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Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation

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Abstract | The prevalence of alcohol use disorder (AUD) has been steadily increasing over the past decade. In parallel, alcohol-associated liver disease (ALD) has been increasing at an alarming rate, especially among young patients. Data suggest that most patients with ALD do not receive AUD therapy. Although liver transplantation is the only curative therapy for end-stage ALD, transplant candidacy is often a matter of debate given concerns about patients being under-treated for AUD and fears of post-transplantation relapse affecting the allograft. In this Review, we discuss diagnosis, predictors and effects of relapse, behavioural therapies and pharmacotherapies, and we also propose an integrative, multidisciplinary and multimodality approach for treating AUD in patients with cirrhosis, especially in the setting of liver transplantation. Notably, this approach takes into account the utility of AUD pharmacotherapy in patients on immunosuppressive medications and those with renal impairment after liver transplantation. We also propose a comprehensive and objective definition of relapse utilizing contemporary biomarkers to guide future clinical trials. Future research using the proposed approach and definition is warranted with the goal of optimizing AUD treatment in patients with cirrhosis, the transplant selection process and post-transplantation care of patients with AUD.

Alcohol use disorder (AUD) is a chronic disease characterized by unhealthy alcohol use and several neurobiological features that can include positive reinforcement, compulsive search for alcohol and negative emotional state when alcohol is not used[1]. It consists of a constellation of symptoms, including withdrawal, tolerance and craving, among others. It is categorized as mild, moderate or severe depending on the number of diagnostic criteria fulfilled, as per the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[2], including loss of control, craving and failure to fulfil major role obligations. AUD is a major public health issue, the prevalence of which has been increasing at an alarming rate. In 2017, a national epidemiological survey in the USA that included >36,000 participants showed an increase in the prevalence of AUD from 8.5% to 12.7% between 2001–2002 and 2012–2013, which constitutes an increase of approximately 50%. This increase was more pronounced in women, minority ethnic groups, urban residents, and those with limited education and/or income[3].

Alcohol-associated liver disease (ALD) is a term that describes a wide range of liver disease entities that result from alcohol use, ranging from hepatic steatosis to steatohepatitis and eventually cirrhosis. In the USA, the prevalence of alcohol-associated cirrhosis rose from 0.07% to 0.1% between 2009 and 2015. These patients were more ill and their health-care cost was markedly higher than in patients who had cirrhosis due to other aetiologies[4]. The demographic pattern of ALD has also changed over the past few decades; it now affects higher percentages of women and younger people[5–8]. In parallel to the increase in prevalence of AUD and alcohol-associated cirrhosis, the percentage of liver transplantations in the USA for ALD has increased from 24.2% in 2002 to 36.7% in 2016, which makes ALD the most common indication for liver transplantation after the advent of direct-acting antivirals for chronic hepatitis C infection[9]. In a French multicentre study, severe AUD relapse after transplantation occurred in 20% of liver transplant recipients with prior ALD, of whom 35% developed allograft cirrhosis that affected their post-transplantation survival[10]. These data highlight the importance of early recognition of relapse and the implementation of therapeutic interventions for AUD to prevent development of advanced ALD in the general population and also recurrence of ALD in liver transplant recipients. The definition of relapse is not

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Key points

- The prevalence of alcohol use disorder (AUD) and alcohol-associated liver disease has increased over the past few decades globally.
- Definitions of relapse after liver transplantation vary widely.
- Currently, our understanding of the predictors and effects of relapse after liver transplantation is growing and together with a multidisciplinary approach might improve patient outcomes.
- The use of pharmacotherapies for AUD is feasible in patients with cirrhosis after tailoring the regimen to account for comorbid illnesses such as renal dysfunction.
- Relapse-prevention medications do not have notable interactions with immunosuppressants commonly used after liver transplantation.
- Combining medications and behavioural treatments with medical care at the transplant centre might maximize relapse prevention potential.

standardized in the field. Therefore, the implementation of consensus definitions and a dedicated task force are key for clinical use and research.

AUD treatment in patients with ALD is a challenge both before and after liver transplantation, given complexities surrounding access, selection, referral, specific pharmacological and behavioural treatments, and follow-up. Interestingly, in a retrospective study of 93,612 veterans with cirrhotic-stage ALD, only 12% of patients received behavioural therapy after diagnosis of AUD, whereas 1% received behavioural and pharmacotherapy and 0.4% received pharmacotherapy alone. Those who received AUD treatment were at significantly lower risk of hepatic decompensation (adjusted odds ratio (AOR) 0.63, 95% CI 0.52–0.76) and long-term mortality (51% versus 58%, AOR 0.87, 95% CI 0.80–0.96)[11]. The strikingly low rate of pharmacotherapy in the study is not completely surprising given the potential lack of appropriate medical education and training in addiction medicine among hepatologists, potential lack of comfort among addiction specialists about using pharmacotherapies for patients with advanced liver disease, and other factors such as patients' reluctance to seek treatment and stigma around AUD. Furthermore, data regarding utilization of behavioural therapy and/or pharmacotherapy in the setting of recurrent AUD after transplantation are limited. The field of AUD is certainly in need of definitions of key concepts and identification of different phenotypes. In this Review, we discuss management of AUD in patients with ALD with a special focus on the setting of liver transplantation, relapse predictors and effects after liver transplantation, and prevention of relapse (including available data on pharmacological and behavioural therapies for AUD). Additionally, we propose a definition of post-transplantation relapse and a multidisciplinary care approach, and discuss future research directions to fill the knowledge gaps in the field.

Diagnosis of AUD in patients with ALD

The presence of an unhealthy alcohol use, often associated with a diagnosis of AUD, should be assessed in all patients presenting with liver disease, ideally starting with validated screening questionnaires[12]. The Alcohol Use Disorders Identification Test (AUDIT) comprises ten questions with a specific scoring system[13]. An AUDIT score of >8 is considered a positive screening test result, which indicates the presence of AUD. AUDIT scores of 15 for men and 13 for women have a 100% specificity but low sensitivity (20% and 18%, respectively) for detecting alcohol dependence that prompts brief intervention and monitoring. Additionally, a score of >20 implies the presence of alcohol dependence and should lead to a referral to addiction specialists[14]. To facilitate a wide implementation of this questionnaire, a shorter version was developed (AUDIT-C), which consists of three questions with a specific scoring system that ranges from 0 to 12. A result of ≥3 for women and ≥4 for men are considered a positive screening result[15]. With these cut-off values, AUDIT-C has 73% sensitivity and 91% specificity for hazardous alcohol consumption in women and 86% sensitivity and 89% specificity in men[15–18]. Self-interview and audio computer-assisted self-interview have been implemented and could facilitate effective and efficient screening for substance use in medical settings, including primary care[19]. It is important to highlight that most of these tools used for heavy alcohol consumption screening were designed and tested in the general population; therefore, patients with severe ALD also need to be assessed regarding the specific amount and time frame of alcohol consumption (for example, grams of pure alcohol per day for a specific period of time), which better correlates with liver-related outcomes. Additionally, only a small proportion of patients with severe AUD will develop cirrhotic-stage ALD[20], and individual susceptibilities, including, for example, genetic background and obesity, can have a role.

