REVIEW

Alcohol Use Disorder in Alcohol-Associated Liver Disease: A Practical Continuum-of-Care Framework from Screening to Transplantation

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Résumé :
Objectif : Le trouble lié à l'usage d'alcool (TUA) est le principal facteur modifiable de la progression de la maladie du foie liée à l'alcool (MFLA), mais il reste sous-diagnostiqué et sous-traité en hépatologie. Cette revue propose un cadre pratique de continuum de soins visant à intégrer la médecine des addictions dans la prise en charge des MFLA. **Méthodes** : Nous avons réalisé une revue à orientation clinique des lignes directrices internationales, des revues systématiques, des essais contrôlés randomisés, des études de cohorte observationnelles et des revues cliniquement pertinentes publiées en anglais jusqu'en mai 2026. Nous avons effectué des recherches dans PubMed/MEDLINE, la Cochrane Library et les principales bases de données de recommandations des sociétés médicales à l'aide de termes liés à l'ALD, à l'AUD, au sevrage, à la pharmacothérapie de prévention des rechutes, aux biomarqueurs et à la transplantation hépatique. La priorité a été donnée aux recommandations, aux revues systématiques, aux essais randomisés et aux études de cohorte à grande échelle traitant directement de la prise en charge de l'AUD chez les patients atteints d'une maladie hépatique. **Résultats** : L'abstinence durable reste l'objectif pronostique central dans la maladie du foie liée à l'alcool (MFLA). Le dépistage, l'intervention brève et l'orientation active vers des services spécialisés devraient être intégrés dans les protocoles de prise en charge hépatologique. La prise en charge du sevrage nécessite une stratification précoce des risques, une supplémentation en thiamine et le recours préférentiel à des benzodiazépines à métabolisme non oxydatif en cas d'insuffisance hépatique. Pour la prévention des rechutes, les pharmacothérapies peuvent être orientées vers l'abstinence, la réduction de la consommation ou être mixtes/dépendantes du contexte ; dans les cas d'ALD cliniquement significative, le traitement axé sur la réduction de la consommation doit généralement être considéré comme une stratégie transitoire de réduction des risques plutôt que comme un objectif à long terme équivalent. L'acamprosate et le baclofène sont généralement privilégiés chez les patients atteints d'une maladie hépatique, tandis que la naltrexone, le disulfirame et les agents utilisés hors AMM nécessitent une évaluation individualisée des risques et des bénéfices. **Conclusion** : Le traitement de l'AUD doit être considéré comme un élément central de la prise en charge de l'ALD plutôt que comme un complément facultatif. Des modèles intégrés associant l'hépatologie – dont les services de transplantation, l'addictologie, le soutien psychosocial et l'utilisation des biomarqueurs peuvent améliorer l'adhésion au traitement, l'abstinence et les résultats hépatologiques.
Mots clés : trouble lié à la consommation d'alcool ; maladie hépatique d'origine alcoolique ; syndrome de sevrage alcoolique ; baclofène ; acamprosate ; phosphatidyléthanol ; transplantation hépatique ; prise en charge intégrée.

Abstract:
Aim: Alcohol use disorder (AUD) is the principal modifiable driver of alcohol-associated liver disease (ALD) progression, but it remains underdiagnosed and undertreated in hepatology settings. This review proposes a practical continuum-of-care framework for integrating addiction medicine into ALD management. **Methods**: We performed a narrative, clinically oriented review of international guidelines, systematic reviews, randomized controlled trials, observational cohort studies, and clinically relevant reviews published in English through May 2026. PubMed/MEDLINE, the Cochrane Library, and major society guideline repositories were searched using terms related to ALD, AUD, withdrawal, relapse-prevention pharmacotherapy, biomarkers, and liver transplantation. Priority was given to guidelines, systematic reviews, randomized trials, and large cohort studies directly addressing AUD management in patients with liver disease. **Results**: Sustained abstinence remains the central prognostic goal in ALD.

Screening, brief intervention, and active referral should be embedded in hepatology pathways. Withdrawal management requires early risk stratification, thiamine supplementation, and preferential use of benzodiazepines with non-oxidative metabolism when hepatic impairment is present. For relapse prevention, pharmacotherapies may be framed as abstinence-oriented, reduction-oriented, or mixed/context-dependent; in clinically significant ALD, reduction-oriented treatment should generally be considered a transitional harm-reduction strategy rather than an equivalent long-term endpoint. Acamprosate and baclofen are commonly favored in patients with liver disease, whereas naltrexone, disulfiram, and off-label agents require individualized risk-benefit assessment.

