Management of alcohol use disorder: a gastroenterology and hepatology-focused perspective

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Alcohol use disorder is a prevalent and major but preventable cause of morbidity and mortality worldwide, causing several important health consequences, including chronic liver disease. Despite its substantial effects, most clinicians do not adequately assess alcohol intake in clinical practice, and there are several barriers to providing integrated management to patients with alcohol use disorder. Standardised questionnaires, such as the Alcohol Use Identification Test (AUDIT), can facilitate the identification of individuals at risk of alcohol use disorder, and alcohol biomarkers such as phosphatidylethanol aid in quantifying levels of alcohol consumption. Non-pharmacological interventions—including brief interventions, twelve-step facilitation, motivational enhancement therapy, contingency management, and cognitive behavioural therapy—are effective for patients with alcohol use disorder, regardless of the presence of advanced liver disease. Pharmacological treatments should be considered according to the severity of liver disease and other comorbidities, safety profile, and local availability. The management of patients with alcohol use disorder and associated liver disease should ideally be performed in the setting of integrated multidisciplinary teams.

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Introduction

Alcohol consumption is a leading risk factor for disease burden worldwide,[1] accounting for nearly 10% of global deaths among individuals aged 15–49 years.[2] In 2019, 7% of adults fulfilled alcohol use disorder criteria, which equates to 400 million individuals affected worldwide.[3] Alcohol use disorder is a chronic, relapsing brain disease,[4,5] and is often associated with other comorbid psychiatric and medical conditions.[6] Many individuals have poor access to specialised treatments and disparate care compared with other disorders, reflecting the social abandonment of some patients. Consequently, most cases of alcohol use disorder are not diagnosed, or if they are, diagnoses are delayed, sometimes restricting the pharmacotherapy options that are available.[7] Alcohol-related liver disease is a direct consequence of alcohol use disorder, and as such should be viewed as a dual pathology. Alcohol use disorder can also exist in the more broad, and often severe, context of other psychiatric disorders such as depression or other addictions. As a result, skilled psychiatric and addiction clinicians are required for patients with alcohol-related liver disease, and there is a need for such support to coalesce with alcohol-related liver disease management. Stigma among health-care providers is another relevant obstacle that biases clinical judgment and often limits the access and availability of treatment to patients with alcohol use disorder.

Alcohol use is associated with alcohol-related liver disease in a dose-dependent manner, in which risk of cirrhosis substantially increases in women who consume more than 24 g and men who consume more than 36 g of alcohol daily.[8] Although alcohol abstinence is a main goal of treatment for alcohol-related liver disease,[9–11] it is often difficult to sustain over time.[12] In addition, the prescription of treatments for alcohol use disorder among individuals with alcohol-related liver disease is low, reaching only around 10–14% of this population.[13,14] Clinicians should prescribe treatment for alcohol use disorder or refer patients for such treatment, which could include psychosocial and behavioural therapies, and pharmacotherapy agents;[15] but this does not happen routinely.[16] Due to the notable barriers to providing adequate treatment for patients with alcohol-related liver disease, we reviewed the different aspects of alcohol use disorder management, providing updated evidence for the daily clinical practice of gastroenterologists, hepatologists, and related health-care providers.

Assessing alcohol use and drinking patterns

Although revealing alcohol intake and quantifying the amount of alcohol intake seems an easy task, clinicians often do not routinely ask for the number and type of drinks in clinical practice. This information can be particularly important as liver transplantation draws nearer, as patients do not accurately disclose their drinking.[17] A careful assessment of alcohol intake should include the estimation of alcohol in grams and the drinking pattern, by appropriate clinical personnel.[18] Unfortunately, standard-drink definitions vary widely across academic societies and countries. Whereas the UK has settled on a standard drink of 8 g of alcohol, France and Australia use a standard of 10 g. In the USA, the guidelines consider that 14 g of alcohol is roughly the same as 350 mL of beer (5% weight/volume), 150 mL of wine (12–13% weight/volume), or 45–50 mL of liquor (40–45% weight/volume).[19] Consideration of these regional differences in standard drink definition can facilitate the quantification of alcohol use over time, the identification of individuals with hazardous consumption, and the proper diagnosis of steatotic liver disease subtypes.[20]

Several classifications of drinking patterns have been proposed in the literature. Binge-drinking is defined by the US National Institute on Alcohol Abuse and

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Alcoholism as a pattern of drinking that brings blood alcohol concentration to 0·08 g/dL (0·08%) or higher, which is usually observed after a woman consumes four drinks (56 g) or a man consumes five drinks (70 g) in a 2-h time frame.[21] The National Institute on Alcohol Abuse and Alcoholism also defines heavy alcohol use as the consumption of four or more drinks (56 g) on any day or eight or more drinks (112 g) per week in women and five or more drinks (70 g) on any day or 15 or more drinks (210 g) per week in men. Heavy episodic drinking is defined by WHO as consuming 60 g or more of pure alcohol on at least one occasion in the past 30 days, and is particularly useful in assessing the prevalence of high-risk alcohol consumption globally.[22] Still, other risk factors for alcohol-related harm must be considered to recommend lower thresholds of alcohol use for clinical practice, including age, pregnancy, individuals with a medical condition that alcohol can aggravate, users of medications that interact with alcohol, and people driving vehicles or operating machinery.[21]

Of note, hazardous drinking and alcohol use disorder are also two distinct concepts of relevance in clinical practice. On the one hand, hazardous drinking reflects a substantial increase in the risk of negative alcohol-related outcomes (both acute and chronic), but does not necessarily imply the presence of health-related consequences.[23] On the other hand, alcohol use disorder is a psychiatric syndrome characterised by impaired control over alcohol consumption and other related symptoms. Although hazardous drinking typically could require counselling or brief interventions (evidence-based, structured conversations designed to motivate individuals to recognise and address risky or harmful behaviours related to alcohol use) to develop skills to stop or reduce alcohol consumption, alcohol use disorder presents multiple additional challenges in terms of risk stratification and treatment. In this review, we will focus particularly on the management of alcohol use disorder.

Diagnostic criteria for alcohol use disorder

In contrast to previous versions, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) follows the gradual differentiation of pathological alcohol consumption and offers a dimensional approach for alcohol use disorder. In particular, alcohol use disorder is defined as a pattern of alcohol

Panel: DSM-5 diagnostic criteria for alcohol use disorder and ICD-11 diagnostic criteria for alcohol dependence

Diagnostic and Statistical Manual of Mental Disorders, fifth edition: alcohol use disorder

The presence of at least two of these symptoms indicates alcohol use disorder. The severity of the alcohol use disorder is defined as:
Mild: 2–3 criteria
Moderate: 4–5 criteria
Severe: ≥6 criteria

- Alcohol is often consumed in larger amounts or over a longer period than intended
- A desire or unsuccessful effort to cut down or control alcohol use
- A substantial amount of time spent in activities needed to obtain alcohol, use alcohol, or recover from the effects of alcohol
- Craving, or a strong desire or urge to use alcohol
- Recurrent alcohol use is associated with failure to fulfil responsibilities at work, school, or home
- Continued alcohol use despite related social or interpersonal problems
- Stopping or reducing social, occupational, or recreational activities due to alcohol use
- Recurrent alcohol use in physically hazardous situations
- Continued alcohol use despite knowledge of a physical or psychological problem likely to be caused or exacerbated by alcohol
- Tolerance, defined by either a need for markedly increased amounts of alcohol to achieve intoxication or desired effect or a markedly reduced effect with continued use of the same amount of alcohol
- Withdrawal, manifesting as either the alcohol withdrawal syndrome or alcohol, or a closely related drug, is taken to relieve or avoid withdrawal symptoms

International Classification of Diseases, revision 11: alcohol dependence (6C40.2)

