Drugs (2023) 83:1459–1474
https://doi.org/10.1007/s40265-023-01939-9

LEADING ARTICLE

Alcohol-Associated Liver Disease: Evolving Concepts and Treatments

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Accepted: 3 September 2023 / Published online: 25 September 2023

Abstract
Alcohol is a prominent cause of liver disease worldwide with higher prevalence in developed nations. The spectrum of alcohol-associated liver disease (ALD) encompasses a diverse range of clinical entities, from asymptomatic isolated steatosis to decompensated cirrhosis, and in some cases, acute or chronic liver failure. Consequently, it is important for healthcare practitioners to maintain awareness and systematically screen for ALD. The optimal evaluation and management of ALD necessitates a collaborative approach, incorporating a multidisciplinary team and accounting for concurrent medical conditions. A repertoire of therapeutic interventions exists to support patients in achieving alcohol cessation and sustaining remission, with complete abstinence being the ultimate objective. This review explores the existing therapeutic options for ALD acknowledging geographical discrepancies in accessibility. Recent innovations, including the inclusion of alcohol consumption biomarkers into clinical protocols and the expansion of liver transplantation eligibility to encompass severe alcohol-associated hepatitis, are explored.

Key Points

Alcohol is a leading cause of liver disease globally yet historically receives less attention than other hepatological conditions.

Many patients remain undiagnosed, particularly in earlier stages of disease, therefore clinical vigilance is required. Management requires a multidisciplinary approach with attention to other comorbid medical conditions.

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1 Introduction

Alcohol is a major cause of liver disease globally and may be a cause or co-factor in up to 80% of liver-related deaths in some countries [1]. There is however significant geographic variation in the rate of alcohol-associated liver disease (ALD) [2]. There is now evidence of a dose-response relationship between alcohol consumption and the risk of liver disease and several evidence-based strategies to reduce overall harm from alcohol. Despite this, ALD receives less attention than other aetiologies of liver disease and remains a significant management challenge for clinicians [3]. In ALD, prevention, early detection, and harm reduction strategies remain critical, particularly given the lack of proven pharmacological options to improve long-term survival in those with advanced disease. In this review, we focus on the spectrum of liver disease that can occur with alcohol intake, and focus on current and emerging management options to address this condition.

2 Epidemiology

2.1 Prevalence

In 2017, it was estimated that 23.6 million people globally had alcohol-associated cirrhosis (AAC), with approximately 10% of these (or 2.5 million) having decompensated disease

[4]. However, the true burden of ALD more broadly is likely underestimated as it is often undiagnosed and can be an unrecognised co-factor in other forms of liver disease. In the United States (US), up to 1% of the population may have ALD [5]. In Europe and North America, alcohol has the greatest impact on liver health, with the alcohol-attributable fraction for cirrhosis being > 60%. This compares to south-east Asian and eastern Mediterranean regions where rates are well below 40% [6].

2.2 Morbidity and Mortality

Alcohol is a leading cause of morbidity and mortality, responsible for more than 5% of global deaths and disability-adjusted life years (DALYs) [2]. Young people are disproportionately affected, with alcohol being the leading cause of death and disability in those aged 15–49 years [7]. In 2016, AAC was responsible for 22.1 million DALYs and 607,000 deaths [2]. Alcohol also causes significant extrahepatic harm through traumatic injuries, cardiovascular disease, mental health problems, various neoplasms, and exacerbation of infectious disease [2, 7]. Alcohol is responsible for 48% of all cirrhosis-related deaths and 10% of all liver cancers, however this is not equally distributed between nations [2]. In developed nations, alcohol accounts for a disproportionately high rate of cirrhosis, which may partly be attributed to declining rates of viral hepatitis. It has been estimated that in Europe between 60 and 80% of all liver-related deaths may feature excessive alcohol use as a factor [1]. In the US, deaths from ALD are modelled to increase by 75% over the next 20 years [8].

2.3 Hospital and Economic Burden

Hospitalisation costs continue to rise, and in the US, ALD-related admissions are now more expensive than those from all other forms of liver disease combined [9, 10]. Hospitalisations for AAC have the highest inpatient mortality of any liver disease, with more than 10% of affected patients dying while in hospital [10]. Direct health care costs of AAC are substantial, and estimated at greater than US$5 billion per year [11]. More broadly, alcohol-related harm costs more than 2.5% of gross domestic product in high income nations, largely through lost productivity [12].

3 Quantifying Alcohol Use

Globally, 2.3 billion people consume alcohol regularly. Consumption is estimated at 6.4 L of pure alcohol/year per capita among people aged 15 years or older, an increase from 5.5 L per capita in 2005 [2]. However, there is significant geographical variation in alcohol use, with the lowest consumption in the Middle East and Northern Africa (less than 1 L/year) and highest in Russia and Eastern Europe (more than 12 L/year).

3.1 Defining a Standard Drink

Quantifying alcohol intake in clinical practice can be challenging, and the gold standard is to measure intake in grams (g) of alcohol consumed per day. Despite this, throughout the world there is a large variation in how many grams of alcohol constitute one standard drink, with a range of between 8 and 20 g [13]. In North America, one standard drink ranges between 13.45 g (Canada) and 14 g (US) and generally equates to a 12-ounce can of beer [14]. In most European nations, a standard drink is between 10 and 12 g, while in the UK it is only 8 g [15, 16]. Although such differences may seem small, when multiplied across several drinks it can result in vastly different amounts of alcohol. The WHO recommend using 10 g of alcohol as a common definition for one standard drink, especially when attempting to intervene in cases of risky drinking [16].