Conclusions: AUD treatment should be regarded as a core component of ALD care rather than an optional adjunct. Integrated models linking hepatology, addiction medicine, psychosocial support, biomarker-informed monitoring, and transplant services may improve engagement, abstinence, and liver-related outcomes.

Key words: alcohol use disorder; alcohol-associated liver disease; alcohol withdrawal syndrome; baclofen; acamprosate; phosphatidylethanol; liver transplantation; integrated care.

1. ALCOHOL-RELATED LIVER DISEASE: WHAT ARE THE ISSUES?

1.1. Background

Excessive alcohol consumption remains a major and insufficiently treated contributor to preventable mortality and disability. The 2024 World Health Organization (WHO) report, based on 2019 estimates, attributed approximately 2.6 million deaths worldwide to alcohol and confirmed a large global population living with alcohol use disorder [1]. Older WHO reports and Global Burden of Disease analyses used different reference periods and methods, but they reached the same practical conclusion for clinicians: alcohol-related morbidity consumes substantial healthcare resources and is not confined to liver services [2-4]. In individual patients, grams of alcohol consumed per week are only one part of risk assessment; deprivation, psychiatric comorbidity, binge patterns, and reduced access to care help explain why alcohol-associated harm is unevenly distributed [5].

Alcohol use disorder (AUD) is a chronic, relapsing-remitting condition characterized by a continuum of severity and frequent medical and psychiatric comorbidity [6]. In clinical practice, stigma and patients' tendency to minimize intake can delay recognition. Systematic, repeated, and non-judgmental assessment of alcohol consumption is therefore essential in all patients with suspected or established liver disease. Current classifications have moved beyond the dichotomy of abuse versus dependence and frame hazardous use, harmful use, and dependence as part of a continuous clinical spectrum. In hepatology, this framework supports identification before irreversible complications develop.

Alcohol-associated liver disease (ALD) is the hepatic expression of chronic harmful alcohol exposure and spans steatosis, alcohol-associated steatohepatitis, progressive fibrosis, cirrhosis, hepatic decompensation, and hepatocellular carcinoma [7-8]. Although cumulative exposure remains central, progression is rarely explained by alcohol alone. Biological sex, nutritional status, metabolic syndrome, viral co-infections, tobacco use, and genetic susceptibility modify the clinical trajectory. The frequent coexistence of metabolic steatosis and alcohol intake is especially relevant: rather than representing two independent labels, these drivers may converge on inflammation, fibrogenesis, and earlier decompensation. The 2023 multisociety Delphi consensus did more than update terminology. By replacing non-alcoholic fatty liver disease with metabolic dysfunction-associated steatotic liver disease (MASLD), the nomenclature anchors steatosis in positive metabolic criteria and avoids defining patients by what they do not consume [9]. The MetALD category, defined by MASLD with alcohol intake above moderate thresholds (140-350 g/week for women and 210-420 g/week for men), is particularly relevant to hepatology clinics. It prompts clinicians to quantify alcohol systematically in all patients with steatotic liver disease rather than treating metabolic and al-cohol-associated injury as mutually exclusive [9]. In patients with ALD, total abstinence is the most powerful modifiable prognostic determinant. A systematic review confirmed improved survival among cirrhotic patients who achieve abstinence [10]. Consequently, treatment of AUD should be embedded in the hepatology care pathway, including liver transplantation settings [11-14].

This review proposes an implementation-oriented continuum-of-care framework for AUD management in patients with ALD, integrating screening, withdrawal management, liver-safe pharmacotherapy, psychosocial treatment, biomarker-supported monitoring, and transplant pathways.

1.2. Methods

This article is a narrative, clinically oriented review. We searched PubMed/MEDLINE, the Cochrane Library, and major society guideline repositories for English-language publications available through May 2026. Search terms included combinations of: alcohol-associated liver disease, alcohol-related liver disease, alcohol use disorder, cirrhosis, alcohol withdrawal syndrome, relapse prevention, baclofen, acamprosate, naltrexone, disulfiram, nalmefene, sodium oxybate, topiramate, gabapentin, glucagon-like peptide-1 (GLP-1) receptor agonists, phosphatidylethanol, liver transplantation, integrated care, and psychosocial interventions. Priority was given to international clinical practice guidelines and practice guidance, systematic reviews and meta-analyses, randomized con-trolled trials, and large observational cohorts relevant to AUD management in patients with ALD or cirrhosis. Evidence from general AUD populations was included when ALD-specific evidence was unavailable, but interpretation was framed around hepatic safety, renal function, encephalopathy risk, frailty, and transplant relevance. The review was not designed as a formal meta-analysis and does not use PRISMA flow reporting; rather, it synthesizes the evidence into a practical care framework for hepatology and addiction medicine services.