A disorder of regulation of alcohol use arising from repeated or continuous use of alcohol. The characteristic feature is a strong internal drive to use alcohol. The diagnosis requires two or more of the three central features to be evident over a period of at least 12 months, but the diagnosis can be made if alcohol use is continuous for at least 3 months:

- Impaired control over alcohol use—in terms of the onset, level, circumstances, or termination of use, often but not necessarily accompanied by a subjective sensation of urge or craving to use alcohol
- Alcohol use becomes an increasing priority in life such that its use takes precedence over other interests or enjoyments, daily activities, responsibilities, or health or personal care. Alcohol use takes an increasingly central role in the person's life and relegates other areas of life to the periphery, and it often continues despite the occurrence of problems
- Physiological features (indicative of neuroadaptation to alcohol) as manifested by: tolerance, withdrawal symptoms following cessation or reduction in use of alcohol, or repeated use of alcohol (or a pharmacologically similar substance) to prevent or alleviate withdrawal symptoms. Withdrawal symptoms must be characteristic for the withdrawal syndrome for alcohol and must not simply reflect a hangover effect

consumption leading to substantial impairment and suffering due to the presence of at least two of eleven DSM-5 criteria within the past year (panel).[24,25] Alcohol use disorder is classified as mild if it meets two or three criteria, moderate if four or five symptoms are present, and severe if six or more criteria are met.[24,26] Alcohol dependence is another diagnostic approach commonly used in epidemiological contexts to identify cases of alcohol addiction; it is defined by the International Classification of Diseases, revision 11, under diagnostic code 6C40.2 (panel).[27]

Alcohol use disorder screening in clinical practice

There are several methods to identify patients at risk of alcohol use disorder, including questionnaires, laboratory measurements based on alcohol consumption (eg, breath alcohol concentration, blood alcohol concentration, and non-oxidative pathway of conjugation products), and indirect biomarkers of alcohol use. All of these methods have benefits and limitations, and can be combined to better characterise alcohol consumption and the risk of related health consequences.

Screening questionnaires

There are several questionnaires based on self-reporting to screen for hazardous alcohol consumption, the presence of alcohol use disorder, or both, including the Single Alcohol Screening Question, Alcohol Use Identification Test (AUDIT), Timeline Followback (TLFB), and Lifetime Drinking History (LTDH).[28–30] A quick and easy way to initiate screening can be the Single Alcohol Screening Question,[18] which can be followed by other questionnaires if positive. The Single Alcohol Screening Question asks, "How many times in the past year have you had (four for women, or five for men) or more drinks in a day?", with a response of one or more being deemed positive. The AUDIT questionnaire, developed by WHO and appropriate for patients with liver disease,[31] comprises ten questions with a specific scoring system. The first three questions are related to quantity and frequency measures, providing retrospective estimates of average or usual consumption, and the remaining seven questions are related to the consequences and individual experiences of alcohol consumption (table 1). An AUDIT score higher than 8 is considered a positive screening for alcohol use disorder,[31] and cutoff scores of 15 for men and 13 for women have 100% specificity but low sensitivity (20% and 18%, respectively) for detecting alcohol dependence.[32] The AUDIT for consumption (AUDIT-C) questionnaire is a shorter version of AUDIT, and includes the questions related to quantity and frequency measures.[33] Since questions from AUDIT-C are restricted to the quantification of alcohol use, an AUDIT-C score of 3 or more for women and 4 or more for men is considered a positive screening result for hazardous alcohol consumption.[33] AUDIT-C has 73% sensitivity and 91% specificity in women and 86% sensitivity and 89% specificity in men for identifying hazardous alcohol consumption.[33] AUDIT-C is appropriate for general medical settings, including primary care, and can be applied by any trained health-care provider. Due to the natural human defensiveness around certain health behaviours such as alcohol use, and the social stigma associated with alcohol use disorder, these assessments must be conducted with a professional, empathic, and non-judgmental attitude.

	Questions	AUDIT score				
		0	1	2	3	4
1	How often do you have a drink containing alcohol?*	Never	Monthly or less	2 to 4 times a month	2 to 3 times a week	4 or more times a week
2	How many standard drinks containing alcohol do you have on a typical day?*	1 or 2	3 or 4	5 or 6	7, 8, or 9	10 or more
3	How often do you have six or more drinks on one occasion?*	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4	How often during the last year have you found that you were not able to stop drinking once you had started?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
5	How often during the last year have you failed to do what was normally expected from you because of drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
6	How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
7	How often during the last year have you had a feeling of guilt or remorse after drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
8	How often during the last year have you been unable to remember what happened the night before because you had been drinking?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
9	Have you or someone else been injured as a result of your drinking?	No	..	Yes, but not in the last year	..	Yes, during the last year
10	Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?	No	..	Yes, but not in the last year	..	Yes, during the last year

AUDIT=Alcohol Use Disorders Identification Test. C=consumption. *AUDIT-C includes questions 1–3 only.

Table 1: **The 10-item AUDIT screening tool to assess alcohol consumption, drinking behaviours, and alcohol-related problems (clinician-administered version)**

Quantifying alcohol consumption

Although AUDIT-C is short and highly applicable in clinical practice, quantity and frequency measures might not adequately assess sporadic days of heavy alcohol consumption. Thus, daily estimates could provide more accurate estimates of drinking patterns than quantity and frequency assessments. The TLFB is a retrospective survey used in alcohol research that estimates daily alcohol consumption over a specific past period and can be used to identify heavy episodic alcohol consumption

or binging. Unfortunately, TLFB is time consuming to use in clinical practice. Moreover, a study in Canada suggested that daily estimates between TLFB and quantity and frequency measures are similar, and quantity and frequency measures are therefore typically used preferentially.[34] LTDH is another retrospective interview-based procedure to identify patterns of alcohol use and misuse, beginning with the onset of regular alcohol consumption and ending with the individual's current pattern of consumption,[35] which could comprehensively assess alcohol use and consumption patterns in patients with severe alcohol-related liver disease.[36]

	Cutoff	Sensitivity	Specificity	Comments
Direct biomarkers				
Ethyl glucuronide[37]	500 ng/mL	76%	93%	Direct ethanol metabolite; detects alcohol use in the last 3–5 days in urine and up to 6 months in hair
Ethyl sulfate[37]	25 ng/mL	82%	86%	Direct ethanol metabolite; detects alcohol use in the last 3–4 days in urine
Phosphatidylethanol[38]	20 ng/mL	73–100%	90–96%	Phospholipids formed primarily in the red blood cell membrane; detects alcohol use in the last 4 weeks in active drinkers with alcohol use disorder
Fatty-acid ethyl esters[39,40]	0·2–0·5 ng/mg	90%	90%	Non-oxidative metabolites of ethanol; hair test
Blood alcohol concentration[41]	0·02 g/L	NA	NA	Strongly correlated with the ratio of alcohol intake (g/kg bodyweight)
Breath alcohol concentration[42,43]	35 µg/100 mL	26–97%	50–100%	Dependant on manufacturer and type
Indirect biomarkers				
Aspartate aminotransferase[44]	×2–4 upper normal level	5–60%	87–98%	80% activity in hepatocyte nucleus; present in muscle, heart, and kidneys
Alanine aminotransferase[44]	×2–4 upper normal level	15–40%	93%	Higher sensitivity and specificity with ×7 cutoff
AST–ALT ratio[44,45]	>2	<40%	90–95%	Proportion of AST to ALT in hepatocytes is about 2·5:1, however, AST is normally removed from serum by the liver sinusoidal cells twice as quickly (serum half-life $t_{½}$=18 h) compared to ALT ($t_{½}$=36 h); ratio over 2 reflects an increase in hepatocellular death; ratio over 5 could be extrahepatic
Carbohydrate-deficient transferrin[46]	2·4%	65–95%	97%	Percent of transferrin sialic acid molecules in a transferrin chain; these increase with alcohol consumption
Mean corpuscular volume[47]	>100 fL	48%	52%	Reflects an increase in ineffective haematopoiesis due to malnutrition
Gamma glutamyl transferase[47]	>55 U/L	64–96%	72–86%	Liver specific enzyme
ALD/NAFLD Index[48]	>–0·66	84–97%	93–96%	Scoring system for avoiding the risks of liver biopsy in diagnosing the cause of metabolic liver disease versus alcohol-related liver disease

ALT=alanine aminotransferase. AST=aspartate aminotransferase. NA=not applicable.