Another important issue is that physicians mostly rely on medical history (from patients and/or their family) to quantify alcohol consumption. Monitoring for alcohol use typically includes patient interview, with direct questioning about quantity, type and frequency of alcohol use. Independent collateral information from a family member or caregiver is also helpful to confirm or add to the patient's self-report[21]. As AUD carries a social stigma, patients might tend to minimize or underestimate

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their use of alcohol[22], especially if they know that this might compromise their liver transplant candidacy, although this might not apply to all patients. Another limitation is that patients with AUD and advanced ALD might present with cognitive dysfunction resulting from hepatic encephalopathy[23]. To overcome these problems, biological markers of alcohol consumption have been developed. Biomarkers have been shown to increase sensitivity for detection of alcohol use beyond self-reporting methods[24,25]. On the one hand, indirect markers of alcohol consumption, such as serum levels of γ-glutamyltransferase, mean corpuscular volume, aspartate aminotransferase and carbohydrate-deficient transferrin, have low specificity[26]. Conversely, direct markers of alcohol metabolism, such as ethyl glucuronide (EtG), ethyl sulfate (EtS) and phosphatidylethanol (PEth), offer higher specificity. EtG and EtS are non-volatile, water-soluble metabolites formed during the elimination of ethanol. They can be detectable in urine up to 90 h after alcohol ingestion, with negligible influence, if any, in patients with liver disease[25,26]. The window for alcohol detection is usually 4–5 days in urine, with a reported sensitivity of 62–89% and specificity of 93–99%[25,26]. These alcohol metabolites can also be found in hair, which is a very specific marker of long-term alcohol use. PEth is a phospholipid formed only in the presence of alcohol and can be identified in whole-blood samples. Its presence indicates alcohol consumption in the last 28 days, with a reported sensitivity of 90–99% and specificity of 100%[27] (TABLE 1). In any case, there is not a single reliable test that alone can define alcohol as a cause of liver disease; indeed, alcohol can coexist with other causes of liver disease and general screening has been suggested. It is important to consider that the sensitivity, specificity and reference values of alcohol-related biomarkers might be affected by the clinical population under study (for example, healthy individuals, patients with AUD, patients with AUD and ALD, patients with concurrent liver diseases such as non-alcoholic fatty liver disease (NAFLD)) as well as by many other factors such as age, lifestyle and concomitant chronic diseases, to name just a few[28].

Selection and timing for referral

Patients with AUD are often referred for liver transplantation evaluation after they develop features of hepatic decompensation (that is, ascites, hepatic encephalopathy, jaundice or variceal bleeding) or are sometimes managed palliatively without consideration of the transplant care pathway. It is not infrequent that the patient first learns of therapeutic options for AUD during the liver transplantation evaluation process. This observation highlights the importance of screening and early diagnosis, including the critical need to increase awareness among primary care and gastroenterology providers about referring patients to addiction and hepatology care once AUD is diagnosed and prior to development of alcohol-related hepatic decompensation.

Transplant centres tend to offer the otherwise eligible patients with ALD listing after 6 months or sometimes 3 months of abstinence, during which completion of behavioural therapy for AUD is mandated. Although

Table 1 | **Available methods for detecting alcohol consumption in patients with ALD**

Method	Population tested	Pros	Cons
Self-report, clinical interviews, questionnaires[12–19,21,22]	General population and ALD at all stages	Inexpensive and quick; it can be combined and validated with other biomarkers	Low accuracy in many clinical settings
Serum markers (ALT, AST, GGT and MCV)[25,126,127]	General population, ALD at all stages and patients with AUD	Inexpensive and readily available; AST to ALT ratio is a good indicator of chronic excessive alcohol use	Results are non-specific; many sources of false-positives, especially with advanced liver disease
Breath samples (for example, breathalysers or passive alcohol sensors)[127,128]	General population and patients with AUD	Accurate and rapid results	Only detects acute intoxication; sensitive to temperature and breathing pattern
Alcohol levels in saliva[129]	Patients with AUD	Inexpensive and quick	Cannot always predict blood alcohol content
Serum levels of ethanol or methanol[127,130,131]	General population, ALD and patients with AUD	Gold standard for detecting acute alcohol consumption	Rapid elimination in chronic heavy drinkers; quality of laboratory procedures influences results
Serum levels of CDT[25,126,132]	ALD pre-LT and post-LT and patients with AUD	Rare false positives; good indicator of relapse	Reflects more extended heavy drinking
Urine levels of EtG or EtS[25,26,133]	ALD pre-LT and post-LT	Results are easily determined; EtG: inexpensive, longer detection window than for ethanol	Short detection window compared to PEth
Hair testing (EtG or FAEE)[134,135]	General population, patients with AUD	Very specific marker of long-term alcohol use	Expensive; not widely available; collection can be difficult
Serum PEth[24,25,27,136]	ALD pre-LT and post-LT	Very specific; easy to collect; detect longer period of time than EtG or EtS	Expensive; not widely available
Transdermal sensors[137–139]	Patients with AUD	Allows continuous monitoring; tamper-resistant	Not clinically validated; expensive; technical difficulties

ALD, alcohol-associated liver disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUD, alcohol use disorder; CDT, carbohydrate-deficient transferrin; EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEE, fatty acid ethyl esters; GGT, γ-glutamyl transpeptidase; LT, liver transplantation; MCV, mean corpuscular volume; PEth, phosphatidyl ethanol. Adapted from REF.[140], Springer Nature Limited.

this approach might be feasible in patients with alcohol-associated decompensated cirrhosis or patients with hepatocellular carcinoma (HCC) due to ALD, patients with severe acute alcohol-associated hepatitis represent a challenge to this approach when survival for 3 or 6 months is not expected, and urgent liver transplantation is needed. Under these circumstances, some programmes contract with the patient to undergo AUD therapy after transplantation, whereas others might not offer transplantation for these patients. However, data demonstrate that patients with alcohol-associated hepatitis whose clinical and psychosocial profiles are otherwise favourable have a low risk of post-transplantation relapse to harmful drinking (<20%), which is comparable to that of patients who underwent pre-transplantation abstinence and AUD therapy. However, data about long-term relapse risk in alcohol-associated hepatitis are lacking[29,30].

Proposal of definition of alcohol relapse

The first step to improving care in patients with ALD is to have a consensus definition of relapse. This definition would have an effect on patient care and on the design of future studies. Issues surrounding definition and diagnosis of relapse to drinking are somewhat intertwined because the methods for diagnosing relapse might differ depending on which definition is used. Relapse is a preferable term to recidivism. Recidivism is used in the criminal justice system, and contributes to the social stigma of the disease[31]. Notably, relapse to drinking is not the same as relapse to AUD itself, as relapse to drinking involves frequency and quantity of alcohol consumption, whereas relapse to AUD or recurrence of AUD involves re-developing clinical and behavioural features that meet the diagnostic criteria for AUD[2].

Definitions of relapse vary widely, ranging from any deviation from abstinence from alcohol to consequences of drinking such as alcohol-related readmission to hospital or physical, social and legal consequences. Although lack of abstinence is the most commonly used definition because of the emphasis placed on the recommendation to completely refrain from alcohol, there is no evidence that mild relapse (defined as occasional 'slips') is associated with effect on the graft or patient survival[32]. On the other hand, AUD is characterized by impaired control over alcohol drinking, and, therefore, any alcohol consumption could trigger alcohol-seeking conduct and hazardous drinking[33]. A prospective study of 724 undergraduates and adolescents found that 'controlled' drinking cannot be sustained for long periods (more than 3 years) without the patient returning to excessive alcohol use[33].

We propose a three-level definition of relapse: (1) mild relapse (occasional 'slips', less than once per month); (2) moderate relapse (continuous drinking, at daily and weekly doses within recommended standards of the National Institute on Alcohol Abuse and Alcoholism (NIAAA)[3,34]: ≤4 drinks per day for men, ≤3 drinks per day for women; and ≤14 drinks per week for men, and ≤7 drinks per week for women); and (3) severe relapse (regular use above recommended standards of the NIAAA or with associated morbidity or mortality, which includes alcohol-related pancreatitis, acute alcohol-associated hepatitis, graft loss or other medical problems directly associated with return to drinking). Our proposed approach for relapse reflects the opinion of the authors, but reaching consensus definitions for relapse and other outcomes is needed to move the field forward and improve research and patient care in ALD.