2 . EARLY IDENTIFICATION AND MEDICAL MANAGEMENT OF AUD

Despite its high prevalence, AUD remains under-identified and undertreated. This gap is documented in primary care and is amplified in hepatology settings by stigma, time constraints, and fragmentation between hospital-based liver care and community addiction services [15]. Evidence supports structured screening and brief intervention strategies to reduce hazardous consumption across multiple populations [16-19].

SBIRT (Screening, Brief Intervention, and Referral to Treatment) should be understood as a clinical workflow, not merely as the administration of a questionnaire. Screening can begin with standardized quantity-frequency questions and assessment of binge episodes, supported by validated tools such as the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) or the Alcohol Use Disorders Identification Test (AUDIT) [16-18]. In liver wards and emergency departments, the value is practical: an admission for ascites, jaundice, trauma, pancreatitis, or infection can become the first structured contact with AUD care rather than another missed opportunity. The brief intervention in ALD should be brief in duration, but precise in content. It should provide individualized risk feedback, explicitly connect alcohol exposure with liver prognosis, agree on an abstinence-oriented plan, define early follow-up, and anticipate barriers to engagement. A staged approach may be necessary when a patient is not yet able to stop drinking, but the long-term message should remain clear: once clinically relevant liver disease is present, reduction alone should not be presented as equivalent to abstinence. Communication should avoid moralizing language, because shame and stigma reduce disclosure; the same encounter should assess psychiatric comorbidity, cognitive impairment, social support, and other substance use disorders.

Referral should also be operational rather than advisory. For many patients with ALD, telling them to contact an addiction service is insufficient. A more reliable approach includes a scheduled appointment before discharge, clinician-to-clinician communication, case manager involvement when available, and documented linkage with addiction medicine, psychiatry, psychology, or community services. The COMBINE study and subsequent treatment models support the principle that medical management, psychosocial intervention, and relapse-prevention pharmacotherapy are most effective when delivered within structured care rather than as isolated recommendations [20].

3. TREATMENT AND MANAGEMENT OF ALCOHOL WITHDRAWAL SYNDROME

Alcohol withdrawal syndrome (AWS) requires timely recognition and risk stratification to prevent seizures, delirium tremens, aspiration, arrhythmias, and prolonged hospitalization [21]. Management should not be limited to sedative medication: it also includes hydration, correction of electrolyte and glucose abnormalities, evaluation for infection or gastrointestinal bleeding, and vitamin supplementation. Thiamine should be administered early, ideally before glucose-containing fluids when Wernicke's encephalopathy is a concern.

Benzodiazepines remain the standard treatment for moderate-to-severe AWS because they reduce seizures and delirium tremens [22]. In patients with hepatic impairment, the key prescribing issue is not only dose but also metabolic pathway. Long-acting agents and drugs dependent on hepatic oxidative metabolism can accumulate

and deepen sedation. Lorazepam and oxazepam, which undergo direct glucuronidation, are therefore generally preferred when significant liver disease is present [12,23]. Symptom-triggered regimens are appropriate when trained staff can reassess the patient repeatedly; fixed-dose or front-loading schedules may be safer when continuous as-sessment is not feasible. The care setting should be chosen before complications develop, taking into account previous delirium tremens or seizures, current withdrawal severity, medical instability, psychiatric risk, frailty, and social support. The Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-Ar) can guide symptom-triggered therapy, but it is less reliable when delirium, cognitive impairment, overt hepatic encephalopathy, or poor communication prevents valid symptom reporting [21,23]. In advanced ALD, the practical danger is misclassification: confusion, tremor, agitation, or somnolence may reflect hepatic encephalopathy, sepsis, hypoglycemia, hyponatremia, gastrointestinal bleeding, AWS, or several processes at the same time.

Gabapentin, sodium oxybate, and baclofen have been evaluated as alternative or adjunctive options acting on gamma-aminobutyric acid (GABA)-related pathways in selected settings [24-28]. Their role is narrow in severe AWS and should be defined by local expertise, monitoring capacity, and the patient's competing risks. In decompensated cirrhosis, renal dysfunction, respiratory disease, frailty, or encephalopathy risk, any sedating drug should be introduced cautiously, reassessed frequently, and discontinued promptly if mental status worsens. Examples of AWS regimens and approximate benzodiazepine equivalences are summarized in Table 1.