Table 2: **Main direct and indirect biomarkers of alcohol use for clinical practice**

Direct biomarkers of alcohol use

Alcohol can be directly measured through blood alcohol concentration or breath alcohol concentration. Additionally, when alcohol undergoes non-oxidative metabolism, several end products are detectable, including ethyl glucuronide, ethyl sulphate, ethyl phosphate, phosphatidylethanol, and fatty-acid ethyl esters. The main characteristics of these biomarkers are summarised in table 2. Phosphatidylethanol is a group of phospholipids formed primarily in the red blood cell membrane. Ethanol attaches to phosphatidylcholine by a transphosphatidylation reaction via the action of phospholipase D, which leads to the formation of phosphatidylethanol.[49,50] Phosphatidylethanol has a half-life of approximately 4–10 days, with detection windows of up to 4 weeks in alcohol use disorder.[51,52] Phosphatidylethanol concentrations of 20 ng/mL or higher has a sensitivity of 73% and specificity of 96% for detecting any amount of alcohol use in the past month, and a phosphatidylethanol concentration of 80 ng/mL or higher has a sensitivity of 91% and specificity of 77% for identification of those consuming at least four drinks daily.[38] Phosphatidylethanol is therefore one of the best available direct biomarkers of alcohol use, yet its widespread use is restricted by measurement costs that are still high.

Indirect biomarkers of alcohol use

Alcohol generates products formed during damaging processes in tissues and organs that can be used to measure and track indirect biomarkers of alcohol use, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), AST–ALT ratio, carbohydrate-deficient transferrin, mean corpuscular volume, and gamma glutamyl transferase (table 2).[53] Unfortunately, these biomarkers do not revert to normal immediately with abstinence. Of note, the ALD/NAFLD Index (ANI) is a model used to predict if liver disease is due to alcohol consumption,[48] which includes simple variables (eg, mean corpuscular volume, AST–ALT ratio, body mass index, and sex), and has been validated in several cohorts, including ambulatory patients and candidates listed for liver transplantation who have been abstinent for 6 months. When indirect biomarkers are compared, ANI has better performance in predicting alcohol-related liver disease than AST–ALT ratio, gamma glutamyl transferase, and carbohydrate-deficient transferrin (table 2).[48]

Integrated care in alcohol use disorder and alcohol-related liver disease management

Due to the high prevalence and complexity of alcohol use disorder and alcohol-related liver disease, no single discipline provides sufficient training and skills to independently manage this dual medical comorbidity.[54] Too few patients receive optimal care; several factors contribute to this. For example, patients with

alcohol-related liver disease usually receive contradictory or different indications and prescriptions from their health-care providers and specialists, as health-care professionals often do not collaborate. Health-care providers can also differ in terms of the level of training they have received and their stigma towards patients with alcohol use disorder.[55,56] Therefore, the ideal integrated care model for alcohol-related liver disease should embrace a multidisciplinary approach that effectively combines psychosocial and biomedical expertise. Given that alcohol-related liver disease is a medical consequence of alcohol use disorder, collaboration between health-care providers yields a greater effect on disease prevention, diagnosis, treatment, and follow-up.[54] In fact, the participation of health-care professionals is fundamental for the screening, evaluation, and follow-up of patients with alcohol use disorder, and the prevention of long-term alcohol-associated health consequences. For example, if patients discharged from an inpatient alcohol use disorder treatment programme are later evaluated in an outpatient liver clinic, they could have lower rates of return to alcohol use and lower rates of hazardous alcohol consumption.[57] The core elements of such care include being team-driven, population-focused, measurement-guided, evidence-based, and committed to accountability and quality improvement (figure 1).[58] The success of this approach hinges on strong team relationships and a cohesive clinical culture.

In a resource-limited setting, however, certain adaptations might be necessary. Although the ideal model involves robust interprofessional collaboration, such as co-located care in which hepatology and addiction specialists work together in the same clinic, this might not always be feasible. Instead, a scalable model could start with basic interdepartmental awareness and informal affiliations, gradually moving towards more structured peer-to-peer consultations. At the very least, establishing a care manager—a role that could be filled by a nurse with psychosocial training or a social worker with biomedical expertise—would be essential. This individual would coordinate between the various specialists, ensuring that patients' needs are met holistically despite potential resource limitations. Such a role is particularly crucial given the chronic and relapsing nature of alcohol-related liver disease, for which ongoing management and seamless communication between care providers are crucial.

Non-pharmacological treatments for alcohol use disorder

Psychosocial and behavioural therapies are considered a cornerstone of treatment for alcohol use disorder in patients with alcohol-related liver disease. Whereas certain medications could be contraindicated in advanced alcohol-related liver disease, psychosocial and behavioural therapies can be used in all individuals without overt hepatic encephalopathy (grade 2–4 according to the West-Haven classification).[59] Of note, brief interventions consist of a short counselling approach delivered by a health-care provider and aimed at educating the patient about the harmful effects of alcohol consumption.[60] It is carried out for 5–20 min at a time and typically for one to three sessions.[61] Brief interventions aim to provide skills that could increase the motivation to address alcohol misuse and can be easily implemented in primary care settings.[62,63] For patients at risk for alcohol use disorder, brief intervention conselling should be accompanied by early referral to more intensive treatment.[60] In particular, brief interventions—adminstered by a trained health-care professional—comprise four stages. First, the health-care professional gives brief advice. In this stage, the patient is informed that screening results indicate hazardous alcohol use, and risks associated with the alcohol use are highlighted. Second, they must assess and tailor advice; for example, this can be done by adapting

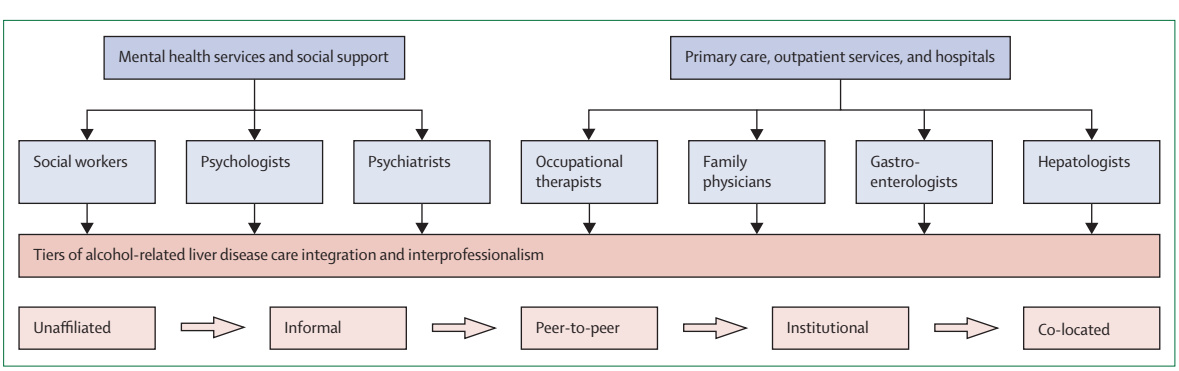

Figure 1: **Levels of care integration and interprofessional relationships in alcohol-related liver disease**
Patients with alcohol use disorder are commonly treated by different health-care professionals, but addiction and hepatology services are unaffiliated. When some clinicians are aware of the existence of other professionals and specialties, and they start referring between them, an informal relationship begins. The existence of an informal interprofessional relationship is the standpoint to develop deeper connections between providers, which could be furthered by weekly or monthly meetings involving all members of the medical team to discuss the main medical emergencies associated with alcohol-related liver disease (peer-to-peer). Institutional relationships can contribute to education around alcohol-related liver disease and the existence of workflows based on local protocols, which could be even better when psychiatrists and liver clinicians treat the same patients with alcohol-related liver disease in the same place at the same time (co-located).