3.2 The Effect of Alcohol on the Liver

It is now clear that there is a direct dose-dependent relationship between the amount of alcohol consumed and the risk of serious liver disease. A meta-analysis has demonstrated that even very low levels of alcohol consumption increases the risk of cirrhosis-related mortality (any drinking in women, or more than 12 g/day in men) [17]. This risk rises sharply with increased consumption, with men and women consuming more than 60 g of alcohol per day being at 14- and 22.7-fold increased risk of cirrhosis-related death, respectively, compared with non-drinkers [17].

3.3 Binge Drinking

Heavy episodic drinking, often referred to as ‘binge’ drinking, is a pattern of drinking characterised by large-volume consumption of alcohol (typically on weekends) with interceding days of minimal or no drinking [18]. It is generally defined as the consumption of four or more standard drinks for women or five or more standard drinks for men within a 2-h period, and is associated with a range of health-related harms [19]. Heavy episodic drinking occurs in approximately 40% of all drinkers but is particularly common in Eastern Europe and Sub-Saharan Africa [2]. Repeated episodes of binge drinking (weekly or more frequently) may predispose to the development of liver disease longer term [18].

3.4 Impact of Coronavirus Disease 2019 on Alcohol Use

The coronavirus disease 2019 (COVID-19) pandemic was associated with a significant rise in alcohol consumption, with monthly sales increasing up to 40% compared with the pre-COVID era [20]. Lockdowns and other pandemic restrictions also led to the proliferation of online ordering of alcohol [21] and were associated with higher rates of alcohol-related mortality [22].

4 Spectrum of Alcohol-Associated Liver Disease (ALD)

ALD comprises a broad spectrum of disease ranging from asymptomatic isolated steatosis to steatohepatitis with or without fibrosis through to advanced cirrhosis (Fig. 1).

ALD is defined as clinical, radiological or biochemical evidence of liver injury in the setting of harmful alcohol consumption (usually defined as consumption > 20 g/day in women and > 30 g/day in men). Of note, many patients with early ALD may exhibit no laboratory abnormalities, and as such, a high clinical suspicion is required. Symptoms of ALD are often mild or non-specific such as fatigue [23].

4.1 Hepatic Steatosis

Alcohol-associated hepatic steatosis is the earliest histological stage of ALD characterised by the accumulation of triglycerides, phospholipids and cholesterol esters within hepatocytes [24]. It develops in 20–30% of patients who drink > 30 g/day (20 g/day in women) over a 10-year period [23] and may be present in as many as 90% of patients who drink heavily long-term [25]. It is often detected incidentally on liver imaging or as the result of investigation for minor liver function abnormalities. Liver ultrasound has a sensitivity of 85% for detecting moderate to severe steatosis (20–30% fat in liver on biopsy) and is a good initial screening test [26]. Alcohol-associated steatosis is not an entirely benign condition, with a mortality rate of 6% per year (1% liver rated, 5% non-liver related) [27]. Isolated steatosis usually regresses with cessation and improvements can be seen within as little as 2 weeks with non-invasive tests such as controlled attenuated parameter [28]. Alcohol-associated hepatic steatosis has approximately a 10% risk of progression to cirrhosis over a 10-year period [13, 25].

4.2 Alcohol-Associated Steatohepatitis

Continued use of alcohol predisposes to development of hepatic inflammation—so-called alcohol-associated steatohepatitis (ASH). The characteristic changes seen on liver histology include hepatocellular ballooning, necrosis, and a neutrophil predominate lobular inflammation. If ASH persists long term, it almost universally leads to some degree of liver fibrosis. As such, ASH is regarded as a more concerning condition, with rates of progression to cirrhosis of approximately 10% per year [27]. Total cessation of alcohol consumption will usually result in histological normalisation in patients with ASH without significant fibrosis [29]. ASH exists on a spectrum that ranges from mild to life-threatening. In severe cases, steatosis may become less prominent, or even absent, with inflammation predominating [13].

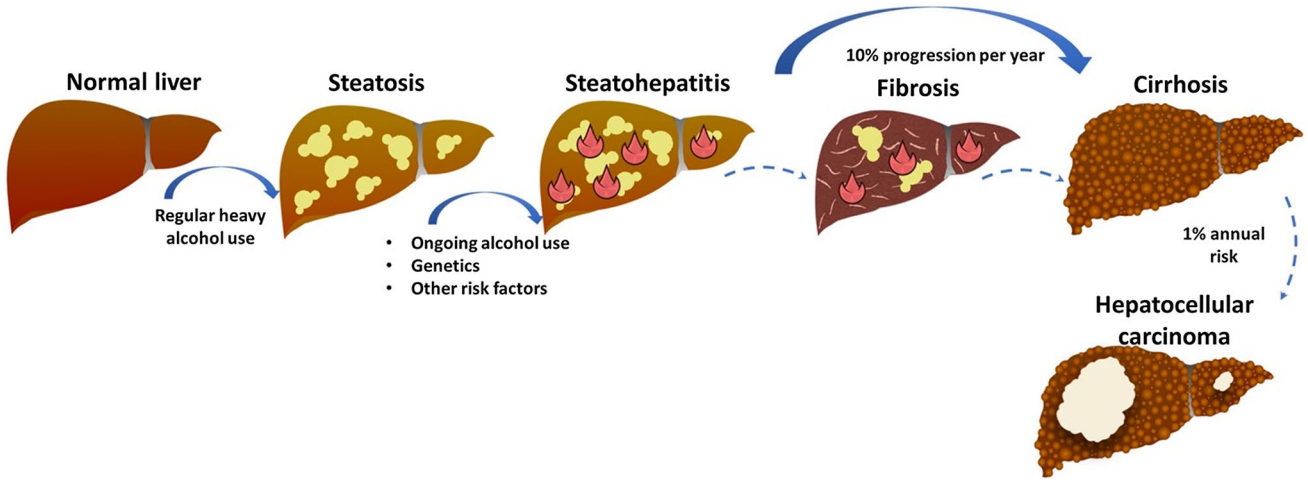

Fig. 1 Spectrum of alcohol-associated liver disease. Alcohol-associated liver disease exists on a clinical spectrum. After prolonged heavy alcohol consumption, patients almost universally develop alcohol-associated steatosis. This is asymptomatic and is reversible with cessation of drinking. With continued drinking, a proportion of patients progress to develop associated hepatic inflammation (steatohepatitis) that over time leads to fibrosis formation. Significant fibrosis can progress to cirrhosis and the associated sequelae of hepatitic decompensation and hepatoceullar carcinoma