Item	Practical guidance
Fixed-dose regimen (example)	Diazepam 10 mg four times/day on day 1; 5 mg four times/day on day 2; followed by progressive reduction in subsequent days. In significant liver impairment, avoid long-acting oxidatively metabolized agents when possible.
Approximate equivalent doses (oral benzodiazepines)	Diazepam 10 mg approximately corresponds to chlordiazepoxide 25 mg, lorazepam 1-2 mg, and oxazepam 20-30 mg. Equivalences vary between protocols and patients; conversion must be individualized.
Preferred benzodiazepines in hepatic impairment	Lorazepam or oxazepam, because they undergo direct glucuronidation and have lower accumulation risk.
Selected alternatives or adjuncts	Gabapentin or carbamazepine may be considered for mild/moderate withdrawal or as adjuncts when appropriate; phenobarbital only by experienced clinicians with close monitoring. In ALD, avoid valproate and use sedating or misuse-prone agents cautiously; baclofen or sodium oxybate only in specialist/local-protocol settings.
Essential supportive care	Thiamine before glucose; hydration/electrolyte correction; assess infection or bleeding; repeat risk stratification.

Table 1. Examples of dosing regimens for the management of alcohol withdrawal syndrome (to be adapted to the individual patient and monitoring setting).

4. PHARMACOTHERAPY FOR RELAPSE PREVENTION: GENERAL PRINCIPLES

The prescribing question in ALD is not whether medication for AUD is permissible, but which agent can be matched to hepatic reserve, renal function, encephalopathy risk, concomitant medications, adherence, psychiatric profile, and treatment goal. In many patients, the prognostic danger of recurrent harmful drinking is greater than the risk of a carefully selected and monitored medication. Evidence from general AUD populations supports acamprosate and naltrexone, whereas ALD-specific evidence is strongest for baclofen in cirrhosis [29-33].

The evidence base has a clinically important imbalance. Many AUD medications have been tested mainly in general addiction populations, whereas trials in advanced ALD remain limited; conversely, hepatology cohorts often describe liver outcomes without detailed AUD treatment exposure. Observational studies suggest that integrated AUD treatment in cirrhosis is associated with improved outcomes, but these data are non-randomized and should not be overinterpreted [34-37]. The practical conclusion is to make treatment decisions explicitly, balancing medication toxicity against the well-established harm of continued drinking.
At the bedside, a useful sequence is to define the intended endpoint, review liver and renal function, exclude drug-specific contraindications, discuss adherence and supervision, and schedule laboratory and clinical monitoring before the prescription is written. Table 2 summarizes the main options according to treatment orientation and safety profile, while Table 3 proposes a stage-based approach.

Medication	**Treatment orientation / clinical endpoint**	**Safety notes in liver disease**
Acamprosate	Predominantly abstinence-oriented; maintenance of abstinence after detoxification.	Renal elimination; often preferred in liver disease. Reduce dose when eGFR/CrCl is 30-50 mL/min and avoid when eGFR/CrCl is <=30 mL/min.
Naltrexone	Predominantly reduction-oriented; reduction of craving, heavy drinking, and binge episodes.	Monitor liver tests; avoid in acute hepatitis, severe hepatic failure, decompensated cirrhosis, unexplained marked cytolysis, and current opioid use or opioid dependence; use caution in significant renal impairment.
Disulfiram	Abstinence-enforcing deterrent; requires motivation and supervision.	Avoid along the spectrum of ALD because of hepatotoxicity risk; if ever used outside ALD, requires supervision and liver-test monitoring.
Baclofen	Predominantly abstinence- and craving-oriented; strongest ALD-specific evidence in cirrhosis.	Start low and titrate slowly; dose-adjust/avoid escalation in renal impairment; monitor sedation, encephalopathy, dyspnea, falls, and adherence.
Nalmefene	Reduction-oriented; as-needed reduction of drinking.	Limited ALD data; not appropriate when abstinence is mandatory or in established advanced liver disease.
Sodium oxybate	Abstinence-/craving-oriented in selected supervised settings.	Risk of sedation, respiratory depression, and misuse; specialist use only, with caution in liver disease.
Topiramate (off-label)	Reduction-oriented; reduction of heavy drinking and binge episodes.	Risk of sedation, respiratory depression, and misuse; specialist use only, with caution and dose adjustment in hepatic impairment according to local product information.
Gabapentin (off-label)	Mixed/context-dependent; withdrawal symptoms, craving, or reduction in selected patients.	Titrate slowly; dose-adjust in renal impairment; monitor cognition, paresthesias, weight loss, metabolic acidosis, and rare liver injury; limited advanced ALD data.