To better inform clinical care, future studies and end point selection, this relapse definition should be complemented with objective assessment of alcohol consumption given the advent of biomarkers whose reliability is independent of the presence of liver disease such as PEth and ethyl glucuronide. The design of prospective studies in patients with ALD before and after transplantation utilizing these definitions in conjunction with objective data might aid in establishing reproducible relapse risk prediction models. Studies in AUD and ALD after liver transplantation should consider the assessment of interventions based on validated end points, including a clear widespread universal definition of relapse and, ideally, biomarkers reliably evaluating outcomes of clinical trials regarding behavioural therapy and pharmacotherapy in patients with ALD. Such approach can ultimately optimize transplant candidate selection and guide the offering of effective interventions to enhance transplant candidacy and prevent post-transplantation AUD. It is important to emphasize that patients with severe ALD are particularly sensitive to any amount of alcohol and that in this population a reduction in the number of heavy drinking episodes might not be sufficient to modify the natural course of the disease and to reduce mortality. In other alcohol-related diseases, such as alcohol-associated myopathy, controlled drinking is less harmful than heavy drinking[35]. However, in patients with ALD any drinking can be deleterious[36]. It is possible that reducing the episodes of heavy drinking would be a valuable end point in patients with early stages of ALD (that is, no advanced fibrosis or cirrhosis). However, any drinking in patients with liver-related decompensation and/or alcohol-associated hepatitis and even in patients with compensated cirrhosis should be considered deleterious. For this reason, most international guidelines on ALD recommend complete abstinence[37–39]. Unfortunately, there have been few well-designed studies of interventions that aim to improve the outcomes in patients with AUD after liver transplantation[40].

Post-transplantation relapse

Predictors of relapse: risk stratification

Liver transplantation is the preferred treatment and the standard therapy for patients with end-stage liver disease[41]. Reluctance to perform transplantation in patients with ALD can be based on the stigma associated with AUD and concerns about possibly resuming alcohol use after liver transplantation[42,43], despite the current scientific evidence that AUD is a medical problem[44]. To select the most appropriate patients with advanced ALD for liver transplantation, most programmes globally require a 6-month abstinence period before patients can be considered. Nevertheless, data regarding the 6-month rule as a predictor of long-term sobriety are

controversial[45]. Moreover, early liver transplantation has been shown to improve survival in patients who have a first episode of severe alcohol-associated hepatitis but who do not respond to medical therapy[46,47].

The magnitude of post-transplantation alcohol relapse is an issue of concern. Reported post-transplant alcohol relapse rates in recipients with ALD range from 15% to 50%[48–51]. A prospective study[48] of 167 patients found that 42% of the individuals included in the cohort had taken at least one drink by the end of 4.5 years after transplantation, and 26% had engaged in binge drinking. Whereas another study of 118 adults who underwent liver transplantation found that, among their cohort, 34% relapsed to some degree of alcohol use, with a mean post-transplant follow-up duration of 55 months[52]. In a controlled study from Sweden, 'structured management' was shown to substantially reduce relapse in a cohort of 103 patients with ALD from 48% to 22% after a 5-year follow-up. Their pre-transplantation process included an interview by a psychiatrist and AUD treatment based on 12 steps[53]. Another study found similar results, with a 19% relapse rate with a mean follow-up time of 7.4 years. Pre-transplantation abstinence for 6 months was mandated for listing, although the study did not otherwise specify candidate involvement in AUD treatment interventions or Alcoholics Anonymous[32]. A study from the USA found that, at 5 years after transplantation, 16.3% and 8.2% had relapsed to any alcohol use and to high-dose drinking, respectively[54]. The correct identification of risk factors of post-transplantation alcohol relapse is important to the appropriate stratification of risk of relapse in candidates undergoing evaluation for liver transplantation.

Multiple studies have investigated associations between demographic and clinical factors and post-transplantation relapse. These studies have shown that younger age, poor social support, family history of AUD, history of previous treatment for AUD, shorter length of pre-transplantation abstinence, smoking, comorbid mental health and/or substance use disorders, and non-compliance with clinic visits all affect post-transplantation relapse risk[48,49,55]. A study[54] from a large North American centre found that the main risk factors for post-transplantation relapse were diagnosis of depression after transplantation (HR 3.1), smoking within the previous 6 months prior to transplantation (HR 3.8), age (older age is protective (HR 0.6 per 10-year increase)) and steatohepatitis (in explant, HR 3.6). Smoking during the 6 months before transplantation was associated with any relapse (HR 3.8) and high-dose relapse (HR 10.2), and smoking at the time of transplantation was associated with death ($P=0.001$). High-dose relapse (defined as drinking above the NIAAA recommended standards[34]) was associated with death (HR 3.5, $P<0.0001$)[54]. These data suggest that psychiatric assessment and AUD treatment might be critical factors in lowering the post-transplantation relapse rate. A meta-analysis[56] aimed to identify risk factors of alcohol relapse after liver transplantation. The authors defined relapse as any amount of consumption after transplantation, and heavy relapse as consumption associated with harmful consequences. Considering 8,000 patients from 92 studies the authors showed that relapse rate and heavy relapse rate after liver transplantation were 22% and 14%, respectively, during the mean follow-up time of 48.4 months. Psychiatric comorbidities (OR 3.46), pre-transplantation abstinence of less than 6 months (OR 2.76), unmarried status (OR 1.84) and smoking (OR 1.72) were predictive of relapse after liver transplantation. However, the researchers noted publication bias with unpublished negative studies and high heterogeneity of results. Monitoring of psychiatric comorbidities, and pre-transplantation alcohol abstinence for at least 6 months might decrease the risk of alcohol relapse after liver transplantation[56].

In the context of acute alcohol-associated hepatitis, a study including 142 patients with biopsy-proven alcohol-associated hepatitis who survived the first episode, with an overall mortality of 38% and a median follow-up of 55 months, found that 30% of patients had complete abstinence, which was associated with better long-term survival (HR 0.53). Older age and lack of past AUD treatments were independently associated with complete abstinence during follow-up, and might be useful to differentiate between a low risk and high risk of relapse[36].

Currently, there are efforts to develop prediction tools to identify patients before transplantation with a low risk of sustained alcohol use after transplantation to inform selection of candidates for early liver transplantation for acute alcohol-associated hepatitis. The Sustained Alcohol Use Post-Liver Transplant (SALT) score (range 0–11) includes >10 drinks per day at initial hospitalization (+4 points), multiple prior rehabilitation attempts (+4 points), prior alcohol-related legal issues (+2 points) and prior illicit substance use (+1 point). In a retrospective study, the *C* statistic was 0.76. A SALT score of ≥5 had a 25% positive predictive value and a score of <5 had a 95% negative predictive value for sustained alcohol use after liver transplantation[57].

Even after meeting centre-specific criteria for transplant listing, the aforementioned demographic and clinical risk factors for relapse should still be taken into consideration when formulating the AUD care plan in these patients. It might be reasonable to consider an intensified therapeutic approach consisting of behavioural therapy and prolonged pharmacotherapy for high-risk patients, especially in view of the reassuring safety profile of most of the pharmaceutical agents before and after transplantation.

Effect of relapse on outcomes

After liver transplantation, the return to heavy alcohol use is associated with worse outcomes including graft injury, graft loss and death[32,55,58–60]. Given the worldwide organ shortage, which results daily in the death of those on liver transplant waiting lists, the allocation of organs to candidates with higher risk of post-transplantation alcohol relapse presents an ongoing clinical and ethical concern. On the one hand, epidemiological studies have shown that the long-term prognosis in patients with ALD depends on abstinence[61]. On the other hand, the overall survival rate of patients transplanted for ALD is 79% at 5 years, which is comparable to or higher than

the survival rates of patients transplanted for other aetiologies[62]. Notably, the progressive allograft fibrosis found in studies among patients with ALD and chronic HCV infection in the era before direct-acting antiviral agents probably reflected HCV recurrence rather than relapse of AUD[32,63].