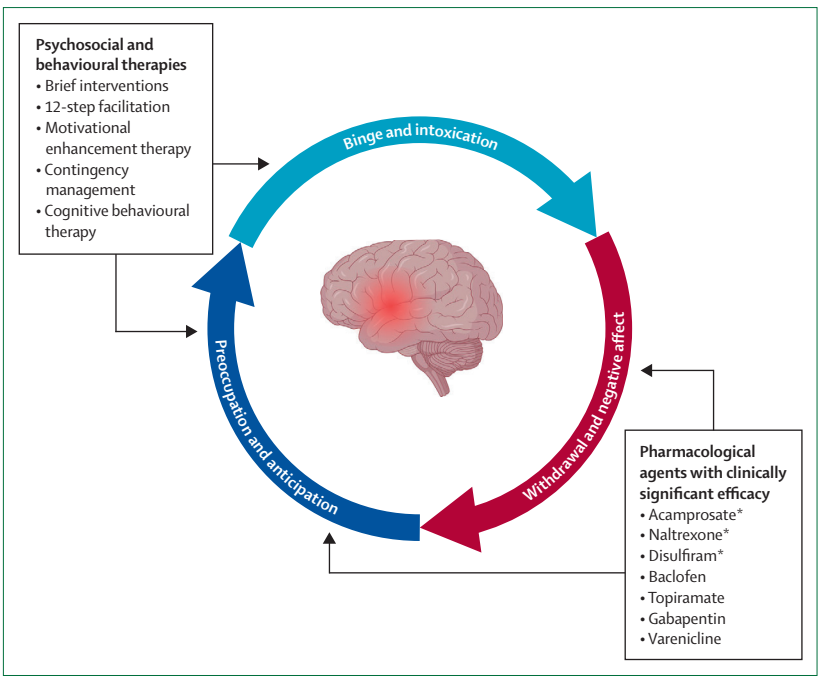

Figure 2: **Therapies in alcohol use disorder and their neurobiological basis**
Binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation are the three stages of addiction in the addiction cycle. *Approved by the US Food and Drug Administration to treat alcohol use disorder.

the approach and communication style based on where the person is in their readiness to change their behaviour, which in this context involves a broad analysis of the factors contributing to and maintaining a patient's excessive alcohol consumption, the severity of the problem, and the consequences associated with it. Third, the health-care professional must provide skills training; this could take the form, for example, development of a personalised action plan, which can include identifying triggers for alcohol consumption and strategies to address them, enhancing coping skills and support systems, and referral to specialist services if needed. The fourth stage is follow-up, including maintenance strategies (ie, approaches designed to help individuals sustain positive behaviour changes and prevent relapse after addressing harmful alcohol use, such as self-monitoring, setting long-term goals, continued education, relapse prevention planning, regular check ins, and encouraging self-sufficiency).[64]

12-step facilitation is another therapy that focuses on alcohol abstinence and regular participation in groups (eg, Alcoholics Anonymous) and other mutual help organisations. The 12-step facilitation approach reduces health-care costs and is an effective alcohol use disorder treatment to reach abstinence of alcohol use.[65] Motivational enhancement therapy is a standardised method to conduct motivational interviewing and uses evidence-based approaches for eliciting and strengthening personal motivation to change. Motivational enhancement therapy is especially helpful for patients who are ambivalent about or resistant to positive behaviour change, and has supporting evidence in individuals with alcohol-related liver disease.[66] Cognitive behavioural therapy is a therapy focused on modifying dysfunctional thoughts, emotions, and behaviours. Cognitive behavioural therapy helps identify triggers for relapse, improve coping strategies, and increase focus on alcohol-free activities, and can be applied to individuals or groups and integrated with other approaches such as family or couple therapy.[67] Finally, contingency management is based on an operant conditioning approach, in which the patient receives a financial incentive dependent on their ability to provide biologically based evidence of alcohol use reduction or abstinence.[68] All of these interventions are supported by evidence in treating alcohol use disorder in patients with alcohol use disorder and alcohol-related liver disease.[60,66]

Pharmacotherapies in alcohol use disorder

Pharmacological treatments for alcohol use disorder can be offered alone or combined with behavioural therapies (figure 2). Naltrexone and acamprosate are both approved for alcohol use disorder by the US Food and Drug Administration (FDA), and in many other countries, and should be the main medications used to treat alcohol use disorder (as they have more supporting evidence), including in patients with alcohol use disorder and alcohol-related liver disease. The benefits of these medications include less craving, abstinence prolongation, less drunk driving, and shorter alcohol relapses than without any medication. Another medication approved by the FDA is disulfiram, a deterrent medication that reduces alcohol consumption by causing acute side-effects when patients consume alcohol. Other unapproved pharmacological therapies that have evidence of efficacy for alcohol use disorder include topiramate, gabapentin, baclofen, and varenicline.[25] Topiramate and gabapentin are recommended by the American Psychiatric Association as a second-line treatment (off-label) for alcohol use disorder.[69] Varenicline might be particularly effective in people with alcohol use disorder who are also smokers.[70,71] Evidence on the efficacy of baclofen for alcohol use disorder in patients with alcohol use disorder and alcohol-related liver disease is supported by randomised controlled trials (RCTs),[72,73] and both the American Association for the Study of Liver Diseases[9] and American College of Gastroenterology[74] have endorsed baclofen, and the FDA-approved medication acamprosate, as a treatment (off-label) for alcohol use disorder in people with alcohol use disorder and alcohol-related liver disease. By contrast, formal scientific evidence for efficacy and safety in patients with alcohol use disorder and alcohol-related liver disease is scarce for topiramate, gabapentin, and varenicline, although their overall pharmacology and safety profiles suggest these medications do not cause harmful effects in patients with underlying liver disease.[60,75–77]

The end goal in treating alcohol-related liver disease patients is to reach and maintain abstinence, given the substantial risks with any ongoing alcohol consumption. These medications, along with behavioural treatments, are useful during the intermediate steps of alcohol use reduction before abstinence is reached. These medications can be used to support patients with early-stage alcohol-related liver disease (hepatic steatosis and mild fibrosis), as long as liver function is monitored strictly.[78,79] In advanced liver disease, close monitoring and careful consideration of liver function is required due to the potential effects and toxicity of some medications, particularly in patients with Child-Pugh B or C liver disease or with decreased renal function.[60] In the following sections, we discuss the main evidence supporting pharmacological therapies. An algorithm for the prescription of pharmacological therapies is provided in figure 3.