Medication	Treatment orientation / clinical endpoint	Safety notes in liver disease
Glucagon-like peptide-1 (GLP-1) receptor agonists (research)	Experimental reduction-/craving-oriented strategy.	Promising but not approved for AUD; insufficient data in advanced ALD, cirrhosis, frailty, or sarcopenia.

Table 2. Medications for relapse prevention in alcohol use disorder: treatment orientation and practical notes in the presence of liver disease

The distinction between abstinence-oriented and reduction-oriented pharmacotherapy should be used as a clinical aid rather than a rigid classification. Abstinence-oriented strategies support complete cessation of alcohol use and are most relevant after detoxification, in patients with established organ damage, and throughout trans-plant pathways. In ALD, acamprosate and baclofen are the most clinically relevant examples, whereas disulfiram and sodium oxybate require highly selected and supervised use because hepatic safety, sedation, and misuse risks narrow their indication. Reduction-oriented strategies primarily target heavy drinking days, binge episodes, craving, or total alcohol intake; naltrexone, nalmefene, topiramate, gabapentin, and experimental agents such as GLP-1 receptor agonists are usually discussed in this category.
For patients without established organ damage, reducing heavy drinking can be a meaningful therapeutic endpoint. In ALD, the hierarchy changes. Abstinence remains the preferred prognostic target, particularly in advanced fibrosis, cirrhosis, alcohol-associated hepatitis, transplant candidates, and transplant recipients [10-14]. Reduction-oriented pharmacotherapy can still have value, especially as a transitional harm-reduction step in early disease or in patients who are not yet ready for abstinence, but it should not be communicated as an equivalent long-term goal once clinically significant liver disease has developed.

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Glucagon-like peptide-1 (GLP-1) receptor agonists (research)	Experimental reduction-/craving-oriented strategy.	Promising but not approved for AUD; insufficient data in advanced ALD, cirrhosis, frailty, or sarcopenia.

Table 2. Suggested relapse-prevention pharmacotherapy according to liver disease stage and comorbidities

4.1. Disulfiram

Disulfiram inhibits aldehyde dehydrogenase and produces an aversive acetaldehyde reaction after alcohol ingestion [38]. Evidence of efficacy is heterogeneous, and tolerability is limited, particularly when administration is not supervised [39]. Because disulfiram can cause clinically relevant hepatotoxicity, it should generally be avoided in advanced liver disease and should not be initiated in the presence of significant cytolysis or signs of hepatic failure [11]. In clinical practice, disulfiram may have a limited role in highly motivated patients with preserved liver function when supervised administration is feasible. Liver tests should be monitored, especially during the first weeks of treatment. The aversive mechanism also requires careful informed consent and clear discussion of potential reactions with alcohol-containing products.

4.2. Opioid Antagonists: Naltrexone and Nalmefene

4.2.1. Naltrexone

Naltrexone reduces the rewarding effects of alcohol and craving and is best conceptualized as a predominantly reduction-oriented medication, particularly useful for decreasing heavy drinking days and binge episodes; a Cochrane review and subsequent meta-analyses support its benefit on consumption outcomes [29,33,40]. The standard oral dose is 50 mg/day; long-acting injectable formulations are available in some countries. In ALD, nal-trexone should not be considered universally contraindicated, but it should be assessed on a case-by-case basis. It should be avoided in acute hepatitis, severe liver failure, or unexplained marked cytolysis, and liver tests should be monitored. It is contraindicated in patients receiving opioid therapy [41].

4.2.2. Nalmefene

Nalmefene is an opioid receptor modulator approved in Europe for reducing alcohol consumption in patients with AUD who do not have an immediate indication or motivation for abstinence [42-43]. Because the primary

goal in ALD is abstinence, nalmefene is best considered only in selected patients with early-stage disease who are temporarily unable to achieve abstinence, while ensuring that reduction is not miscommunicated as an adequate long-term target in established ALD [11].