Distinction of the type of alcohol use relapse is clinically relevant. For example, whereas mild relapse (occasional 'slips') is not associated with effects on graft survival, moderate relapse (continuous drinking) increases the risk of advanced fibrosis and graft injury, and severe relapse (harmful levels of drinking) is associated with early mortality and graft loss[32]. Interestingly, mortality after liver transplantation for ALD is rarely due to recurrent alcohol-associated cirrhosis. A study of 305 liver transplant recipients with underlying ALD found that post-transplantation mortality was mainly related to aerodigestive malignancies, rather than recurrent ALD. In this study, only 3% of deaths were related to alcohol-related allograft cirrhosis after liver transplantation and only 0.7% of the patients transplanted for ALD died from recurrent ALD[64]. This observation is consistent with those of another study, in which only 1% of deaths were related to alcohol relapse and the majority of deaths were attributed to cancer[65]. In a study from the USA in 236 patients with cirrhotic-stage ALD who underwent liver transplantation, only 16.3% of them resumed drinking during the first 5 years after transplantation and 22.0% at 10 years. Of those, less than half resumed high-dose drinking, and only 3% of the total cohort had died of alcohol-related causes at the time of study completion. Of note, those who had a high-dose relapse had an increased hazard of death of over threefold ($P < 0.0001$)[54]. In a Swedish cohort[53], deaths in patients who resumed drinking were not directly related to ALD. Although in that study minor relapse did not affect post-transplantation survival, moderate and severe relapse, leading to advanced fibrosis, did. A 2015 study showed that of 1,894 adult liver transplant recipients,<6% developed recurrent alcohol-associated cirrhosis; however, those who developed cirrhosis had a poor prognosis compared with those who did not develop alcohol-related cirrhosis (10-year survival 49.7% vs 69.9%, $P < 0.001$)[66]. Consistently, another study in 54 individuals found no difference in survival up to 5 years between liver transplant recipients who abstained from alcohol versus those who relapsed. However, 10-year survival was significantly worse in those who relapsed and drank >30 g of alcohol per day (45.1% vs 85.5%, $P < 0.01$). Again, mortality was not liver-related, but it was associated with de novo malignancy and cardiovascular events[58]. In summary, long-term survival mortality after liver transplantation in patients with ALD seems to be related to cardiovascular disease and malignancy rather than recurrent ALD.

Another important issue is the fact that alcohol relapse might lead to reduced compliance with medications and office visits, leading to significantly increased rates of graft rejection[67–69]. In a study in France there was no significant difference in graft rejection between those who were abstinent, occasional drinkers or heavy drinkers; the rejection episodes observed in the heavy drinker category were related to poor compliance with immunosuppressant medications[68]. Thus, alcohol relapse after liver transplantation might be associated with non-adherence to medications and might therefore predict graft rejection. Although graft loss due to rejection is uncommon nowadays, rejection is associated with increased risk of advanced allograft fibrosis[58,59].

Another study showed that any alcohol relapse increased the risk of graft failure, but upon sub-analysis by drinking pattern, a single slip or intermittent relapse was not associated with graft failure, but continuous heavy drinking was significantly associated with allograft loss (HR 2.57, $P = 0.006$). On liver biopsy, significant steatosis (OR 3.46, $P = 0.01$), steatohepatitis (OR 6.2, $P = 0.006$) and advanced fibrosis (stage 3 or higher; OR 23.18, $P = 0.003$) were associated with alcohol relapse. In this study, of 300 patients, 20.8% had a single relapse event (slip), 45.8% intermittent relapses and 33.3% continuous heavy drinking[67]. Steatotic changes and pericellular fibrosis are the most relevant histological signs of heavy alcohol intake[63]; however, these are commonly found even in the context of NASH related to post-transplantation metabolic syndrome and type 2 diabetes mellitus[70,71]. To this end, actions need to be taken to avoid relapse and the other consequences of heavy alcohol consumption (for example, cancer development and cardiovascular disease), similar to the actions needed for obesity in patients with NASH, starting the screening early after liver transplantation. Finally, it is important to highlight that severe psychiatric comorbidities (for example, depression, post-traumatic stress disorder and chronic pain) can also increase the likelihood of mortality after liver transplantation, including suicide-related mortality[72].

In summary, it is key to identify patients who are at high risk of relapse by multidisciplinary evaluation of risk factors, aiming to intervene early both before and after transplantation to prevent or at least mitigate the effects of alcohol relapse after liver transplantation. This aim is especially important in the context of the ethical dilemma of prioritization of graft use to patients who need it most and have the potential to maintain it for longest. Examples of patients with ALD for whom this ethical dilemma is relevant include patients who require early liver transplantation for severe acute alcohol-associated hepatitis or patients who are actively consuming alcohol at the time of transplantation and/or re-transplantation in the setting of allograft ALD. The precise criteria used by each centre to accept adding a patient to the waiting list largely depends on local factors and policies. If a patient has multiple high-risk criteria that predict a poor outcome despite the implementation of available multimodal interventions or have not followed and/or failed interventions to treat AUD, liver transplantation might be precluded.

Behavioural therapy

Behavioural therapy has been the mainstay of AUD treatment in liver transplant candidates and recipients. Most liver transplant programmes mandate completion of intensive outpatient behavioural therapy followed by regular attendance in Alcoholics Anonymous meetings

prior to listing. The concept of intensive therapy resembles that of induction therapy used in autoimmune hepatitis or in the immediate post-transplantation setting, and Alcoholics Anonymous mirrors the maintenance therapy needed afterwards. The length of intensive outpatient behavioural therapy and behavioural modalities included in it are determined by the addiction specialist on the basis of the severity of AUD, patient's insight, and concurrent psychiatric illness. These modalities can include cognitive behavioural therapy (CBT), which involves addressing drinking triggers, enhancing coping skills and utilizing non-drinking activities to prevent relapse. Motivational enhancement therapy (MET), another behavioural treatment modality, is focused on stimulating the patient's own motivation for change and encouraging this change over time. A commonly used behavioural therapy approach is mutual support that utilizes in-person social networking to promote a sober environment, for example Alcoholics Anonymous. Limited data on the utility of these different modalities in patients with chronic liver disease and liver transplant recipients exist. A randomized controlled trial (RCT) in 91 patients with ALD awaiting liver transplantation demonstrated that the MET group (46 patients) had fewer drinks per drinking day compared with controls (45 patients) observed for up to 96 weeks (3.5 vs 4.3 drinks, $P = 0.03$)[73]. Patients in the MET group received seven sessions over 6 months with an encouragement to attend Alcoholics Anonymous meetings, and patients in the control group were referred to community Alcoholics Anonymous meetings and MET-free intensive outpatient therapy. A systematic review evaluated the effect of various modalities of behavioural therapy, supportive care and psychoeducation on inducing abstinence in patients with AUD with chronic liver disease. Interestingly, it found that a combination of CBT, MET and comprehensive medical care was the only intervention that significantly increased induction of abstinence (74% in the intervention group vs 48% in the control group, who underwent different modalities of psychotherapy, pharmacotherapy or standard of care; $P = 0.02$)[74]. Furthermore, it found that an integrative approach with CBT and medical care reduced drinking relapse.

Pharmacotherapy for AUD

In 2018, the American Psychiatric Association (APA) issued new guidelines for the treatment of AUD[75], which are the most recent guidelines issued by a psychiatric society to address AUD. These guidelines discuss five pharmacological agents, of which three had been approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for the treatment of AUD. In addition to discussing these five medications, in this section we also discuss baclofen which, to the best of our knowledge, has been the only pharmacotherapy for AUD formally studied via RCTs in patients with ALD. The utility of these agents in patients with cirrhotic-stage ALD (that is, pre-transplantation settings) and in liver transplant recipients, including their interactions with commonly used immunosuppressive medications, is summarized in TABLE 2.