Naltrexone

Naltrexone is an opioid receptor antagonist; its ability to reduce alcohol consumption is hypothesised to occur through modulation of dopamine-mediated reward pathways associated with alcohol intake,[80] although several other mechanisms might be involved. This medication can be administered orally (50 mg once a day) or by intramuscular injection (380 mg once a month). Pharmacokinetic data show that naltrexone undergoes hepatic metabolism, and active metabolites of naltrexone accumulate in the blood to a greater degree than in those with normal liver function, and have a longer half-life than in those with normal liver function. The FDA has removed the black box warning for the use of naltrexone use in advanced alcohol-related liver disease, and it is best used in patients who wish to reduce alcohol consumption or craving, even if abstinence cannot be reached. Adverse effects include somnolence, nausea, vomiting, decreased appetite, abdominal pain, insomnia, and dizziness.[81] Naltrexone is contraindicated in acute hepatitis or fulminant liver failure, and patients with current opiate use or medication should not be treated with naltrexone as it induces acute onset of opioid withdrawal.

Acamprosate

Acamprosate is an N-methyl-D-aspartate receptor antagonist, thus modulating the glutamatergic system,[82] although its exact mechanism of action has not been fully understood. It is administered orally in a dosage of 666 mg three times daily. Acamprosate is not metabolised hepatically and is not known for liver toxicity.[83] Nonetheless, it has not been formally tested in patients with alcohol use disorder with alcohol-related liver disease and should be used carefully if severe liver disease is present,[83] including potential dose adjustment dependent on kidney function. Acamprosate is used in patients with alcohol use disorder to maintain abstinence and prevent relapse of alcohol consumption. The number needed to treat (NNT) is lower for acamprosate

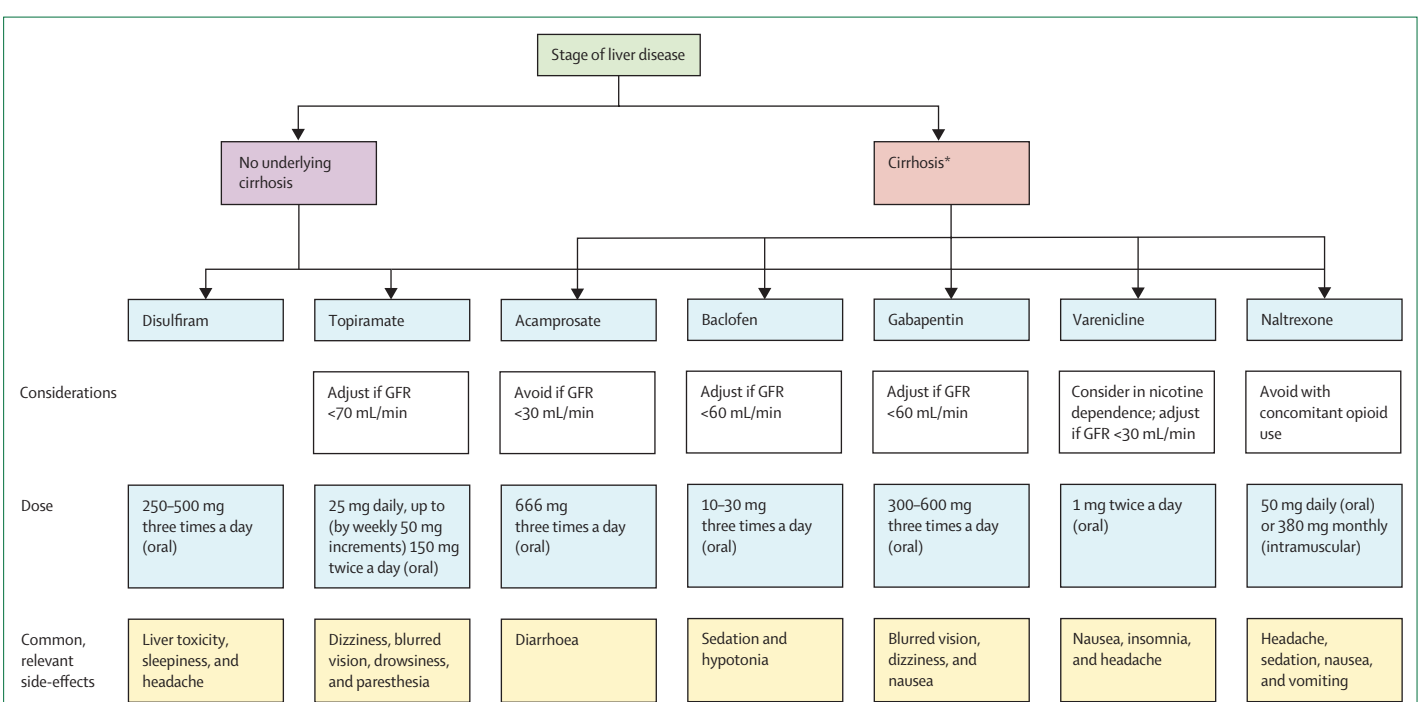

Figure 3: **Algorithm for the use of pharmacological therapies to treat alcohol use disorder in individuals with alcohol-associated liver disease**
GFR=glomerular filtration rate. *Current data suggest that pharmacological therapies for alcohol use disorder can be safe in individuals with cirrhosis Child-Pugh A or B, however, data to support pharmacological therapies are scarce in individuals with Child-Pugh C disease.

than naltrexone for abstinence, and lower for naltrexone than acamprosate for reduction of heavy alcohol consumption.[84,85] A Cochrane meta-analysis including 24 RCTs confirmed the drug's potential to reduce the risk of alcohol consumption and increase the cumulative duration of abstinence by a clinically significant amount compared with placebo.[86] In particular, acamprosate was especially effective in so-called relief drinkers (ie, patients who drink alcohol to relieve symptoms such as chronic pain).[81]

Disulfiram

Disulfiram is an inhibitor of aldehyde dehydrogenase and causes increased serum levels of acetaldehyde when alcohol is ingested,[83] leading to an acute aversive response (eg, nausea, vomiting, flushing, or increased sweating).[82,87] However, the need for acute medical treatment and, possibly, life-threatening effects can occur (ie, sudden cardiac arrest due to arrhythmia). Especially in patients with a history of cardiovascular disease or psychotic disorders, caution is advised. Thus, abstinence under disulfiram medication is obligatory, and usage is to be advised for patients seeking a reduction in alcohol consumption only.[80,81] Disulfiram can be administered orally at doses between 250–500 mg once a day. Data suggest that supervised ingestion can lead to better outcomes than unsupervised ingestion. In a systematic review that included two controlled trials, efficacy of disulfiram could not be proven.[85] Disulfiram is metabolised hepatically, and idiosyncratic cases of hepatotoxicity associated with disulfiram have been documented. Disulfiram should not be used in patients with advanced liver disease, especially in individuals with an AST or ALT greater than three times the upper limit of normal or a total bilirubin above 3 mg/dL.[83] Importantly, the risk of hepatotoxicity is not dose-dependent and is thought to result from a hypersensitivity reaction involving cytochrome P450 enzymes.[88] Hepatotoxicity usually appears within 2–12 weeks following initiation of disulfiram, and could decompensate those with advanced liver disease, but cases of acute liver failure are uncommon.[88]

Topiramate

The anticonvulsant topiramate blocks α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic receptors, targets gamma-aminobutyric acid (GABA) receptors, and inactivates voltage-gated sodium channels. It works by suppressing GABAergic neurotransmission.[69,89] Topiramate is approved for the treatment of epilepsy and migraine, and for weight loss as an extended release formulation combined with phentermine. RCTs have shown that topiramate reduces heavy drinking,[90] subsequent RCTs have further shown the efficacy of topiramate in reducing heavy drinking.[91] When compared with placebo, topiramate was shown to increase abstinence and reduce the rate of heavy drinking, number of drinking days, and drinks per day.[80,92,93] The American Psychiatric Association recommends topiramate as a second-line intervention in alcohol-related liver disease, and does not require alcohol abstinence before starting.[69] The initial oral dose of topiramate is 25 mg once daily, with increases in increments of 50 mg once every 7 days. The maintenance dose ranges from 200 mg to 400 mg daily, divided into two doses. In patients with moderate-to-severe renal impairment, a 50% dose reduction is advised as it undergoes only limited hepatic metabolism, predominantly glucuronidation, and is excreted renally.[89] It is possible to use topiramate in patients with alcohol use disorder with liver diseases, but caution is advised in patients with a history of hepatic encephalopathy,[83] since adverse events of topiramate itself include cognitive impairment.[80]