4.3. Acamprosate

Acamprosate modulates glutamatergic and GABAergic neurotransmission and is best placed among abstinence-oriented treatments, particularly after detoxification, when the clinical objective is to maintain alcohol cessation [30,44-45]. Its pharmacokinetic profile is a major advantage in ALD: the drug is predominantly renally eliminated and has no clinically relevant hepatic metabolism. Acamprosate is therefore often a practical first option when renal function is adequate; a short-randomized study in Child-Pugh class A or B alcoholic cirrhosis did not show acute worsening of subclinical hepatic encephalopathy after acamprosate administration [46]. The usual dose is 666 mg three times daily in individuals weighing more than 60 kg and 333 mg three times daily in individuals weighing 60 kg or less, with dose adjustment or avoidance in renal impairment. Diarrhea is the most common ad-verse event. Acamprosate should be embedded within psychosocial support and follow-up rather than prescribed as a stand-alone intervention.

4.4. Sodium Oxybate

Sodium oxybate (gamma-hydroxybutyrate, GHB) is approved for AUD treatment in selected European settings, including Italy and Austria. Its GABAergic effects may reduce craving and support abstinence, and it has also been studied in AWS [24-26]. In routine ALD practice, however, its indication is narrowed by the same properties that make it pharmacologically active: sedation, respiratory depression, and misuse potential become particularly relevant in patients with psychiatric comorbidity, polysubstance use, advanced liver disease, sleep-disordered breathing, or encephalopathy risk. In ALD, sodium oxybate should be considered only within specialized settings with careful patient selection, supervised dosing when appropriate, and close monitoring. The risk-benefit ratio is particularly delicate in decompensated cirrhosis or in patients with sleep-disordered breathing, frailty, or polypharmacy.

4.5. Baclofen

Baclofen is a selective gamma-aminobutyric acid type B (GABA-B) receptor agonist with limited hepatic metabolism and predominantly renal elimination. It remains the medication with the most specific randomized evidence in patients with cirrhosis. In a randomized double-blind trial, baclofen 10 mg three times daily increased abstinence rates and reduced craving compared with placebo in alcohol-dependent patients with cirrhosis [32]. The BacALD study confirmed efficacy across patients with and without liver disease, while highlighting dose-related adverse effects such as sedation and dyspnea [47]. In clinical practice, baclofen should be started at low doses, commonly 5-10 mg three times daily, and titrated slowly according to efficacy and tolerability. Sedation, dizziness, asthenia, and confusion are clinically relevant in cirrhosis, particularly in patients with minimal or overt hepatic encephalopathy. Dose adjustment is required in renal impairment, and high-dose strategies should be avoided un-less managed by experienced clinicians [48].

4.6. Off-Label Drugs and Emerging Pharmacological Strategies

4.6.1. Topiramate

Topiramate is an off-label option whose main AUD endpoint is reduction in drinking rather than maintenance of abstinence. Randomized trials and meta-analyses suggest reductions in alcohol consumption, heavy drinking days, and binge episodes [49-51]. In ALD, the limiting issue is as much tolerability as efficacy: cognitive slowing, paresthesia, appetite or weight changes, frailty, possible worsening of hepatic encephalopathy, and rare hepatotoxicity reports all require caution [52].

4.6.2. Gabapentin

Gabapentin is better viewed as mixed or situation-dependent, with evidence for withdrawal symptoms and selected AUD subgroups [53-54]. It requires renal dose adjustment and close monitoring for sedation, dizziness, falls, cognitive effects, and misuse potential.

4.6.3. GLP-1 receptor agonists

GLP-1 receptor agonist, particularly semaglutide, represent an experimental research area focused on reduction and craving. A large real-world cohort study found that semaglutide was associated with lower incidence and recurrence of AUD diagnoses in patients with obesity or type 2 diabetes [55]. A small randomized clinical trial in adults with AUD who were not actively seeking treatment suggested that low-dose once-weekly semaglutide reduced alcohol intake in a laboratory setting and improved some craving and heavy-drinking outcomes compared with placebo [56]. These findings are promising but hypothesis-generating rather than practice-changing. At pre-sent, GLP-1 receptor agonists should not be regarded as established AUD therapy in patients with ALD or cirrhosis. Their use should generally be limited to clinical trials or highly specialized contexts. Their possible role should be interpreted as an investigational reduction-oriented strategy, not as a substitute for abstinence in clinically significant liver disease. In advanced ALD, their use is complicated by nausea, vomiting, reduced caloric intake, sarcopenia, frailty, gallbladder events, and uncertain safety in decompensated cirrhosis. Future trials should include liv-er-related outcomes, nutritional assessment, frailty endpoints, and transplant-relevant safety monitoring.