Table 2 | **Pharmacotherapy agents for AUD in patients with ALD and cirrhosis and liver transplant recipients**

Medication	FDA/EMA-approved	APA recommendation	Dose	Use in advanced liver disease	Interaction with post-transplant immunosuppressants	Hepatotoxicity	Use in renal impairment[a]	Common adverse effects
Naltrexone[75,78,79,82]	Yes	First line	50 mg daily oral, 380 mg monthly, IM	Avoid in Child-Pugh class C	None	Possible	Allowed	Diarrhoea, nausea, somnolence
Acamprosate[79,87–90]	Yes	First line	666 mg three times a day, oral	Allowed	None	None	Reduce dose if Cr Cl 30–50 ml/min/1.73 m^2, avoid if Cr Cl <3 ml/min/1.73 m^2	Diarrhoea
Topiramate[b] (REFS[79,92–94])	No	Second line	Initially 25 mg daily, titrated up to 150 mg twice a day, oral	Allowed	None	Possible, if used with valproate-based medication	Reduce dose if Cr Cl <70 ml/min/1.73 m^2	Paraesthesia, altered taste, anorexia, difficulty concentrating
Baclofen[76,79,95–102,104]	No	NA	10–30 mg three times a day, oral	Allowed	None	None	Reduce dose	Fatigue, sleepiness, and dry mouth
Gabapentin[79,105,106,108,109]	No	Second line	300–600 mg three times a day, oral	Allowed	None	Possible (in case reports)	Reduce dose if Cr Cl <60 ml/min/1.73 m^2	Fatigue, headache, insomnia
Varenicline[112]	No	NA	1 mg two times a day, oral	Allowed	None	Possible (in case reports)	Reduce dose if Cr Cl <30 ml/min/1.73 m^2	Fatigue, nausea, somnolence

APA, American Psychiatric Association; Cr Cl, creatinine clearance; IM, intramuscular; NA, not available. [a]Based on manufacturer's recommendation. [b]Topiramate should be avoided in patients with hepatic encephalopathy.

Medications approved by the FDA/EMA

Disulfiram. Disulfiram is an alcohol-sensitizing medication that alters the patient's response to alcohol, making it an unpleasant and aversive experience. It works via non-reversible inhibition of aldehyde dehydrogenase, which oxidizes acetaldehyde into acetic acid. Disulfiram is hepatically eliminated and has been associated with severe hepatotoxicity[76] and, therefore, its use in patients with advanced liver disease is not recommended[77].

Naltrexone. Naltrexone is an opioid receptor antagonist that reduces alcohol drinking and craving, thereby improving AUD outcomes. One of its mechanisms of action might be related to the ability of naltrexone to reduce central dopamine release via blockade of the opioid receptor, which in turn might reduce the rewarding and pleasurable effects of alcohol. Naltrexone is one of the two first-line agents recommended by the APA for treatment of AUD[75]. Naltrexone exists in two formulations: daily oral 50 mg tablet and monthly intramuscular injection of 380 mg. The metabolism, assessed in terms of naltrexone levels after administration, is different in patients with compensated cirrhosis compared with patients with decompensated cirrhosis (that is, Child-Pugh class C)[78]. Therefore, its use is not recommended in the latter group given the presence of severe hepatic dysfunction[75].

With regard to the post-transplantation setting, naltrexone does not have interactions with the immunosuppressants used in these patients such as antimetabolites, calcineurin inhibitors or mTOR inhibitors[79]. The FDA issued a black box warning about possible hepatotoxicity of naltrexone; however, subsequent studies showed that neither the oral nor the intramuscular formulation is associated with a significant elevation in liver enzymes[80,81]. Notably, the LiverTox database assigned naltrexone grade E, which is the lowest likelihood score for drug-induced liver injury (DILI), a score that reflects a suspected, unproven correlation[76]. There is no need for dose adjustment in patients with renal impairment according to the manufacturer's recommendations[79].

The optimal duration of treatment is unknown. In one of the largest RCTs for AUD (the COMBINE study, 1,383 patients, evaluated for up to 1 year after various AUD treatments), naltrexone given for 16 weeks increased the proportion of abstinence days compared with placebo (73.8% vs 80%) and decreased the proportion of patients who returned to one or more heavy drinking days compared with placebo (71.4 vs 68.52%, $P = 0.02$)[82]. The 1-year post-treatment follow-up was notable for persistently decreased rates of heavy drinking in those who received naltrexone. However, other outcomes such as emergency department visits for alcohol treatment were comparable to those in patients receiving placebo. The most common adverse effects in this study among the naltrexone group were diarrhoea, somnolence and nausea. Notably, nalmefene is a related oral compound to naltrexone. Several RCTs have shown the efficacy of nalmefene in reducing heavy drinking in patients with AUD[83,84] and nalmefene was approved by the EMA for the treatment of patients seeking reduction in heavy drinking and daily consumption[85]. However, it is important to note that data about its efficacy in achieving abstinence are limited. Therefore, its utility might be limited in the specific population discussed in this Review, where abstinence is often the goal.

Acamprosate. Acamprosate has shown efficacy in treating AUD, especially in preventing alcohol relapse in already-abstinent patients. Its mechanism of action is not fully understood, but it is likely to act as a glutaminergic antagonist and a γ-aminobutyric acid agonist[86]. It is the other first-line agent recommended by the recent APA guidelines for the treatment of AUD[75]. Acamprosate is formulated in 666 mg tablets taken three times a day. A study in patients with ALD (Child-Pugh class A or B) showed a reassuring safety profile and, although data in patients with Child-Pugh class C are limited[87], the manufacturer's recommendations state that there is no need for dose adjustment in patients with Child-Pugh class C[79].

Acamprosate does not interact with post-transplantation immunosuppressive medications or cause DILI[76,79]. In patients with mild-to-moderate renal insufficiency, the APA recommends against using it as a first-line agent and, if it is eventually used, the dose needs to be decreased to 333 mg three times a day. Its use is contraindicated in patients with severe renal insufficiency (creatinine clearance ≤30 ml/min/1.73 m^2). The most common side effect of acamprosate is diarrhoea.

In a meta-analysis of 15 placebo-controlled studies including 3,309 patients, extending duration of acamprosate had progressive benefit in reducing relapse severity in terms of rates of uncontrolled drinking, from 41% after 30 days of therapy to 33% after 360 days, compared with 53% and 51% for placebo, respectively[88]. However, the COMBINE trial showed no effect on relapse-related outcomes for acamprosate compared with placebo[82,87–89]. Subsequently, a large meta-analysis of 123 studies evaluating >22,000 patients showed that both acamprosate and naltrexone were associated with decreased relapse rates with the number needed to treat (NNT) to prevent relapse being 12 and 20 for acamprosate and naltrexone, respectively[90]. The variability in results between different studies might be attributed to different patient characteristics and study designs.

Medications not approved by the FDA/EMA

Topiramate. Topiramate is an FDA-approved anticonvulsant that works via glutamate antagonism in addition to GABA agonistic activity. These effects on neurotransmission are believed to be the mechanism by which topiramate favourably affects AUD. The APA recommend its use in moderate to severe AUD when there is intolerance or suboptimal response to first-line medications (that is, naltrexone and acamprosate) or if the patient prefers its use over others on the basis of an informed discussion with the prescribing provider[75]. Topiramate is also a recommended treatment for AUD in the US Department of Veterans Affairs guidelines[91]. Its complex administration might affect compliance: the initial dose is 25 mg daily, to be titrated up to 150 mg twice daily over several weeks[92]. No dose adjustments are needed for hepatic dysfunction according to the manufacturer's recommendations[79].

Topiramate does not interact with any immunosuppression medications[79]. It has an indirect effect on liver toxicity as it is metabolized by cytochrome P3A4; thus, it increases the level of valproate and other anticonvulsants that might cause liver injury[76]. Creatinine clearance <70 ml/min/1.73 m^2 warrants dose reduction to 50%, while being on haemodialysis requires a twice daily dose of 50–100 mg combined with supplemental dose (50 to 100 mg) after dialysis given drug clearance by haemodialysis[79].