Gabapentin

Gabapentin is an anticonvulsant gabapentinoid that targets the α(2)δ-subunit of voltage-gated calcium channels, which has been approved by the FDA as an adjunctive therapy of partial seizures and in post-herpetic neuralgia. The mechanism of action in alcohol use disorder is explained by the inhibition of calcium influx in nerve terminals, modulating neurotransmitters such as glutamate and norepinephrine.[94] For gabapentin, possible dosages range from 900 to 1800 mg orally once a day and the drug is not metabolised via the liver. Several studies have shown a clinically significant reduction of heavy alcohol consumption days and alcoholic drinks per day compared with placebo, constituting a potential therapeutic option in patients with heavy drinking with an NNT of 8 for 1800 mg.[95–97] In an RCT, compared with placebo, gabapentin significantly increased the number of people with total abstinence and reduced alcohol consumption, mostly in patients receiving pretreatment for alcohol withdrawal symptoms. Data on craving and promoting abstinence are inconclusive,[97,98] however, some evidence points to the potential use of gabapentin in insomnia, pain, anxiety, and alcohol withdrawal.[99,100] It is important to note that these effects were observed with the immediate release formulations and not the extended release formulations.[101]

Baclofen

Baclofen is a GABA-B receptor agonist and FDA-approved as a muscle relaxant. Due to its activity as a GABAergic drug, its use as a medication for alcohol use disorder has been proposed.[102] Baclofen dosage is typically 10–30 mg three times a day.[83] However, the use of baclofen at high doses (>90 mg per day; the dose hypothesised to suppress the symptoms and consequences of alcohol dependence) for alcohol use disorder has been proposed and indeed this approach led to the wide off-label use and eventually approval of baclofen for alcohol use disorder in France.[103] Furthermore, an RCT published in 2021 showed a

dose–response in the use of baclofen in patients with alcohol use disorder that 90 mg/day was more effective than 30 mg/day, and overall suggesting that dose and sex could be moderators of baclofen's response and tolerability.[104] Baclofen is eliminated via urine with only minimal hepatic metabolism, hence making its use in patients with liver disease safe.[83] Indeed, baclofen is the only agent whose effectiveness and safety have formally been tested in RCTs and observational studies in patients with alcohol use disorder with underlying cirrhosis due to alcohol-related liver disease,[72,105] and alcohol-related liver disease regardless of fibrosis stage.[73] Although previous data suggest its effectiveness and efficacy in maintaining abstinence, some results are inconsistent.[106,107] Furthermore, additional data indicate possible benefits in reducing anxiety—a comorbidity frequently seen in patients with alcohol use disorder.[106,108,109] As stated in a 2018 consensus statement,[110] RCTs with baclofen in alcohol use disorder have led to inconsistent results, yet its off-label use, especially in liver settings, could be considered. As previously mentioned, both American Association for the Study of Liver Diseases[9] and the American College of Gastroenterology[74] have included baclofen, along with the FDA-approved medication acamprosate, as pharmacotherapies for alcohol use disorder that health-care providers should consider, with moderate evidence for baclofen (based on American College of Gastroenterology guidelines[74]) in treating patients with alcohol use disorder and alcohol-related liver disease. Some side-effects of which to be mindful are sedation and worsening of hepatic encephalopathy.[109]

Varenicline

Varenicline is a nicotinic acetylcholine receptor partial agonist approved by the FDA for tobacco cessation, and some evidence suggests that those with both alcohol use disorder and tobacco cessation can decrease alcohol use when on varenicline.[70,111] Varenicline is usually administered at doses of 0·5 mg twice daily during the first week and 1 mg twice daily after that, however, dose must be reduced in individuals with glomerular filtration rate less than 30 mL/min.[112]

Other potential therapeutic agents

Multiple promising agents have shown potential for treatment of alcohol use disorder in mice and preclinical models. However, more research and RCTs are necessary to recommend its widespread use in clinical practice. These agents include pregabalin, prazosin or doxazosin, ondansetron, N-acetylcysteine, spironolactone, glucagon-like peptide 1 (GLP-1) receptor agonists, memantine, drugs blockading the ghrelin receptor, ketamine, psilocybin, apremilast, and ibudilast, among others.[113]

Pregabalin is widely available, and clinicians are accustomed to using it in other clinical settings (eg, chronic pain). However, pregabalin only has shown potential benefits in patients with comorbid generalised anxiety disorder[94] and has a substantial risk for dependence, especially in patients with comorbid substance use disorders.[82] Prazosin and doxazosin, two α-adrenergic antagonists, could reduce stress-induced craving and improve neuroendocrine and autonomic response to stress cue exposure and alcohol cue exposure during early abstinence.[114] However, although prazosin and doxazosin can reduce levels of alcohol use, evidence is inconclusive to support their use in alcohol use disorder.[115] Ondansetron, a 5-HT_3 antagonist, could act in the serotonergic system in regulating the severity of alcohol consumption.[116] Suggested doses range from 1 µg/kg to 16 µg/kg, administered twice daily.[83] Despite ondansetron undergoing hepatic metabolism, use in patients with alcohol-related liver disease under surveillance could be a treatment option; however, caution should be exercised due to reports of liver toxicity.[117] Particularly for patients with early-onset alcohol use disorder, ondansetron is postulated to be a potential medication.[118] There is also evidence for ondansetron being a potential precision medicine agent in the treatment of patients with alcohol use disorder who drink heavily and have specific genetic subtypes.[116,119] However, more recent studies have not replicated the initial findings, from 2000, on the use of ondansetron for alcohol use disorder, hence its potential role for alcohol use disorder remains uncertain.[120]

N-acetylcysteine is a precursor to the antioxidant glutathione and, as a modulating agent of glutamatergic, dopaminergic, neurotropic, and inflammatory systems, it is being investigated for its potential use in patients with alcohol use disorder.[121] Given orally, N-acetylcysteine undergoes extensive first-pass metabolism. Importantly, it is one of the few treatment options for alcohol use disorder available during pregnancy.[122] N-acetylcysteine could potentially reduce craving,[123] but data is inconclusive.[124,125] Spironolactone is a non-selective mineralocorticoid receptor antagonist and is commonly used in individuals with cirrhosis. An association between aldosterone, mineralocorticoid receptor expression in the amygdala, and alcohol consumption has been described in studies across different species.[126] Typical dosages range from 25 mg to 200 mg, with a daily maximum of 400 mg. Spironolactone undergoes extensive hepatic metabolism. Data from preclinical studies is inconsistent yet promising,[127,128] including work from 2022 that shows spironolactone reduces alcohol binge drinking in mice and alcohol self-administration in rats.[129] A pharmacoepidemiological cohort study found an association between significant reduction of weekly alcohol use and spironolactone prescription for any indication.[130] In another pharmacoepidemiological cohort study, an association between a reduction in AUDIT-C score and receiving spironolactone was observed. The most pronounced effect was seen in those patients reporting excessive alcohol consumption at baseline.[129] The most

common side-effects are acute kidney injury, hyperkalaemia, cramps, and gynaecomastia. Although spironolactone is the first-line diuretic in the treatment of ascites,[131] further studies are necessary to recommend its use in alcohol use disorder.