4.2.1 Acute Alcohol-Associated Hepatitis

Acute alcohol-associated hepatitis is a unique clinical syndrome characterised by jaundice, anorexia, fever, hepatomegaly, neutrophilia and moderately elevated transaminases with an aspartate aminotransferase (AST): alanine aminotransferase (ALT) ratio of ≥ 2:1 [30]. The severity can be assessed by the Maddrey discriminant function (calculated from bilirubin and prothrombin time). Severe alcohol-associated hepatitis, defined by Maddrey discriminant function > 32, is often accompanied by acute-on-chronic liver failure (ACLF, discussed further below) and carries a poor prognosis with a 1-month mortality as high as 40% [31].

4.3 Hepatic Fibrosis and Cirrhosis

With ongoing ASH, patients are at risk of progressive hepatic fibrosis. Of note, only 35% of heavy drinkers will progress to develop significant fibrosis [24]. Alcohol-associated fibrosis begins in the perivenular region and extends in a perisinusoidal pattern, giving a characteristic 'chicken wire fibrosis' appearance [32]. As fibrosis develops, it progresses to involve portal tracts, with eventual development of bridging fibrosis and cirrhosis.

4.4 Decompensated Cirrhosis and Acute-on-Chronic Liver Failure

Cirrhosis begins with an asymptomatic, compensated stage where liver synthetic function is preserved. Further liver injury in patients with cirrhosis (such as with ongoing alcohol use) may precipitate decompensation heralded by the development of ascites, encephalopathy, and/or variceal haemorrhage. Those with acute decompensation and the presence of organ failures have ACLF that is associated with a high short-term mortality [33]. Indeed, alcohol consumption is a common precipitant for ACLF in patients with liver disease.

4.5 Hepatocellular Carcinoma

Like other forms of cirrhosis, AAC places affected individuals at increased risk of development of hepatocellular carcinoma (HCC) [34]. Acetaldehyde (formed from alcohol metabolism) has pro-mutagenic and carcinogenic effects that can contribute to cancer development, and it has also been demonstrated that alcohol can act synergically with hepatitis C virus to promote tumourigenesis [35, 36]. This risk of HCC in advanced ACC is estimated to be approximately 1% per year [37].

5 Risk Stratification and Setting of Care

As aforementioned, ALD encompasses a spectrum of conditions ranging from steatosis to cirrhosis with or without decompensation. However, only a minority of excess alcohol drinkers develop ALD and even fewer develop cirrhosis [38]. Therefore, the identification of those with severe disease or at increased risk of disease progression allows for patients to be triaged to the appropriate level of care (e.g., primary care vs. multidisciplinary tertiary hospital care). This will become increasingly important given the growing prevalence of ALD worldwide.

5.1 Identifying Patients with Advanced Fibrosis or Cirrhosis

As with all chronic liver diseases, the degree of liver fibrosis in ALD is strongly associated with development of complications, including decompensation, HCC and liver-related death [39]. In particular, patients with advanced fibrosis or cirrhosis should be referred to a gastroenterologist or hepatologist [23]. Although liver biopsy is often considered the gold standard for fibrosis assessment, its invasiveness limits its utility and acceptance. Instead, non-invasive radiologic and serum biomarkers are used to identify advanced ALD. Serum-based tests such as the FIB-4 score, Enhanced Liver Fibrosis score and FibroTest have modest sensitivity (58–79%) but good specificity (89–91%) for diagnosing advanced fibrosis or cirrhosis in ALD [40]. Hence, they are useful for ruling out severe disease in primary care (negative predictive values 88–94%). However, transient elastography (using a liver stiffness measurement of ≥ 15 kPa) is more accurate (86% sensitivity, 94% specificity) than serum-based tests for diagnosing advanced fibrosis or cirrhosis when a reliable measurement can be obtained. The sequential application of these non-invasive tests can help risk-stratify ALD patients [23]. In patients with established cirrhosis, Child–Pugh and Model for End-Stage Liver Disease (MELD) scores should be used to prognosticate and determine liver transplant (LT) referral. One notable exception is severe alcohol-associated hepatitis, which can occur in the absence of advanced fibrosis or cirrhosis and carries a poor prognosis without LT [41].

5.2 Identifying Patients at Risk of Disease Progression

Patients without advanced fibrosis may still require closer monitoring if they are at increased risk of disease progression. Traditional risk factors for fibrosis progression in ALD have included older age, increased body mass index,

presence of diabetes, and female sex [42]. The presence of concomitant liver diseases such as non-alcoholic fatty liver disease, chronic hepatitis C infection, haemochromatosis, and alpha-1-antitrypsin deficiency, promotes the development of advanced fibrosis and cirrhosis [43–45]. Certain patterns of hazardous drinking (daily drinkers, drinking outside of mealtimes, binge drinking, and excess drinking early in life) have been shown to be associated with more severe ALD [46, 47], however the impact of the type of alcohol consumed (wine vs. other) remains controversial [48]. Coffee consumption has consistently been demonstrated to be protective against cirrhosis development [48–50].