In an RCT (n = 150 patients with AUD), topiramate given for 12 weeks increased days of abstinence by 26.2% and decreased heavy drinking days by 27.6% compared with placebo (P = 0.0003)[92]. The most common adverse effects were paraesthesia, altered taste, anorexia and difficulty concentrating, which can conceivably be masking hepatic encephalopathy[92]. Notably, in another study, this benefit in reducing heavy drinking was shown to be exclusive to patients who are homozygous to a single nucleotide polymorphism (rs2832407) in *GRIK1*, which encodes the glutamate receptor ionotropic, kainate 1 (REFS[93,94]). Notably, a large meta-analysis (22,803 patients) showed that although patients on naltrexone were at increased risk of withdrawal from clinical trials due to severity of adverse effects, patients on topiramate or acamprosate were not at increased risk compared with those on placebo[90].

Baclofen. Baclofen is a GABA-B agonist approved by the FDA for the treatment of muscle spasticity, but data have emerged over the past two decades about its potential efficacy in AUD[95]. In 2018, baclofen up to 80 mg/day was approved for the treatment of AUD in France. The most-studied dose for AUD seems to be 10 mg three times a day; however, some studies have also investigated its use in different regimens, including 25 mg three times a day, 20 mg four times a day and 30 mg three times a day. There is no need for dose adjustment in patients with cirrhosis[79], and no interactions with immunosuppressive medications have been reported[79]. DILI is rare, mild and self-limiting in patients receiving baclofen, although it was not observed in the clinical trials in patients during chronic therapy[76]. Dose adjustment is recommended in patients with renal insufficiency[79].

An RCT enrolled 84 patients with cirrhotic-stage ALD, half of whom were randomized to baclofen for 12 weeks, and showed that abstinence while on baclofen was achieved in 71% of patients compared with 29% of those on placebo. Baclofen was well tolerated in the study[96]. This relapse-prevention benefit was confirmed in an RCT in 104 patients, some of whom had ALD with or without cirrhosis, conducted in Australia[97]. However, another RCT in 168 veterans with concomitant chronic hepatitis C infection and AUD did not demonstrate benefits of baclofen 30 mg taken for 12 weeks[98]; however, this study was characterized by low levels of baseline drinking and of AUD severity. Moreover, a multicentre RCT that randomized 151 patients with AUD to high-dose baclofen, low-dose baclofen or placebo showed no benefit of baclofen over placebo[99]. Dose-related adverse effects were fatigue, sleepiness and dry mouth. Given these results and others[100,101], the APA elected not to endorse baclofen for the treatment of AUD in their 2018 guidelines. However, baclofen

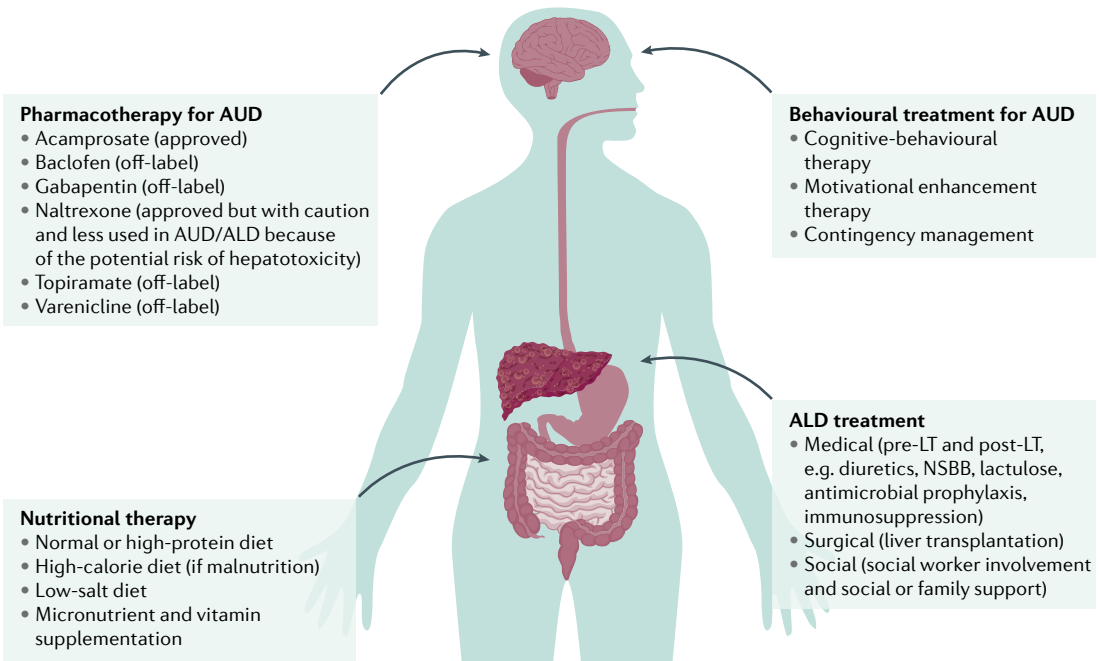

Fig. 1 | **Patient-centred integrative care model for AUD in patients with ALD with cirrhosis (transplant candidates) and liver transplant recipients.** The figure illustrates the core contents of the multidisciplinary, multimodality approach to the management of alcohol use disorder (AUD) in patients with alcohol-associated liver disease (ALD) in the setting of cirrhotic-stage disease and after liver transplantation. The application of the various modalities listed will need to be personalized based on a patient's clinical and psychosocial characteristics. LT, liver transplantation; NSBB, non-selective β-blocker.

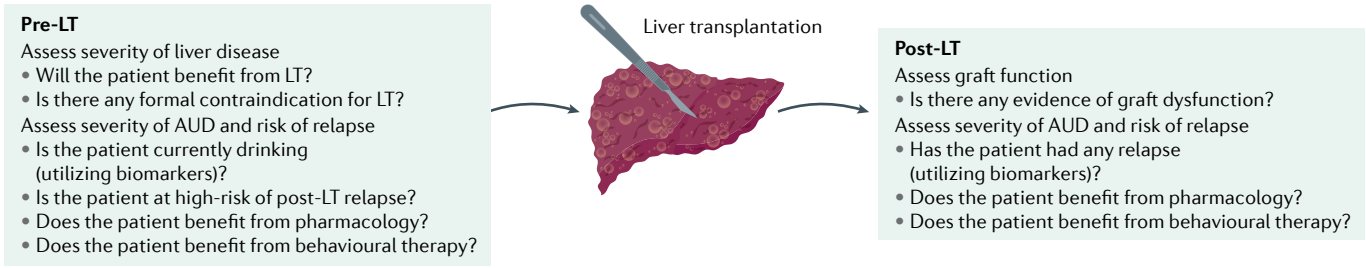

Fig. 2 | **Considerations in the integrative care model for AUD.** Key questions to address while providing integrative care for alcohol use disorder (AUD) in patients with alcohol-associated liver disease (ALD) with cirrhosis (transplant candidates) and liver transplant (LT) recipients.

represents the only pharmacotherapy for AUD formally investigated in patients with severe ALD, and the potential use of baclofen in this specific population was considered in 2018 American College of Gastroenterology guidelines[102]. Nonetheless, in addition to the ongoing debate about its efficacy, attention should be paid to retrospective data showing events of life-threatening overuse in patients on baclofen for AUD — it is noteworthy that most overuse events were in the setting of suicide attempts[103], which are known to be more common in patients with AUD than in those without AUD[104].