5. PSYCHOSOCIAL INTERVENTIONS

Psychosocial treatment is not an optional add-on to pharmacotherapy; in many patients with ALD, it is the intervention that determines whether medical recommendations are translated into sustained behavior change. The choice of approach should be individualized according to liver disease stage, cognitive function, frailty, social sup-port, travel burden, and hospitalization frequency. This is especially important because reduced hepatic reserve, renal dysfunction, or increased encephalopathy risk may limit pharmacological options.
Brief interventions and motivational approaches should be implemented early, including during hospital ad-missions. Motivational Interviewing and Motivational Enhancement Therapy aim to resolve ambivalence and strengthen intrinsic motivation for change [57]. In ALD, motivational work should explicitly connect abstinence with liver prognosis while avoiding shame-based or moralizing communication. The objective is to improve engagement and continuity rather than merely provide information. Cognitive-Behavioral Therapy (CBT) remains a structured reference intervention for relapse prevention. It addresses triggers, craving, coping strategies, mood symptoms, and high-risk situations; meta-analyses support its efficacy in substance use disorders [58]. Contingency Management can reinforce verifiable target behaviors, including attendance, medication adherence, or biomarker-supported abstinence, although feasibility depends on local resources [59].

Family and caregiver participation is often decisive in ALD. Caregivers can reduce alcohol-related cues at home, supervise medication intake, help patients attend appointments, and facilitate early recognition of hepatic decompensation or relapse. Mutual help groups and Twelve-Step Facilitation provide access to long-term support and have evidence for improving abstinence outcomes in AUD [60]. These community resources should be considered adjunctive to, not substitutes for, structured medical and psychological care.

Third-wave interventions, including mindfulness-based relapse prevention, Acceptance and Commitment Therapy, and Dialectical Behavior Therapy, may help selected patients who can engage with reflective and skills-based work [61-67]. They should not be presented as universally applicable in advanced ALD. Minimal or overt hepatic encephalopathy, fatigue, sleep disturbance, and impaired attention can limit the mental processes on which these interventions depend. A systematic review focused on ALD supports a pragmatic message: psychosocial care is most effective when connected to hepatology management rather than delivered as a parallel, detached service [68].

6. INTEGRATED FOLLOW-UP AND MANAGEMENT IN THE CONTEXT OF TRANSPLANTATION

Long-term follow-up is the point at which the continuum-of-care model either succeeds or fails. Although there is no universal consensus regarding the professional role assigned to case management, experience from integrated centers suggests that embedding addiction specialists, psychiatrists, psychologists, or dedicated alcohol treatment teams within liver units and transplant centers improves continuity and monitoring [34-36].

At each follow-up visit, abstinence should be assessed using a non-judgmental interview, structured self-report tools, collateral information when appropriate, and biomarkers when clinically indicated. Traditional markers

such as gamma-glutamyl transferase, mean corpuscular volume, and carbohydrate-deficient transferrin are widely available but have limited specificity in liver disease. Direct biomarkers, including urine ethyl glucuronide/ethyl sulfate (EtG/EtS) and blood phosphatidylethanol (PEth), can improve detection of recent or underreported alcohol use [69-71]. Their practical strengths and limitations are summarized in Table 4.

Biomarker	Approximate detection window	Strengths	Limitations in ALD/transplant practice
GGT	Typically weeks; decreases slowly after sustained abstinence.	Widely available; useful trend marker.	Low specificity in liver disease; affected by cholestasis, medications, and liver injury.
MCV	Weeks to months; normalization may take several months.	Simple and inexpensive.	Low sensitivity and specificity; affected by anemia, nutrition, and hematologic disease.
CDT	Approximately 2-4 weeks after sustained heavy drinking.	More alcohol-specific than many indirect markers.	Performance may be altered in advanced liver disease and cholestasis; less useful for very recent drinking.
Urine EtG/EtS	Typically 1-3 days, sometimes longer after heavy exposure depending on cut-off and assay.	Direct markers of recent alcohol exposure; useful for short-term monitoring.	Short detection window; interpretation affected by timing, dilution, incidental exposure, and laboratory thresholds.
PEth	Approximately 2-4 weeks; may be longer after sustained heavy drinking and varies by assay.	Direct blood biomarker; useful for detecting underreported drinking; increasingly used in transplant pathways.	Cut-offs and intervals vary between centers; interpretation can be affected by transfusion, hemolysis, timing of last intake, and assay methodology; should not be used alone.