5.2.1 Genetic Factors

Recently, several genetic polymorphisms have been discovered through genome-wide association studies to influence the risk of ALD. Single nucleotide polymorphisms (SNPs) involved in lipid metabolism and processing, such as patatin-like phospholipase domain protein 3 (*PNPLA3*), membrane-bound O-acyltransferase domain 7 (*MBOAT7*), and transmembrane 6 superfamily member 2 (*TM6SF2*), are reproducibly associated with development of cirrhosis with odds ratios (ORs) in the range of 1.5–2.2, while others such as hydroxysteroid 17-beta dehydrogenase 13 (*HSD17B13*) are protective against disease progression [51–54]. The combination of these variants into a genetic risk score has been studied in a multinational cohort [53]. The combination of three SNPs (*PNPLA3, TM6SF2, HSD17B13*) improved the OR for predicting cirrhosis among heavy drinkers to > 3, while the addition of diabetes status (but not other clinical risk factors) increased the OR further to > 10.

5.2.2 The Microbiome

Alcohol intake can lead to changes in gut microbiota composition, which evolve with advancing liver disease. Like in other pathologies, there is an increase in dysbiosis (reduced diversity) in all forms of ALD. Specifically, gut microbiome signatures include lower abundance of *Bacteroidetes, Lachonospiraceae*, *Ruminococcaceae*, and *Akkermansia muciniphila*, and higher abundance of *Enterobacteriaceae, Streptococcaceae, Bifidobacterium, Streptococcus, Lactobacillus* and *Enterococcus* [55]. Functionally, these bacteria produce more endotoxin and secondary bile acids. Similar changes are also seen in acute alcohol-associated hepatitis. The microbiota of the liver has also been examined by autopsy samples [56]. This showed increased bacterial load within livers of patients with AAC compared with controls, suggesting increased intestinal permeability and bacterial translocation in those with ALD. Recently, machine learning modelling using gut microbial features have been shown to predict for incident ALD, with area under the receiver operating characteristic curves (AUROCs) > 0.85 in a large population-based cohort of > 7000 individuals with a median 15 years follow-up [57]. This predictive performance was similar to conventional clinical risk factors; however, the combination of microbiome and conventional risk factors improved the AUROC further to an impressive 0.956.

Although these genetic and gut microbiome markers appear promising stratification tools in heavy drinkers and those with ALD, they are currently not readily accessible or adopted into routine practice. Furthermore, there is currently no consensus on which patients without significant fibrosis should be referred to a liver and/or addiction specialist for closer monitoring. This will be a focus of ongoing research.

6 Management of ALD

Abstinence from alcohol is the cornerstone of treatment and should be recommended to all patients with ALD. Abstinence reduces the risk of hepatic decompensation and death in both compensated and decompensated cirrhosis patients [58]. Multiple treatment modalities are available, including behavioural therapy, peer-led support programmes, and pharmacotherapy. Treatment recommendations and goals of care should be individually tailored based on the patient preferences, and underpinned by patient-centred care and shared decision making [59]. In patients with ALD, the combination of comprehensive medical care and psychosocial interventions are more likely to result in abstinence, and integrated care approaches are associated with better outcomes [60].

6.1 Integrated Multidisciplinary Model of Care

Single specialties are ill-equipped to manage the complexities of ALD alone, as holistic treatment requires simultaneous consideration of comorbid liver disease, alcohol use disorder (AUD), mental illness, and other psychosocial issues (Fig. 2). Integrated models of care delivery exist as standard of care for the management of other comorbid physical and mental health conditions [61]. However, integrated multidisciplinary models of care delivery in ALD are rare outside LT centres, and have been identified as an area of need to reduce the burden of ALD [4]. Team members may include a hepatologist, addiction specialist, psychiatrist, counsellor, social worker, liver nurse and dietitian [62]. Small studies have shown encouraging results, including a reduction in emergency department visits and inpatient admissions [63]. Barriers to this model of care include financial and resource constraints, lack of specialised staff, logistical issues, siloed specialties, and impaired insight and motivation of patients [61].

6.2 Models of Alcohol Withdrawal Management and Detoxification

For those consuming large quantities of alcohol, abrupt cessation or reduction of alcohol consumption can lead to alcohol withdrawal syndrome (AWS), with symptoms typically commencing 6–24 h after the last drink and lasting for 5–7 days [64]. Release of excitotoxic neurotransmitters such as glutamate, in the absence of alcohol, are responsible for the development of AWS symptoms. Low to moderate severity, but nonetheless unpleasant, AWS symptoms can include tremors, nausea, vomiting, irritability, anxiety, and perceptual disturbance. Severe complications include seizures and delirium tremens, which can involve delirium, psychosis, hyperthermia, cardiac arrest, coma, and death. Mild to moderate AWS can typically be managed in the outpatient setting. Inpatient medicated withdrawal management is indicated where there are risk factors for severe AWS, including high-level chronic alcohol consumption, previous complicated AWS, or severe medical illnesses, including ALD [64].

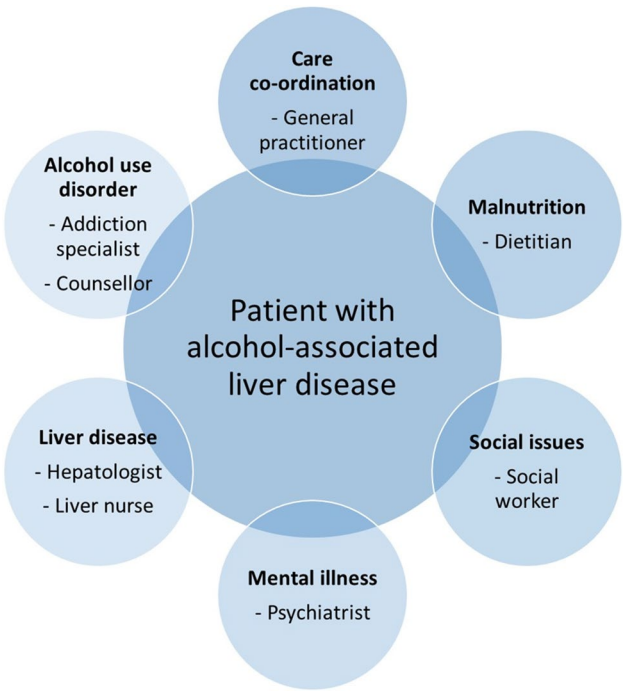

Fig. 2 Multidisciplinary care of patients with alcohol-associated liver disease. Alcohol-associated liver disease is a complex mutifaceted condition that requires simultaneous consideration of comorbid liver disease, alcohol use disorder, mental illness, nutrition, and other psychosocial issues. It is best managed using an integrated model of care involving a broad range of health professionals