GLP-1 receptor agonists are agents approved for the treatment of type 2 diabetes mellitus, and liraglutide and semaglutide are also approved for obesity.[132] The hormone GLP-1 stimulates insulin secretion while inhibiting glucagon secretion, and physiologically regulates appetite and food intake.[132] Also, GLP-1 receptors are found in brain areas associated with reward processing and addictive disorders in rodents and humans.[133] Thus, GLP-1 is postulated to modulate some of the neurobiological mechanisms related to alcohol use disorder.[113] GLP-1 receptor agonists have been shown to reduce alcohol consumption in rodents and non-human primate models of excessive alcohol consumption.[134,135] Semaglutide, which is postulated to have a higher affinity to GLP-1-receptors and be more potent than similar medications such as liraglutide or exenatide, was found to reduce binge-like and dependence-induced alcohol intake in rodents, to prevent relapse-like drinking in rats, and to modulate central GABA transmission.[136,137] In addition, semaglutide use has not been linked to liver toxicity. However, an RCT comparing exenatide with placebo did not find differences in the number of heavy alcohol consumption days among the two groups; a secondary exploratory analysis found exenatide to be superior to placebo only in a subgroup of patients with alcohol use disorder who had obesity (BMI >30 kg/m²).[138] Thus, although initial evidence, especially at the preclinical level, is emerging on the role of GLP-1 receptor agonists in alcohol use disorder,[135] further RCTs are needed to better understand if semaglutide or other GLP-1 receptor agonists, or other incretin-based therapies, can represent new treatments for alcohol use disorder.[139]

Memantine targets the N-methyl-D-aspartate receptor as a non-competitive selective antagonist, and is FDA-approved for the treatment of Alzheimer's disease. Daily dosage for the Alzheimer's indication is 20 mg, although trials for alcohol use disorder also tested dosages up to 40 mg once daily, with no differences found compared with placebo.[138] Only a small fraction of the drug undergoes metabolism, and the majority of memantine is eliminated via the kidneys. Although findings in preclinical rodent studies suggest a reduced rate of alcohol relapse with the drug,[140] data from human trials are still inconclusive.[141–143] Ghrelin is a peptide physiologically responsible for growth hormone regulation, food intake, and glucose homoeostasis, assumed to also play a role in alcohol and substance use disorders, and ongoing work is testing the potential role of the ghrelin receptor GHSR inverse agonist PF-5190457 in alcohol use disorder.[144,145] Evidence also suggests that ketamine could facilitate abstinence in multiple substance use disorders, including alcohol use disorder.[146] Finally, emerging evidence suggests that the psychedelic psilocybin could promote alcohol abstinence.[147] Although these agents seem promising, evidence is insufficient to recommend use in clinical practice.

Assessment and management of alcohol abstinence and withdrawal syndrome

In some people with alcohol use disorder, abrupt cessation or substantial reduction in alcohol consumption can lead to acute alcohol withdrawal syndrome. This syndrome is characterised by autonomic, motor, awareness, and psychiatric symptoms, comprising a spectrum of manifestations that can range from mild symptoms to complicated forms of alcohol withdrawal syndrome with seizures, delirium tremens, or both.[148] Alcohol withdrawal syndrome can affect 8–15% of hospitalised patients with alcohol use disorder.[149,150] These patients have higher morbidity and mortality than those with alcohol use disorder who do not develop alcohol withdrawal syndrome, with double the number of hospital stays for people with severe alcohol withdrawal syndrome than those with mild alcohol withdrawal syndrome, so systematic evaluation and early diagnosis of alcohol withdrawal syndrome among patients with alcohol use disorder is essential to decrease mortality.[151]

Prolonged alcohol consumption causes various changes in the CNS, including functional compensatory changes with increased expression of N-methyl-D-aspartate receptors and decreased GABA activity, generating more glutamate to maintain haemostasis.[152] Thus, the suspension of chronic alcohol consumption can result in overstimulation of the CNS, causing the neuropsychiatric complications described.[153] The initial presumptive diagnosis of alcohol withdrawal syndrome is made through the clinical elements together with the criteria in DSM-5, which has two main components: a clear evidence of cessation or reduction in heavy and prolonged alcohol consumption, and the symptoms of withdrawal are not accounted for by a medical or another mental or behavioural disorder. It is essential to keep in mind differential diagnoses, such as hyponatraemia, hepatic encephalopathy, CNS infections, trauma, thyrotoxicosis, and drug poisoning.[154] Therefore, if necessary, neuroimaging or electroencephalogram studies or lumbar puncture could be considered during the assessment of suspected alcohol withdrawal syndrome. Yet, in many cases, the diagnosis of alcohol withdrawal syndrome is primarily based on clinical evaluation only, without any further diagnostic testing for differential diagnosis.

The Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) is commonly used in patients to evaluate and treat alcohol withdrawal syndrome.[154] CIWA-Ar evaluates the severity of various symptoms associated with alcohol withdrawal syndrome, including

nausea, vomiting, tremor, paroxysmal sweats, agitation, tactile disturbances, auditory and visual disturbances, headache, and sensorium.[155] The CIWA-Ar scoring system ranges from 0 to 67, and a CIWA-Ar score higher than 8 indicates a mild to moderate alcohol withdrawal syndrome, and a score higher than 15 indicates severe alcohol withdrawal syndrome. All patients with alcohol withdrawal syndrome require supportive treatment, and admission to a monitored unit should be considered, especially for those with moderate to severe alcohol withdrawal syndrome. Several therapeutic agents are available in clinical practice, including benzodiazepines and phenobarbital. Benzodiazepines are considered the standard treatment for alcohol withdrawal syndrome, with lorazepam and oxazepam being preferred as they are metabolised by glucuronidation and do not undergo further oxidation, making them unaffected even in severe liver disease.[148] In alcohol-related liver disease, evidence from a retrospective cohort study has suggested that intravenous benzodiazepines and phenobarbital were independently associated with higher mortality compared with oral benzodiazepines.[156] Therefore, sedatives should be carefully used in severely ill patients with underlying liver disease. Further prospective studies and RCTs are urgently needed in patients who develop alcohol withdrawal syndrome to identify the best therapeutic approach to this potentially life-threatening condition.

Nutritional support in alcohol use disorder

Protein-energy malnutrition remains one of the most severe nutritional complications of patients with cirrhosis due to alcohol-related liver disease. Protein-energy malnutrition can promote frailty, immunosuppression, and hepatic decompensation.[157,158] Malnutrition is usually due to inadequate intake of macronutrients (primary malnutrition) and eventually malabsorption of dietary intake (secondary malnutrition). Protein-energy malnutrition should always be evaluated in patients with cirrhosis, and tailored nutritional management should be prescribed according to the presence of liver disease and hepatic decompensations (including ascites, hepatorenal syndrome, and encephalopathy). In patients with cirrhosis, regular day-time snacking (every 2–3 h) and night snacking are encouraged to prevent glycogen depletion and muscle protein breakdown. In those with severe alcohol-associated hepatitis, an adequate enteral nutrition for caloric and protein intake (35–40 kcal/kg per day, with protein 1·5 g/kg per day) should be provided.[159]

When alcohol consumption accounts for more than 30% of overall caloric intake, some individuals present with reduced ingestion of carbohydrates, proteins, fats, vitamin A, vitamin B1 (thiamine), vitamin B9 (folate), and vitamin C.[160,161] In this scenario, thiamine supplementation is essential to prevent the potentially deadly Wernike's encephalopathy and its progression to the irreversible state of Korsakoff syndrome. Also, recent data from a prospective clinical study suggest that supplementation of thiamine could increase memory functioning in patients with alcohol use disorder.[162] Although there is no consensus on the best dose, thiamine can be routinely prescribed at 100 mg daily.[163] Folic acid deficiency manifests as macrocytic anaemia in patients with alcohol use disorder and should be supplemented with 1 mg of folic acid daily. Since alcohol intake could potentiate vitamin A toxicity, supplementation of vitamin A is reserved only for patients with night blindness, using up to 900 µg daily for several weeks accompanied by zinc supplementation.[161] The main recommendations for micronutrient supplementation are summarised in table 3.