Gabapentin. Gabapentin is a calcium channel or GABA neurotransmission modulator that is approved by the FDA for the treatment of epilepsy and for neuropathic pain[105]. The dose shown to have benefit in AUD is 300–600 mg three times a day[106]. The APA recommends gabapentin in patients who prefer using it and those who fail or cannot tolerate first-line therapy. There are no dose adjustments needed for patients with impaired hepatic function[79]. However, dose adjustments are recommended if creatinine clearance is <60 ml/min[79]. Gabapentin does not have any interaction with antimetabolites, calcineurin inhibitors or mTOR inhibitors. Association with mild-to-moderate reversible cholestatic liver injury (within 8 weeks of initiation) has been described in case reports[76], but a causal relationship could not be established. This association has not been observed in a clinical trial setting[76,107].

Following initial promising findings from a proof-of-concept human laboratory study[108], a RCT in 150 patients with AUD compared gabapentin 600 mg three times a day, gabapentin 300 mg three times a day and placebo for 12 weeks, and showed sustained abstinence during the study period in 17%, 11.1% and 4.1% in the three study groups, respectively[106]. The NNT to prevent relapse with gabapentin 600 mg three times a day was 8. Avoidance of heavy drinking was observed in 44.7% of the high-dose gabapentin group, in 29.6% of the low-dose gabapentin group and in 22.5% of the placebo group ($P = 0.02$ for linear dose effect; NNT = 5 for the 1,800 mg per day dose). These benefits were also observed in patients who completed a 24-week post-treatment follow-up. Common adverse effects (for example, fatigue and headache) and study completion rates were not different between the study groups. In a 2020 RCT in 145 treatment-seeking individuals with AUD who were randomized for 16 weeks of gabapentin versus placebo after going through severe alcohol withdrawal symptoms at baseline, gabapentin resulted in total abstinence during the study period in 41% of participants as opposed to 1% in the placebo arm[109]. The NNT was 2.7. In patients with minimal alcohol withdrawal symptoms at baseline, there were no significant differences in outcomes between gabapentin and placebo. Notably, relapse was objectively assessed in this study by measuring carbohydrate-deficient transferrin levels in the blood. Mild to moderate dizziness was more frequently observed in the gabapentin group. Interestingly, another RCT demonstrated no benefit for gabapentin in AUD when used in the extended-release formula, at a lower dose (1,200 mg per day)[110].

In summary, the choice of pharmacological agents should take into consideration compliance profile, medical comorbidities, concurrent psychiatric disorders, interaction with current medications and patient preference based on discussions of adverse effects profiles. Although gabapentin seems to be a potential frontrunner in terms of efficacy and safety, especially in patients with severe withdrawal symptoms at baseline, clinical trials in patients with ALD and liver transplant recipients are needed. Baclofen results are promising, especially in the context of patients with higher severity of alcohol dependence[111], including those with more advanced ALD; however, other RCTs have not confirmed its efficacy in AUD, and larger RCTs to further demonstrate its efficacy, or lack of efficacy, in AUD have not been performed. Naltrexone should be avoided in patients with decompensated ALD but can be considered after liver transplantation, with monitoring of liver enzymes given possible liver injury. Naltrexone is the only once-daily relapse-prevention medication, which underlines its utility in patients whose compliance is in question. Acamprosate seems to be safe in patients with hepatic dysfunction and in liver transplant recipients; however, renal dysfunction, especially when severe (which is not uncommon in these patients), limits its use (or at least a dose adjustment is needed). Given the relative commonality of concurrent hepatitis C infection and/or HCC in this patient population, it is important to note that these pharmacotherapies for AUD do not have known interactions with direct-acting antivirals or commonly used systemic therapies for HCC, such as sorafenib, lenvatinib, nivolumab or the combination of bevacizumab plus atezolizumab. Overall, more studies are needed on AUD pharmacotherapy in patients with ALD.

Emerging pharmacotherapies

The future might bring more medications to the forefront of treating AUD. For example, an RCT showed that varenicline, an FDA-approved smoking cessation medication, decreased heavy and non-heavy alcohol drinking days, and increased smoking abstinence, compared with placebo[112]. It neither requires adjustment in patients with liver disease nor has known interactions with immunosuppressive medications. It does, however, require renal adjustment in patients with advanced kidney disease[113]. It might in the near future become a commonly prescribed medication in patients with dual substance use disorders (that is, alcohol and tobacco). In addition, a preliminary RCT showed that pregabalin, an anticonvulsant and anxiolytic medication used to treat epilepsy, neuropathic pain, fibromyalgia and generalized anxiety disorder, can be effective in the induction of remission and relapse prevention in patients with alcohol dependence[114], but more data are certainly needed. Other promising emerging pharmacotherapies for AUD include, among others, ondansetron and prazosin or doxazosin[115], but are not reviewed here owing to space limitations (for a review, see REF.[115]).

Behavioural and pharmacological therapy

Although active participation in behavioural therapy is a prerequisite for listing in all transplant programmes for patients with cirrhosis and a recent history of AUD, this participation is occasionally limited by multiple barriers, despite patient willingness to undergo therapy. These barriers can include the recurrent hospitalizations due to decompensated liver disease, limited meaningful engagement due to the cognitive impairment resulting from hepatic encephalopathy, logistical barriers to attendance (for example, hepatic encephalopathy-related inability to drive to the frequent therapy sessions), or physical inability to attend due to debilitating volume overload secondary to ascites and/or hepatic hydrothorax. The presence of any of these barriers usually prompts consideration of deferring behavioural therapy to post-transplantation settings, about which different programmes have different stances. Pharmacotherapy might be a reasonable bridging therapy in some patients while they are awaiting transplantation, and then while attending and completing post-transplantation psychotherapy. However, the effect of addiction treatments has been demonstrated to be stronger when clinicians combine psychosocial and behavioural interventions with pharmacological approaches[116]. Severe alcohol-associated hepatitis, when otherwise eligible for transplant, is another clinical scenario in which completion of behavioural therapy might not be feasible before liver transplantation, and addition of pharmacotherapy can be of utility until the patient is able to undergo behavioural therapy, even after liver transplantation. Furthermore, it might be the case that pharmacotherapy has an additional relapse-prevention benefit in patients with ALD who are able to complete behavioural therapy before liver transplantation. Studies are needed to explore the utility of combining pharmacotherapy with psychotherapy, especially in patients with a high risk of relapse with ALD and liver transplant recipients. Despite the lack of strong evidence of the usefulness of different therapeutic modalities in patients with ALD, most centres require that patients receive some kind of behavioural therapy in the form of counselling prior to being listed and that they continue to receive such therapies while on the waiting list[43]. Apart from patients being evaluated for early liver transplantation for severe alcohol-associated hepatitis, some degree of behavioural therapy should be required to list patients with ALD. This is of special importance in patients with a short period of time of sobriety or with a high risk of relapse. The proposed approach can conceivably be applied to liver transplant recipients without pre-transplant AUD who develop AUD after transplantation. However, data are lacking in this regard.

Box 1 | **Proposals for future studies in patients with ALD and liver transplant recipients with AUD**

1. Establishing relapse risk prediction models based on a new definition of relapse utilizing biomarkers
2. Assessing the utility of different modalities of behavioural therapy in treating post-transplantation relapse
3. Randomized controlled trials evaluating the efficacy of various pharmacotherapeutic agents before and after liver transplantation
4. Evaluating the combination of psychotherapy and pharmacotherapy in these patients
5. Evaluating the effect of newly defined different degrees of relapse on graft and patient survival

ALD, alcohol-associated liver disease; AUD, alcohol use disorder.