6.2.1 Benzodiazepines

Long-acting benzodiazepines, commonly diazepam, are the gold standard for treatment of AWS to counteract symptoms and reduce the risk of withdrawal seizures and other life-threatening complications. There are several models of benzodiazepine prescribing for alcohol withdrawal, including fixed dose, front-loading and symptom-triggered regimens, although none has demonstrated superiority [65–67]. Fixed-dose regimens are preferred in those at risk of severe AWS but do carry a risk of oversedation due to benzodiazepine accumulation [64]. Diazepam is primarily metabolised by the cytochrome P450 pathway, which is impaired in patients with severe hepatic impairment, therefore prolonging its duration of action in these patients. Diazepam produces several active metabolites, namely oxazepam, desmethyldiazepam, and temazepam, which can lead to protracted oversedation in patients with severe liver disease. Therefore, in the presence of marked synthetic dysfunction, intermediate-acting benzodiazepines are preferentially used. Oxazepam, lorazepam and temazepam have a shorter half-life than diazepam, do not undergo phase I (cytochrome P450) metabolism, and are easily metabolised via phase II (conjugation) metabolism for excretion in urine, with no active metabolites. In patients with advanced liver disease, conjugation is preserved, while phase I metabolism is not. Therefore, oxazepam is safe to use in hepatic dysfunction, although should not be administered if patients are obtunded, such as with hepatic encephalopathy [68].

6.2.2 Thiamine Deficiency

Chronic alcohol consumption is associated with thiamine deficiency, which can lead to the debilitating amnestic neurocognitive disorders Wernicke's encephalopathy, Korsakoff psychosis, and alcohol-related dementia [69]. Prophylactic thiamine administration is recommended in all patients with high levels of chronic alcohol consumption [70].

6.3 Relapse Prevention

6.3.1 Behavioural Treatment

Provision of behavioural treatment can be through brief interventions, motivational interviewing, cognitive behavioural therapy (CBT) or motivational enhancement therapy [71]. CBT has the most consistent evidence for increasing abstinence in ALD, although data are limited [60, 72]. In ALD, where behavioural treatment is provided as part of an integrated hepatology clinic, rather than by external

providers, there is evidence of improved abstinence and less severe relapse [60, 73, 74]. Peer-led support programmes are widely available and at no financial expense to participants, including alcoholics anonymous (AA), an abstinence-only model based on 12-step principles that has Cochrane review evidence for increased abstinence [75]. Self-Management and Recovery Training (SMART Recovery) is another model, based on self-empowerment and self-efficacy [76]. Neither have evidence in a population with ALD specifically.

6.3.2 Alcohol Pharmacotherapy

There is evidence that alcohol pharmacotherapy is well tolerated and effective in patients with AUD, however caution is needed in patients with advanced liver disease due to the lack of safety data and the potential for hepatotoxicity (Table 1). Alcohol pharmacotherapy is underprescribed in ALD and there is also evidence that gastroenterologists and hepatologists lack confidence and experience in prescribing it [77, 78]. Furthermore, safety data in ALD are limited given many trials excluded these patients.

Baclofen has evidence of safety and efficacy in AUD and is the only pharmacotherapy with randomised controlled trial evidence in ALD, including in patients with cirrhosis [79–81]. Acamprosate has evidence of efficacy in AUD, from a meta-analysis of 22 placebo-controlled trials, and is not recommended in Child–Pugh C cirrhosis, although this is based on tolerability of the drug after only a 1-day trial in Child–Pugh A and B cirrhosis [82, 83]. Naltrexone is well tolerated in compensated cirrhosis, but dose-dependent hepatotoxicity has been demonstrated in obesity trials and monitoring of liver function tests is recommended [84]. Disulfiram can also lead to hepatotoxicity and is not recommended in advanced liver disease [85]. Acamprosate, disulfiram and naltrexone (oral tablet and extended-release intramuscular injection) are approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in AUD [13]. Additionally, nalmefene is approved by the EMA, baclofen is approved in France, and sodium oxybate is approved in Italy and Austria [86]. Gabapentin and topiramate are used off-label in AUD [87]. Topiramate is recommended for AUD treatment by the US Department of Veterans Affairs and the American Psychiatric Association (APA) and gabapentin is recommended by the APA [88, 89].

When initiated prior to a diagnosis of ALD, alcohol pharmacotherapy is associated with a reduced incidence of ALD development. One large retrospective study showed that the effect is dose-dependent, with every year taking gabapentin, topiramate, baclofen or naltrexone conferring a reduced risk of developing ALD. Naltrexone or gabapentin use in patients with cirrhosis, whether initiated before or after their cirrhosis diagnosis, is associated with a reduction in the incidence of hepatic decompensation over multiple years [90].

