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Mini Review

Efficacy of Addiction Pharmacotherapy in Alcohol Use Disorder and Their Effects on Liver Health

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Abstract

Both alcohol-associated liver disease (ALD) and metabolic dysfunction-associated steatotic liver disease are leading contributors to chronic liver diseases. These conditions often coexist, exacerbating disease progression. Despite ALD being a leading cause of liver transplantation, many individuals with alcohol use disorder (AUD) do not receive treatment. In this review, we discussed the epidemiology of ALD in AUD, various treatment options for AUD, and their efficacy on liver health. Our critical analysis of current evidence underscores the need for integrated models involving multiple stakeholders to improve ALD management.

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Introduction

The burden of viral hepatitis and its impact on liver transplantation (LT) is declining because of advancements in prevention strategies and treatment options.[1] Conversely, obesity and related metabolic dysfunctions have increased rapidly over the past decades, and parallel to that, metabolic dysfunction-associated steatotic liver disease (MASLD) is becoming a highly prevalent liver disease.[2,3] Both alcohol-associated and metabolic dysfunction-associated steatohepatitis are leading etiologies for chronic liver disease instigating hepatocellular carcinoma and LT.[3–5] Preventing these diseases is pivotal, especially when alcohol-associated liver disease (ALD) and MASLD coexist,[6] as this can accelerate progression towards end-stage liver failure. These liver diseases predominantly affect working-age individuals; for instance, 16% of all lost working hours in England in 2015 were due to alcohol, and more working years were lost to alcohol than the ten most prevalent malignancies combined together.[6] Therefore, tackling the risk factors will not only benefit patients and health care systems in general, but also the global economy.[3] However, strategies and well-integrated models are lacking, including multidisciplinary treatment plans and guidelines to accurately co-treat and follow up this population. These strategies should highlight awareness about alcohol intake limits for high-risk individuals and should emphasize the fact that many patients with alcohol use disorder (AUD) do not receive evidence-based treatment despite the availability of behavioral therapy and addiction pharmacotherapy and their association with reduced liver-related morbidity even in those diagnosed with ALD.

Alcohol consumption in high-risk individuals

In patients with AUD or those consuming harmful amounts of alcohol, ALD can coexist with MASLD or viral hepatitis. For example, alcohol consumption in chronic viral hepatitis leads to an increased all-cause mortality HR 1.69 (95% CI 1.28–2.24) for heavy drinkers (defined as ≥40 g per day) compared to non-drinkers.[7] In another study, hepatic steatosis was found in 46% of normal-weight heavy drinkers (defined as >60 g per day) and in nearly 80% of obese non-drinkers. Notably, hepatic steatosis was observed in 95% of obese heavy drinkers, resulting in a 5.8-fold increase in steatosis rate.[8] Additionally, in a large longitudinal cohort of middle-aged women without liver disease at baseline, alcohol consumption (defined as >150 g per week) was associated with a more than 3-fold increased relative risk of cirrhosis in normal-weight women after 6 years. This association became stronger for obese women showing that they had a more than 6-fold relative risk increase of cirrhosis.[9] Likewise, the combined effects of obesity and alcohol also lead to higher mortality caused by liver disease, as shown by a prospective cohort study depicting a supra-additive interaction between alcohol consumption and obesity regarding liver-related morbimortality.[10] In this cohort, the relative risk for increased BMI (defined as being overweight or obese) in regards to liver disease mortality was RR 1.29 (95% CI 0.60–2.80), while that for overconsumption of alcohol (defined as ≥15 units per week) was RR 3.66 (95% CI 1.74–7.71). However, the risk of liver disease mortality was significantly elevated when being overweight or obese and consuming at least 15 units of alcohol per week with an astonishing risk of liver disease mortality RR 9.53 (95% CI 4.98–18.2).[10] These synergistic effects on liver disease progression, mediated by similar pathways of steatosis-inducing conditions, are likely to accelerate the development of advanced fibrosis and cirrhosis. Pathophysiologically, ALD and MASLD share common pathways leading to steatosis through an imbalance in fatty acid synthesis and β-oxidation. This imbalance results from lipid accumulation in the liver in the case of obesity-related MASLD and from ethanol toxicity within hepatocytes in ALD.[6]

Keywords: Alcohol use disorder; Alcohol-associated liver disease; Addiction pharmacotherapy; Under treatment; Metabolic dysfunctions; Liver health; Multidisciplinary clinics.

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The subsequent oxidative stress and inflammation in the liver will eventually cause advanced liver disease. According to recent changes in the nomenclature and definition of fatty liver disease, steatotic liver disease now encompasses all etiologies causing liver steatosis. The concurrent presence of increased alcohol intake and MASLD, termed MetALD, falls under this new umbrella. Leading European and American guidelines recommend limiting alcohol consumption to no more than 20 or 30 g per day for women and men, respectively.[11,12] However, the above evidence raises questions about whether overweight or obese individuals, with or without possible steatotic liver conditions, should adhere to lower limits compared to those with a normal BMI. Moreover, it remains unclear whether addiction pharmacotherapy for AUD treatment should be initiated sooner in people with MetALD, even if they do not fully meet the ALD definition. Currently, there is no consensus on safe amounts of units in MASLD patients.

