 mg is useful clinically	Fluoxetine – no absolute contraindication. Reduce dose, as half-life may triple with hepatic impairment, drug-drug and 2D6 interactions
	Escitalopram (s-enantiomer of citalopram) – do not exceed 10 mg/d due to increased risk of QTc prolongation as concentrations may increase by 50% or more with cirrhosis	Paroxetine – Most frequently associated with liver toxicity. Short half-life requires strict compliance due to withdrawal symptoms of this SSRI
	Citalopram – do not exceed 20 mg/d due to increased risk of QTc prolongation, potential for doubling of half-life	Caution or minimize co-administration with antiplatelet or NSAIDs due to increased risk of bleeding
SNRI	Desvenlafaxine (metabolite of venlafaxine) - generally preferable to venlafaxine	Duloxetine – do not use in hepatic impairment, up to 85% reduction in clearance
	Venlafaxine – no absolute contraindication; dose reduction up to 50% with liver impairment, more so with cirrhosis	
	Levomilnacipran – no dose adjustment necessary	
NDRI	Bupropion – generally safe; no significant concerns with CTP A r B class, but consider lowered dose or frequency with CTP class C	Not an absolute contraindication but caution if patient is actively consuming alcohol or with history of withdrawal seizures as it lowers threshold for seizures. Also avoid with history of an eating disorder
Antipsychotic	Paliperidone (metabolite of risperidone) – excreted by kidneys, generally safe, no adjustments in CTP A or B, limited data in CTP class C	Risperidone – undergoes hepatic biotransformation; free drug increased up to 35% in CTP class C
	Olanzapine – generally safe, half-life may be increased, consider starting dose of 2.5 to 5mg and slower titration	
	Quetiapine – half-life may be increased but generally safe particularly at lower dosing; start at 25 mg can titrate by 25–50 mg/day	Use haloperidol (first generation) with caution, lower dosing and careful titrations after discussion with pharmacist, generally avoid with active alcohol use
	Ziprasidone – no dose adjustment necessary, avoid with prolonged QTc	
Benzodiazepines	Lorazepam, Oxazepam, Temazepam – generally safe but recommend lower dosing	For anxiety or insomnia, prefer hydroxyzine or gabapentin (minimal liver dependence or clearance) due to benzodiazepine addiction potential
Other	Trazodone – generally safe; may require dose adjustment based on severity of impairment but minimal data; avoid in hepatic encephalopathy due to sedation	Avoid TCA due to lowered seizure threshold, bleeding risk especially when used with antiplatelet or NSAIDs, confusion and sedation. If used, keep the dose 50% of normal
	Mirtazapine – generally safe; decreased clearance by up to a third of normal, careful titration	
	Vortioxetine – no adjustment for CTP A/B; not studied in CTP C	

AUC, area under the curve; CLD, chronic liver disease; CTP, Child-Turcotte-Pugh; NDRI, norepinephrine-dopamine reuptake inhibitor; NSAID, Nonsteroidal Anti-inflammatory Drugs; QTc, corrected QT interval; TCA, tricyclic antidepressant; QTc, corrected QT interval; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, serotonin-selective reuptake inhibitor.

no randomized studies on the use of psychotropics in ALD patients with mental health conditions. In a meta-analysis for treatment of depression in patients with AUD, a modest beneficial effect for patients with dual diagnoses was noted, but also suggested that concurrent counseling targeting the addiction is also indicated. The current practice is based on the safety profile of the medication in the context of liver impairment or ongoing alcohol use (Table 5). Primary health and anxiety questionnaires are completed on follow-up visits, which helps guide psychotropic medication management.

Monitoring alcohol use and AUD treatment

Successful treatment of AUD varies for the individual based on treatment goals. For example, it will differ if the goal is harm reduction versus abstinence. Over a short period of time, alcohol use can be monitored with the use of the alcohol timeline follow back tool (https://www.nova.edu/timeline/index.html), which includes self-report of amounts, frequency, and patterns of use over a given period of time, up to 12 months. TLFB for alcohol use aids in identifying correlations between calendar dates and patterns of use. Feedback on alcohol use assists patients in identifying patterns of relapse which in turn increases their motivation to change.[54] As mentioned earlier, biomarkers can be used for better accuracy of determining alcohol use and defining success of treatment outcomes. Reduction in alcohol use can be gauged from baseline based on five levels of drinking as defined in grams by the World Health Organization. One alcohol-containing drink is equivalent to 14 gm, and the five World Health Organization levels are defined as abstinent (0 gm in both men and women), low risk (1–40 gm in men and 1–20 gm in women), medium risk (41–60 gm in men and 21–40 gm in women), high risk (61–100 gm in men and 41–60 gm in women), and very high risk (> 100 gm in men and > 60 gm in women). Reduction of alcohol use by two or more levels is usually considered a successful treatment outcome. However, whether that outcome is clinically relevant in ALD patients remains to be defined, and currently abstinence is considered the gold standard for improved long-term outcomes, especially in those with advanced ALD including cirrhosis and AH. As far as successful treatment for AUD is considered over the long-term, early remission is defined as not meeting AUD criteria other than craving for over 3 months but less than 12 months, and sustained remission is not meeting AUD criteria other than craving for over 12 months.

Summary

ALD contributes significantly to healthcare and economic burden. Screening for alcohol use should be performed at every healthcare encounter and those at risk should be further screened for presence and to determine severity of liver disease. To improve long-term outcomes of patients with ALD, an integrated multidisciplinary care model involving a hepatologist, psychiatrist, addiction counselor, and social worker should be promoted to provide comprehensive care for the dual pathology of AUD and of liver disease.

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Conflict of interest

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Author contributions

Conception and design of the study (AKS) and drafting the original version of the article (MH, HSDV, AKS). All the authors participated in writing, review, and approving the final version of the manuscript.

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