6.4 Managing Comorbid Mental Illness

Identification of concomitant psychiatric conditions in patients with ALD is important, to provide simultaneous treatment of all conditions with the aim of abstinence [91]. Depression and anxiety disorders, post-traumatic stress disorder, psychotic disorders and other substance use disorders are all seen at a higher prevalence in patients with AUD and can present major barriers to the successful treatment of AUD. Alcohol may be used as a coping mechanism in the setting of chronic pain, sleeping disorders, or sexual, physical or emotional abuse [91]. Consideration should be given to the potential for oversedation in patients prescribed antipsychotics, benzodiazepines or opioids who continue to drink alcohol [92].

6.5 Biomarkers of Alcohol Consumption

Testing for biomarkers of alcohol consumption can aid in diagnosis and follow-up of ALD by providing objective information about alcohol intake, in addition to self-report. Biomarkers are often used as part of screening of LT candidates, and when monitoring for relapse in the post-LT setting [93]. Indirect biomarkers of alcohol consumption include the commonly measured and inexpensive liver function tests γ-glutamyltransferase (GGT), AST, ALT, as well as mean corpuscular volume (MCV) and percentage carbohydrate-deficient transferrin (CDT) [94]. These are crude markers of alcohol consumption, and, in particular, the sensitivity of percentage CDT is reduced in patients with cirrhosis, often resulting in false negative results [13]. Direct biomarkers have much higher sensitivity and specificity than indirect biomarkers and include breath, urine and serum alcohol testing, but these are limited by a short window of detection following alcohol intake. Other direct biomarkers measure non-oxidative metabolites of alcohol, which indicate the level of alcohol consumption over the preceding days to months and include urine ethylsulphate (EtS), urine or hair ethyl glucuronide (EtG), and serum phosphatidylethanol (PEth) [94]. There is no current gold standard, however PEth is a very useful biomarker for confirming active drinking and has been validated in cohorts of patients with chronic liver disease [94, 95]. Sensitivity has been shown to be 73–100% and specificity 90–96% for detection of alcohol consumption in the prior 1–4 weeks [94]. PEth is a phospholipid that forms on red blood cell membranes only in the presence of ethanol. The half-life of PEth is 3–10 days depending on the level of ongoing drinking, and therefore demonstrates alcohol consumption in the preceding month for regular drinkers

Table 1 Alcohol pharmacotherapy in alcohol-associated liver disease [81, 84, 87, 92, 94, 118–120]

Drug name	Liver disease	Can commence while drinking?	Dose	Mechanism of action	RCT evidence	Adverse effects	Contraindications	Caution
Acamprosate [82, 83, 92, 121]	Avoid in Child–Pugh C cirrhosis No hepatic metabolism	No	666 mg three times daily	Glutamatergic receptor modulator Reduces unpleasant symptoms of alcohol withdrawal Reduces cravings	Meta-analysis of 16 RCTs showed NNT = 12 (95% CI 8–26) to prevent one person returning to drinking (moderate-quality evidence) Not ALD specific	Diarrhoea, nausea, headache	Child–Pugh C cirrhosis. Renal impairment (creatinine > 120 µmol/L or creatinine clearance < 30 mL/min)	Pregnancy. Acute alcohol withdrawal. Dose adjustment in renal impairment (renally excreted)
Baclofen [79, 80, 83, 91, 118, 122, 123]	Well tolerated. Minimal hepatic metabolism Avoid in hepatorenal syndrome or hepatic encephalopathy	No	5 mg three times daily and increase every 3–5 days as tolerated to 10 mg three times daily, maximum 80 mg daily	GABA-B receptor agonist	RCT of 84 subjects with cirrhosis showed 12 weeks of baclofen (maximum 30 mg total daily dose) was associated with higher rates of abstinence maintenance (71%) than placebo (29%). This was supported by another RCT of 104 subjects consuming a mean of 15 standard drinks per drinking day, 58 with alcohol-related liver disease (65–69% of days abstinent for baclofen vs. 43% for placebo), which also showed that a 75 mg daily dose of baclofen was no more efficacious than 30 mg and contributed to more sedation These results were not replicated in a study of 180 US Veterans with HCV and less heavy alcohol use, mean of seven standard drinks per drinking day	Fatigue, drowsiness, somnolence, headache, slurred speech, vertigo, abnormal movements	Avoid in renal impairment. Risk of overdose	Tolerance with chronic use. Life-threatening withdrawal syndrome on cessation or reduction

Table 1 (continued)

Drug name	Liver disease	Can commence while drinking?	Dose	Mechanism of action	RCT evidence	Adverse effects	Contraindications	Caution
Disulfiram [85, 92, 119, 121, 124]	For goal of abstinence only Hepatic metabolism Avoid if moderate–severe hepatic impairment Monitor LFTs every 2 weeks for first 3 months, especially if abnormal at baseline	No	200–400 mg once daily	Aldehyde dehydrogenase inhibitor. Results in unpleasant effects with alcohol consumption due to elevated blood acetaldehyde concentrations	Meta-analysis of 22 RCTs showed no efficacy of disulfiram over placebo in blinded studies, suggesting that psychological fear of a reaction may be a mechanism of action (Skinner), as open-label RCTs showed a medium effect size (g = 0.70) in achieving each trial's primary endpoint. Not ALD-specific	Rash, headache. Can be severe including seizures, respiratory depression, myocardial infarction, arrythmia, exacerbation of congestive cardiac failure	Current alcohol intoxication. Ischaemic heart disease. Severe myocardial disease. Severe renal impairment. Moderate–severe hepatic impairment. Acute psychosis. Cirrhosis	Cardiovascular disease. Diabetes. Hypothyroidism. Epilepsy. Chronic kidney disease. Hepatic impairment Drug interactions
Gabapentin [87, 89, 125]	Well tolerated. No hepatic metabolism Avoid if hepatorenal syndrome	Yes	900–1800 mg once daily	GABA modulator	Meta-analysis of 7 RCTs showed a significant reduction in heavy drinking days (g = 0.64, 95% CI −0.64 to −0.06)	Dizziness, somnolence, ataxia, peripheral oedema		Substance use disorder, given abuse potential
Naltrexone, oral tablet and extended-release IMI [83, 84, 87, 121]	Well tolerated in compensated cirrhosis Monitor LFTs monthly, especially Child–Pugh B and C cirrhosis	Yes	PO: 50 mg once daily; IMI: 380 mg monthly	Mu-opioid receptor antagonist Reduces cravings and the pleasurable effects of alcohol consumption by modulating dopamine surges in the reward pathway	Meta-analysis of 16 RCTs of oral naltrexone 50 mg showed NNT = 20 (95% CI 11–500) to prevent one person returning to drinking (moderate quality evidence), and for injectable naltrexone (2 RCTs) there was a reduction in heavy drinking days (WMD −4.6%, low-quality evidence). Not ALD-specific	Diarrhoea, abdominal cramping. Risk of hepatotoxicity in hepatic and renal impairment Black-box warning for hepatotoxicity (seen at suprathrapeutic doses)	Will precipitate withdrawal in opioid dependence. Severe hepatic impairment. Acute hepatitis	Renal impairment. Cease 1 week prior to elective surgery