Preventing relapse after transplantation

ALD is far more complex than just the management of the complications of cirrhosis. Abstinence is pivotal in the long-term prognosis of ALD[36,117]. So, how do we integrate both hepatology care and addiction care to improve outcomes after liver transplantation? Integrative care models, such as a multidisciplinary ALD clinic, are key to the adequate treatment of these patients[118] (FIG. 1). Frequently, patients with ALD who are looking for care are seen in multiple specialized clinics with poor integration of care, giving piecemeal information to the patient and not broadly seeing the patient's agenda[119]. Patients commonly receive mixed messages from providers about their own tasks, biases and training backgrounds[120]. In this sense, innovation is needed to fill this gap with the development of initiatives such as the multidisciplinary clinical models staffed by cross-trained clinicians. Integrative care models have potential barriers that need to be overcome, such as financial sustainability, logistical complexity, disparities in geography (for example, patients living far from the transplant centre), insurance coverage and alterations in patients' cognitive status that might alarm providers, interrupt psychological interventions owing to an inability to participate in a meaningful way, and complicate the use of pharmacology[118]. This integrative approach can shift the paradigm of pre-transplantation psychiatric care, which has often been limited to non-medical disciplines and largely reliant on community-based intensive outpatient psychotherapy and Alcoholics

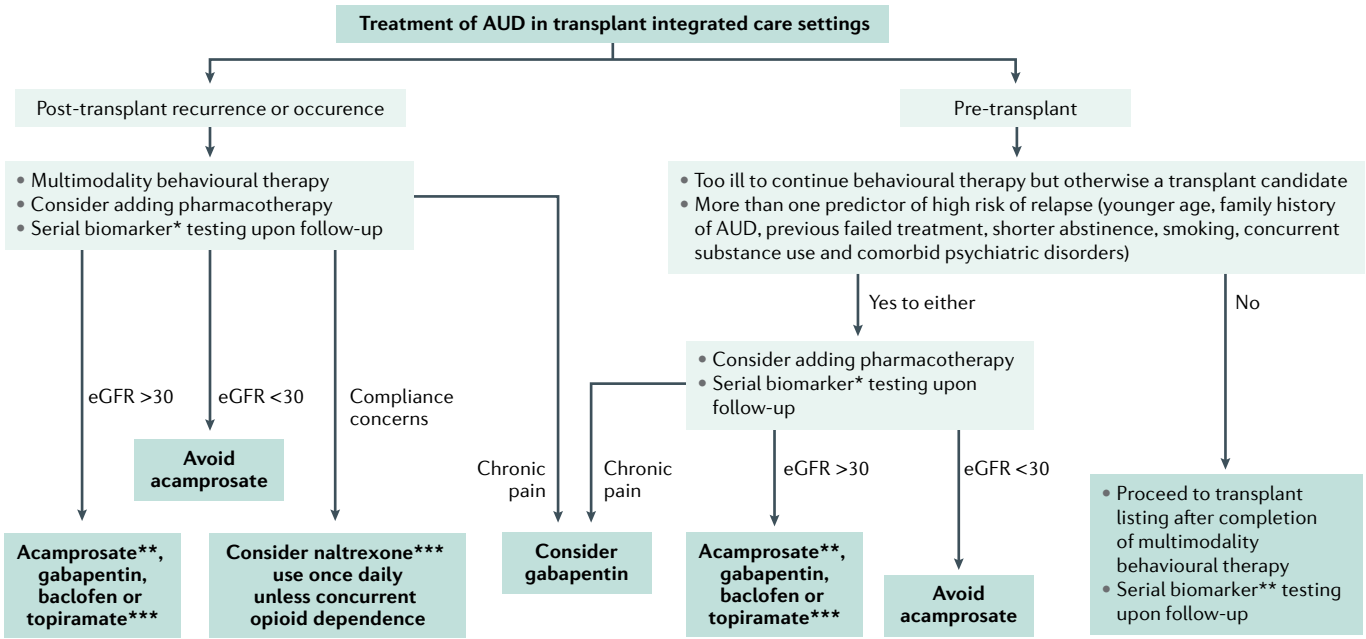

Fig. 3 | **Proposed care pathway for AUD in patients with ALD with cirrhosis (transplant candidates) and liver transplant recipients.** ALD, alcohol-associated liver disease; AUD, alcohol use disorder; eGFR, estimated glomerular filtration rate. *Preferred biomarker is phosphatidyl ethanol (PEth) given its ability to detect moderate to severe alcohol use up to 4 weeks prior. **FDA/EDA-approved medication for AUD. ***Topiramate should be avoided in patients with hepatic encephalopathy. This proposed algorithm has not yet been validated or tested in clinical practice, so further studies are needed to assess its broad use.

Anonymous attendance. The multidisciplinary team approach, together with blood, urine and/or hair tests, enables identification of early recurrences and improves survival after liver transplantation for ALD. In particular, an Italian study among 756 liver transplant recipients, of whom 102 had been diagnosed with AUD, found that the multidisciplinary approach allowed an earlier diagnosis of relapse compared with patients not evaluated by a multidisciplinary team. Additionally, they found a significantly lower mortality in patients evaluated by the multidisciplinary team than in those not assessed by this approach ($P = 0.02$)[121] (FIG. 2). With regard to maintenance of abstinence in the post-transplantation setting, a single-centre observational study in 92 patients with cirrhosis-stage ALD compared post-transplantation relapse (that is, any drinking after transplantation) in patients whose pre-transplant AUD was cared for when addiction specialists were not affiliated with the transplant centre to those who received care after integration of addiction specialists within the transplant centre. The post-transplantation relapse was 16.4% after integration compared with 35.1% before integration ($P = 0.038$)[122]. Alcoholics Anonymous attendance was recommended but not mandatory in the study. Another study showed that receiving AUD therapy in a centre different from the hospital to which the patient is admitted for alcohol-associated hepatitis is associated with an increased risk of alcohol relapse over the long term[123]. These findings emphasize the critical importance of an integrative approach to the care of patients with ALD, whereby they can receive psychiatry care and hepatology care in the same facility[124] (FIG. 1). However, although they are complementary and in need of integration, there needs to be a degree of management independence, when it comes to the decision-making process related to patient care, between hepatology and addiction psychiatry providers to preserve the confidence of patients in both disciplines and to facilitate multidisciplinary decision-making. Telemedicine, which is being revamped by the ongoing COVID-19 pandemic, might provide useful tools for comprehensive management of relapsing AUD in the post-transplantation setting[125]. Further research is needed to assess the effect and feasibility of integrated care clinics in different care settings and regions of the world (BOX 1); however, they have the potential to build multidisciplinary collaborations, stimulate innovation, improve patient care, and thereby move the field forward. FIGURE 3 shows a proposed algorithm for the treatment of AUD in the pre-transplantation and post-transplantation integrative setting. This proposed algorithm has not yet been validated or tested in clinical practice, so further studies are needed to assess its broad use.

Conclusions

A multidisciplinary multimodal integrative approach is critical for the care of patients with ALD and AUD (FIG. 1). Efforts need to be made to identify and treat patients with AUD regardless of their transplant candidacy. Standardized protocols for transplant centres are needed to identify patients before transplantation with a high-risk of relapse after transplantation, not to deny them the possibility of liver transplantation but to offer effective multidisciplinary integrative AUD treatment accordingly, and eventually make them eligible for liver transplantation. However, the ultimate decision on

transplantation must be made based on the overall risk of graft loss and mortality, similar to transplantation for other aetiologies. To this end, post-transplantation relapse needs to be assessed, closely followed, and intervened upon. Offering patients with ALD equal opportunity and access to liver transplantation when success rates are comparable to those for other transplant indications is a key issue to consider in our decision-making process regarding transplantation in this patient population.

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J.P.A. and M.I. researched data for the article, made a substantial contribution to discussion of content, wrote the article, and reviewed/edited the manuscript before submission. L.L., R.B. and V.H.S. made a substantial contribution to discussion of content, wrote the article and reviewed/edited the manuscript before submission.

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Review criteria
PubMed was searched using the terms 'liver transplantation', 'alcoholic liver disease', 'alcohol-associated liver disease', 'alcohol-related liver disease', 'alcoholic cirrhosis', 'alcoholic hepatitis', 'alcohol-associated hepatitis', 'alcohol use disorder' and 'alcohol relapse'. Guidelines were also consulted. Original articles, reviews, editorials and their reference lists were considered. There were no language restrictions. The literature search was performed in December 2020.

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