Conclusions

Although alcohol is the leading cause of death due to cirrhosis worldwide, most clinicians do not adequately assess alcohol intake in clinical practice and there are several barriers to providing integrated management for alcohol use disorder.[166] Assessment of alcohol use is mandatory for all patients in liver clinics regardless of the reason for consultation, with AUDIT-C a being brief and valid tool to screen for patients with a diagnosis of alcohol use disorder. In patients with alcohol use disorder, non-pharmacological treatments can be used in patients with comorbid liver disease, such as brief interventions, 12-step facilitation, motivational enhancement therapy, cognitive behavioural therapy, and

	Individuals without cirrhosis	Individuals with alcohol-associated cirrhosis
Macronutrients		
Overall energy intake (daily)	25–30 kcal/kg	Compensated: 25–30 kcal/kg; decompensated: 30–35 kcal/kg
Carbohydrates	45–65% of daily caloric intake per DRI	45–65% of daily caloric intake per DRI
Proteins	1·0–1·5 g/kg per day	Compensated: 1·2–1·5 g/kg per day; decompensated: 1·5–2·0 g/kg per day
Fats	25–30% of daily caloric intake per DRI	25–30% of daily caloric intake per DRI
Micronutrients*		
Fat-soluble vitamins (A, D, E, and K)	Up to RDA levels	Up to RDA levels
Vitamin B1†	100 mg/day	100 mg/day
Vitamin B9	1 mg/day (if deficient)	1 mg/day (if deficient)
Vitamin C	Up to RDA levels	No consensus
Sodium	Up to 2·3 g/day	<2 g in patients with ascites or oedema

Recommendations are based on the European Society for Clinical Nutrition and Metabolism Guidelines[164] and National Institutes of Health database.[165] DRI=dietary reference intake. RDA=recommended dietary allowance. *Treat only if the patient has micronutrient deficiency, except vitamin B1 (as thiamine should be supplemented in all patients with alcohol use disorder).

Table 3: **Nutritional requirements and supplementation in patients with alcohol use disorder and liver disease**

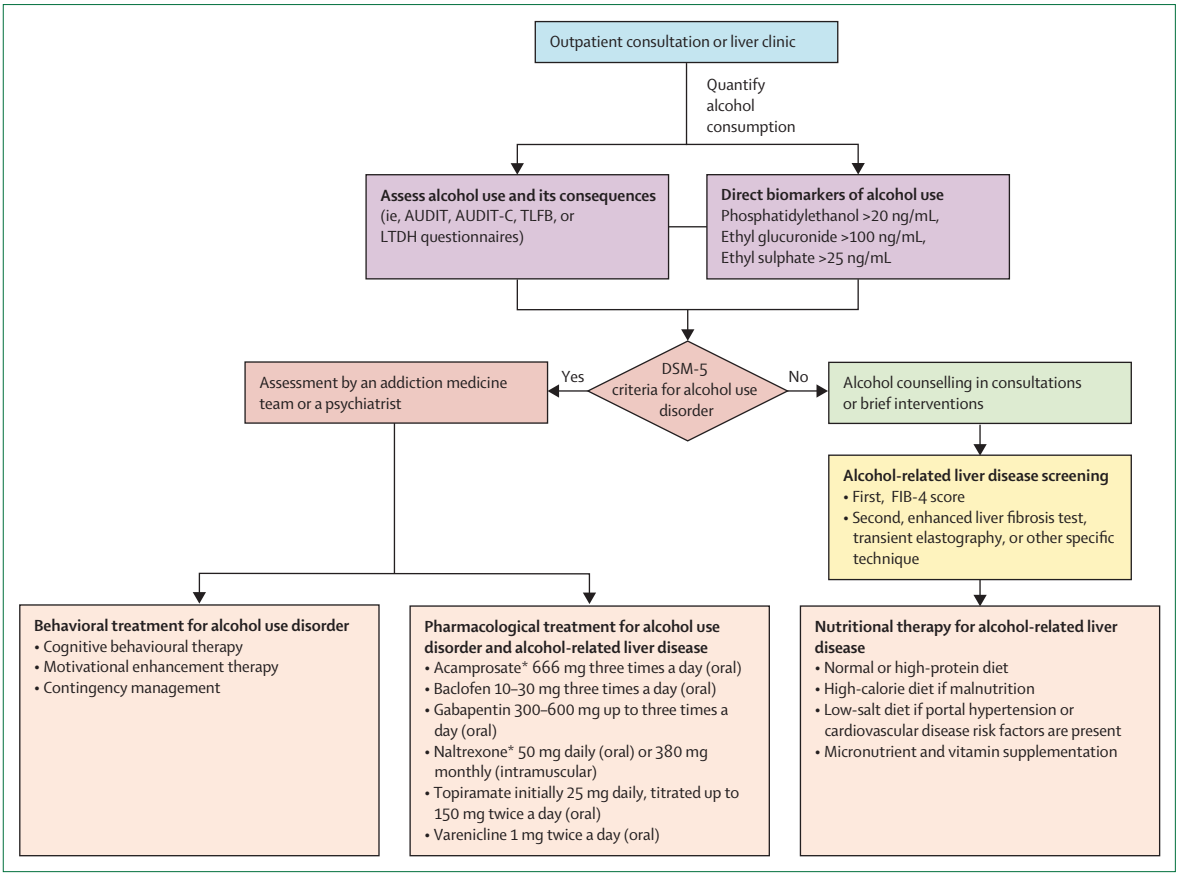

Figure 4: **Recommended screening and treatment approach for a patient with suspected alcohol use disorder in the liver clinic**
AUDIT=Alcohol Use Identification Test. AUDIT-C=Alcohol Use Identification Test for consumption. DSM-5=Diagnostic and Statistical Manual of Mental Disorders, fifth edition. FIB-4=Fibrosis-4. LTDH=Life Time Drinking History. TLFB=Timeline Followback. *Approved by the US Food and Drug Administration to treat alcohol use disorder.

contingency management. Pharmacological treatments should be considered according to the history of liver disease and other comorbidities, safety profile, and local availability. A recommended comprehensive approach to screening of and treatment for alcohol use disorder is presented in figure 4, which is particularly applicable in an outpatient setting.

The assessment of alcohol use and drinking patterns has multiple challenges to overcome. Screening for alcohol use disorder should be considered in any medical consult, and not only in patients with suspected liver disease. Unfortunately, differences in the definition of a standard drink among countries, and the lack of consensus for which are the best questionnaires and biomarkers to use in routine clinical practice, make it difficult to properly assess the severity of alcohol use in daily clinical practice. A recent consensus in alcohol use disorder to standardise quantification of alcohol could help solve these issues.[167] Finally, strengthening of public health policies that aim to decrease hazardous alcohol consumption,[168,169] increase the availability of screening methods to detect patients at risk in earlier stages of the disease,[76] and provide treatments in a timely fashion can also help decrease the burden of alcohol use disorder.[170]

Search strategy and selection criteria

References for this Review were identified through searches of PubMed with the search terms "alcohol use disorder", "alcohol-related liver disease", "alcoholic cirrhosis", "alcohol withdrawal", "liver fibrosis", and "cirrhosis" from 1993 until April, 2024. Articles were also identified through searches of the authors' files. Only papers published in English and Spanish were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Contributors
LAD and JPA. contributed to the design of the Review. LAD, DK, SW, GA, JMF, VV, GSW, and LL prepared the first draft. All authors reviewed, revised, and approved the final version of the manuscript.

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