Table 1 (continued)

Drug name	Liver disease	Can commence while drinking?	Dose	Mechanism of action	RCT evidence	Adverse effects	Contraindications	Caution
Nalmefene [83, 87, 121, 126, 127])	For reduction of heavy drinking. Consider use if unable to achieve abstinence Hepatic metabolism, therefore reduce dose in hepatic impairment No evidence of hepatotoxicity Avoid in Child–Pugh C cirrhosis	Yes	18 mg daily as needed, taken 1–2 h prior to or at the onset of drinking	Opioid mu and delta receptor antagonist, and partial kappa agonist. Reduces dopamine release in alcohol reward pathway	Moderate-quality evidence from 2 RCTs for less heavy drinking days per month (WMD −2.0%, 95% CI −3.0 to −1.0%). Not ALD-specific	Nausea, vomiting, dizziness, insomnia, headache	Will precipitate withdrawal in opioid dependence Pregnancy, breastfeeding, Child–Pugh C cirrhosis	Cease 1 week prior to elective surgery
Sodium oxybate (salt of γ-hydroxybutyric acid) [86, 128]	Mainly hepatic metabolism. Reduce dose in hepatic impairment	No	50 mg/kg/day divided into 3–6 doses	GABA-B receptor agonist	For mild AUD (4 RCTs), conflicting results compared with placebo For severe AUD (2 RCTs), 18–22% more likely to be abstinent after 3 months vs. placebo. Not ALD-specific	Dizziness, vertigo	Other sedative drugs	Substance use disorder, given abuse potential
Topiramate [83, 120]	Partial hepatic metabolism. Caution in hepatic encephalopathy given cognitive adverse effects	Yes	300 mg once daily (slow uptitration starting at 25 mg)	Potentiates GABA-A and inhibits glutamatergic activity	RCT evidence that topiramate 300 mg daily for 14 weeks reduces heavy drinking days (mean difference 8.4%) vs. placebo. Not ALD-specific	Dizziness, parasthesiae, anorexia, cognitive impairment, pruritus		Slow dose titration and close monitoring is recommended

ALD alcohol-associated liver disease, *AUD* alcohol use disorder, *CI* confidence interval, *GABA* γ-aminobutyric acid, *HCV* hepatitis C virus, *LFTs* liver function tests, *NNT* number needed to treat, *PO* per oral, *IMI* intramuscular injection, *RCT* randomised controlled trial, *WMD* weighted mean difference

or heavy binge drinkers [94]. In practice, use of biomarkers tends to be limited by the geographical availability of testing.

6.6 Prevention of ALD Complications

While alcohol cessation is the most effective way to limit ongoing liver damage and reduce the complications of ALD, several aspects of care require ongoing attention. Patients with AAC are at increased risk of developing HCC and benefit from 6-monthly surveillance with abdominal ultrasound with or without serum α-fetoprotein [96]. Similar to risk stratification for ALD discussed above, the risk of incident HCC can also be estimated using robust scoring systems such as the aMAP score (consisting of age, male sex, ALBI [albumin-bilirubin] grade and platelet count) [97]. Unsurprisingly, the same genetic SNPs that confer increased risk of liver disease mentioned earlier are also associated with increased HCC risk [52]. Greater efforts should also be made to encourage alcohol cessation and adherence to HCC surveillance in high-risk patients.

Patients with AAC with high liver stiffness measurements and/or thrombocytopenia are at increased risk of having gastro-oesophageal varices that need treatment [98]. Therefore, gastroscopy should be performed to screen for varices in these patients unless they are already taking a non-selective β-blocker. The latter may also be beneficial in preventing decompensation (especially incident ascites) in patients with clinically significant portal hypertension [99].

Chronic alcohol consumption with or without ALD can lead to malnutrition, which is associated with poorer outcomes in chronic liver disease [100]. Therefore, patients with ALD should be regularly assessed for malnutrition by a dietitian, and if identified, be prescribed nutritional supplementation of calories, protein and vitamins. Patients unable to maintain adequate intake may benefit from nasogastric tube feeding. Both excess alcohol consumption and chronic liver disease are independent risk factors for the development of osteoporosis [101]. Patients with ALD should undergo regular (2-yearly) bone mineral density measurements [102]. Those with malnutrition and/or advanced ALD should be prescribed calcium and vitamin D replacement. Anti-resorptive treatments should be considered in those with fragility fractures or a T score of less than −2.5, although there is no strong evidence that this reduces fracture risk in ALD [101].

7 Liver Transplantation

Liver transplantation is a curative treatment for patients with end-stage liver disease [103]. ALD is the second most common indication for LT worldwide [38] and can be divided into two main categories: AAC and severe alcohol-associated hepatitis [43].