Table 4. Alcohol biomarkers in ALD and transplant settings. GGT: gamma-glutamyl transferase; MCV: mean corpuscular volume; CDT: carbohydrate-deficient transferrin; EtG/EtS: ethyl glucuronide/ethyl sulfate; PEth: phosphatidylethanol.

PEth is particularly useful in transplant settings because it directly reflects ethanol exposure and may detect drinking that is not captured by history or traditional biomarkers [70-71]. However, PEth should not be interpreted in isolation. Cut-offs, reporting units, testing intervals, and clinical thresholds vary across centers; recent transfu-sion, hemolysis, timing of last consumption, and laboratory methodology may influence interpretation. PEth should therefore be embedded in a shared protocol that combines clinical interview, psychosocial assessment, collateral information when available, and transparent communication with the patient.

AUD management in the liver transplantation setting requires a multidimensional rather than purely time-based approach. Rigid application of the '6-month rule' has been progressively replaced by individualized relapse-risk assessment considering prior treatment history, psychiatric comorbidity, insight, social support, adherence, and ability to engage in post-transplant care [12-14,72]. It is also useful to distinguish a brief slip from sus-tained harmful alcohol use, because prognostic and therapeutic implications differ. Early liver transplantation for carefully selected patients with severe alcohol-associated hepatitis who do not respond to

medical therapy has changed the transplant debate [73-75]. Its relevance to this review is not simply that transplantation can occur ear-lier, but that addiction assessment and treatment must start immediately rather than after a fixed abstinence inter-val. Such programs require transparent selection criteria, structured psychosocial evaluation, and linkage to addic-tion treatment before and after transplantation. Embedding an alcohol addiction unit within the transplant team allows relapse risk to be managed proactively and has been associated with benefits in graft and clinical outcomes [34].

Comorbid risk factors must be actively addressed. Anxiety and depression can trigger relapse and should be treated. Tobacco smoking is common in AUD and contributes to cardiovascular disease, malignancy risk, and post-transplant morbidity; smoking cessation should be considered an integral component of the care plan rather than an optional recommendation [13,76]. Linkage with community addiction services and mutual-help networks should be documented to reduce loss to follow-up.

7. RESEARCH GAPS AND FUTURE DIRECTIONS

Several gaps limit translation of AUD pharmacotherapy into ALD care. First, patients with advanced liver disease are frequently excluded from AUD trials, while hepatology trials often under-characterize AUD treatment exposure. Second, safety outcomes are inconsistently reported, especially for encephalopathy, falls, frailty, renal impairment, nutritional decline, and drug interactions. Third, biomarkers such as PEth are increasingly used, but clinical algorithms remain heterogeneous across transplant centers.

Future studies should include patients with compensated and decompensated cirrhosis, define standardized liver and renal safety endpoints, and test integrated care models rather than single interventions. Trials of emerging pharmacological strategies, including GLP-1 receptor agonists, should incorporate nutritional and frailty outcomes, liver disease severity, and long-term alcohol outcomes. Implementation studies are also needed to determine how SBIRT, active referral, telemedicine, case management, and biomarker protocols can be embedded sustainably into routine hepatology pathways.

8. CONCLUSIONS

In patients with alcohol-associated liver disease, AUD treatment must move from the periphery of care to the center of the hepatology care pathway. Systematic screening, non-stigmatizing brief intervention, safe withdrawal management, liver-adapted relapse-prevention pharmacotherapy, psychosocial treatment, and longitudinal abstinence monitoring should be implemented as a coherent continuum rather than as disconnected interventions. The practical challenge is as much organizational as pharmacological: hepatology and addiction medicine must operate as a shared care pathway. A continuum-of-care framework can help clinicians identify where patients are most often lost: during screening, referral, detoxification, relapse prevention, transplant evaluation, or subsequent follow-up. This approach can support more reliable integration of evidence-based AUD treatment into ALD care.

Author contributions: All authors contributed to the conception of the review, interpretation of the literature, drafting or critical revision of the manuscript, and approval of the final version for submission.
Funding: The authors declare that no specific funding was received for this work.
Conflicts of interest: The authors declare no conflicts of interest relevant to this manuscript.
Ethics approval and consent to participate: Not applicable. This narrative review did not involve human participants, patient records, or original data collection.
Data availability: No original datasets were generated or analyzed. All sources used for the review are cited in the reference list.

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