7.1 Liver Transplantation for Alcohol-Associated Cirrhosis

The clinical indicators for transplant evaluation for ALD are similar to other aetiologies of cirrhosis: decompensated cirrhosis with a MELD score ≥ 15, or the development of a new HCC [104]. Specific to ALD, an arbitrary minimum duration of abstinence of 6 months (i.e., the '6-month rule') has been traditionally required prior to LT listing [105]. However, there is little evidence to support the 6-month rule (or any other fixed interval of abstinence pre-LT) as a reliable predictor of survival and return to drinking post-LT [106]. Instead, independent predictors of alcohol relapse include lack of social support, comorbid psychiatric conditions, cigarette smoking (and other substance abuse), and noncompliance [107]. The utility of the 6-month rule has been further challenged by results from transplanting patients with alcohol-associated hepatitis (discussed below). Consequently, the 6-month rule has since been discouraged by major international society guidelines in preference for a multidisciplinary psychosocial evaluation involving members of the transplant team such as hepatologists, surgeons, psychologists, psychiatrists and addiction specialists [43, 104]. Nonetheless, one benefit of the 6-month rule is that AAC may recompensate during this time of abstinence, thus avoiding unnecessary LT in some patients. As such, most transplant centres worldwide still enforce a minimum abstinence period of 6 months for transplant consideration.

7.2 Early Liver Transplantation for Severe Alcohol-Associated Hepatitis

Patients with severe alcohol-associated hepatitis have a poor prognosis and may not have 6 months to wait (up to 75% mortality at 6 months in medical therapy non-responders) [41]. In 2011, a prospective multicentre (seven centres in France and Belgium) pilot study transplanted 26 patients with severe alcohol-associated hepatitis who did not respond to medical therapy without 6 months of abstinence [108]. The patients were highly selected (1.8% of those recruited) based on the following stringent criteria: first liver-decompensating event, supportive family members, no severe co-existing conditions, and a commitment to alcohol abstinence. The study reported a significant survival benefit at 6 months (77% vs. 30%), with a low alcohol relapse rate (12%) while using only 2.9% of available grafts during the study period. Several studies have since confirmed the high rates of 1-year patient survival (> 85%) and low rates of return to

drinking (< 20%) with this approach [109–111]. Thus, LT for carefully selected patients with severe alcohol-associated hepatitis has become increasingly accepted worldwide, with a growing number of centres adopting this new indication. The lack of universal access (which is influenced by insurance type in some countries) has raised ethical questions relating to equity and the need for advocacy by the transplant community [112]. Indeed, the healthcare costs of early LT for alcohol-associated hepatitis are large and yield a negative net revenue owing to the severity of the condition and its associated prolonged hospital stay [113].

Heterogeneity also exists in the 'comprehensive psychosocial assessment' used for selection between centres. Attempts have been made to objectify patient selection with scores such as the Sustained Alcohol Use Post-Liver Transplant (SALT) score, which evaluates > 10 drinks daily at initial presentation, rehabilitation attempts, alcohol-associated legal issues, and illicit substance abuse [114]. Although a score of < 5 (out of 11) had a 95% negative predictive value of sustained drinking post-LT, an appropriate cut-off for patient selection has not been proposed. Most recently, the original French-Belgian group performed a prospective study comparing patients with alcohol-associated hepatitis undergoing early LT with those who were transplanted for AAC after 6 months of abstinence [115]. This time the authors selected early LT patients using a cut-off (≥ 220) based on a numerical score derived from their previous psychosocial assessment (out of 250). The 2-year post-LT survival was similar in the two groups (90% vs. 88%), but the 2-year rate of alcohol relapse (34% vs. 25%) and high alcohol intake (22% vs. 5%) were higher in the early LT group. Clearly, this score will require further refinement and validation [116]. This also highlights that LT does not cure AUD, which requires ongoing monitoring and treatment. LT for severe alcohol-associated hepatitis (and even AAC) is an evolving field, and whether to tighten or loosen transplant selection criteria remains a topic of debate [117].

Not all patients will be medically or psychosocially suitable candidates for LT, either for the indication of AAC or severe alcohol-associated hepatitis with or without ACLF. Thus, early referral to palliative and supportive care may be beneficial in terms of improving quality of life and physical and psychological symptoms in these patients with end-stage liver disease.

8 Summary and Conclusions

Alcohol is a major cause of liver disease globally and is overrepresented as an aetiology of liver disease in the developed world. ALD exists on a broad clinical spectrum, with many cases remaining undiagnosed. As such, it is important for clinicians to remain cognisant and screen for it routinely in clinical practice. Ongoing research is underway to develop better tools to both identify and predict patients at risk of disease progression.

Best-practice assessment and management of ALD involves a multidisciplinary team and considers comorbid medical conditions. There are a range of therapeutic options to assist patients with both alcohol cessation and maintenance of remission, with abstinence being the ideal goal. These treatments however remain underutilised in clinical practice with many clinicians lacking confidence to prescribe them. This review has outlined the current therapeutic armamentarium although there remains geographic variation in the availability of some treatments.

Areas of recent innovation include the introduction of biomarkers of alcohol consumption into clinical practice and the expansion of liver transplantation to include patients with severe alcohol-associated hepatitis (a condition with very limited evidence-based treatment options previously). Ongoing work is needed to further refine these strategies and implement them more broadly in clinical practice.

Declarations

Conflict of interest David Stephen Prince, Emily Nash, and Ken Liu have no identified conflicts of interest related to this work.

Funding Open Access funding enabled and organized by CAUL and its Member Institutions.

Author contributions David Prince was invited to contribute this review.

Ethics approval Not applicable.

Informed consent Not applicable.

Data availability Not applicable.

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