The effects of alcohol addiction pharmacotherapy on liver health

A recent meta-analysis investigated the effects of addiction pharmacotherapies on relapse rates in people with AUD, defined as relapsing into either any or heavy drinking.[13] Naltrexone and acamprosate were found to have a reduced risk ratio (RR) for relapsing into any drinking, with RR 0.95 (95% CI 0.92–0.99) and RR 0.88 (95% CI 0.83–0.93), respectively. Disulfiram had no effect, with RR 0.99 (95% CI 0.92–1.06). In regards to relapsing into heavy drinking, results favored naltrexone with RR 0.86 (95% CI 0.80–0.93). When addressing AUD, it is essential to examine the effects of these pharmacotherapies on liver health, although it was out of scope in this study.[13] This is important since a reported 12–51% of patients with AUD suffer from ALD, with an increasing number of younger people being diagnosed with ALD.[1,14] Data are scarce on the efficacy of addiction pharmacotherapies in preventing ALD development in AUD patients. Yet, two recent USA-based cohort studies have provided insight into this. A well-characterized cohort study included 9,635 patients with AUD (with 11.8% having concomitant ALD), of which approximately 40% were treated with addiction pharmacotherapies, demonstrating that the usage of any addiction pharmacotherapy was inversely associated with the incidence of ALD (OR 0.37; 95% CI 0.31–0.43).[14] Additionally, an inverse and significant association was observed between any pharmacotherapy for AUD and incident hepatic decompensation in cirrhotic patients (OR 0.35; 95% CI 0.23–0.53). Similar results for hepatic decompensation were obtained in case pharmacotherapy was initiated after a diagnosis of cirrhosis (OR 0.41; 95% CI 0.23–0.71). The latter is supported by another study performed among veterans with AUD-related liver cirrhosis.[15] Treatment (defined as behavioral and/or pharmacotherapy) was associated with significant reductions in incident hepatic decompensation (OR 0.63; 95% CI 0.52–0.76) and long-term all-cause mortality (OR 0.87; 95% CI 0.80–0.96).[15] In this cohort, 15% of all treated patients received disulfiram, 26% received acamprosate, and the majority (59%) received naltrexone.

Zooming into individual drugs, the usage of most pharmacotherapies was inversely associated with ALD development.[14] Remarkably, acamprosate was associated with increased odds of ALD development (OR 2.59; 95% CI 1.84–3.61).[14] Moreover, naltrexone, gabapentin, and topiramate were inversely associated with hepatic decompensation in cirrhotic patients. Interestingly, acamprosate was again associated with higher odds of hepatic decompensation (OR 1.99; 95% CI 0.99–4.06),[14] although not fully statistically significant (Table 1). Considering the combined evidence in Table 1

Table 1. The effects of addiction pharmacotherapy for AUD on abstinence and liver health

Addiction pharmacotherapy		Efficacy of addiction treatment		Liver health	
FDA approved	Not approved	Return to any drinking	Return to heavy drinking	Development of ALD	Development of hepatic decompensation
Naltrexone	–	RR 0.95 (0.92–0.99)*	RR 0.86 (0.80–0.93)*	OR 0.67 (0.46–0.95)*	OR 0.27 (0.10–0.64)*
Acamprosate	–	RR 0.88 (0.83–0.93)*	RR 1.00 (0.96–1.04)	OR 2.59 (1.84–3.61)*	OR 1.99 (0.99–4.06)
–	Topiramate	Insufficient studies	Insufficient studies	OR 0.47 (0.32–0.66)*	OR 0.43 (0.17–0.99)*
–	Gabapentin	RR 0.92 (0.83–1.02)	RR 0.90 (0.82–0.98)	OR 0.36 (0.30–0.43)*	OR 0.36 (0.23–0.56)*
–	Baclofen	RR 0.83 (0.70–0.98)*	RR 0.92 (0.80–1.06)	OR 0.57 (0.36–0.88)*	OR 1.06 (0.39–2.69)
Disulfiram	–	RR 0.99 (0.92–1.06)	No studies	OR 0.86 (0.43–1.61)	OR 2.59 (0.54–13.26)
Any therapy				OR 0.37 (0.31–0.43)*	OR 0.35 (0.23–0.53)*

Results regarding the efficacy of addiction treatment presented as relative risk (RR) and 95% confidence interval are extracted from a meta-analysis of solely double-blind randomized clinical trials comparing the index treatment versus placebo by McPheeters *et al.*[13] Results regarding associations for incidence development of ALD and related hepatic decompensation presented as odds ratios (OR) and 95% confidence interval are extracted from a well-characterized retrospective cohort study by Vannier *et al.*[14] *Statistically significant results, AUD, alcohol use disorder; ALD, alcohol-associated liver disease.

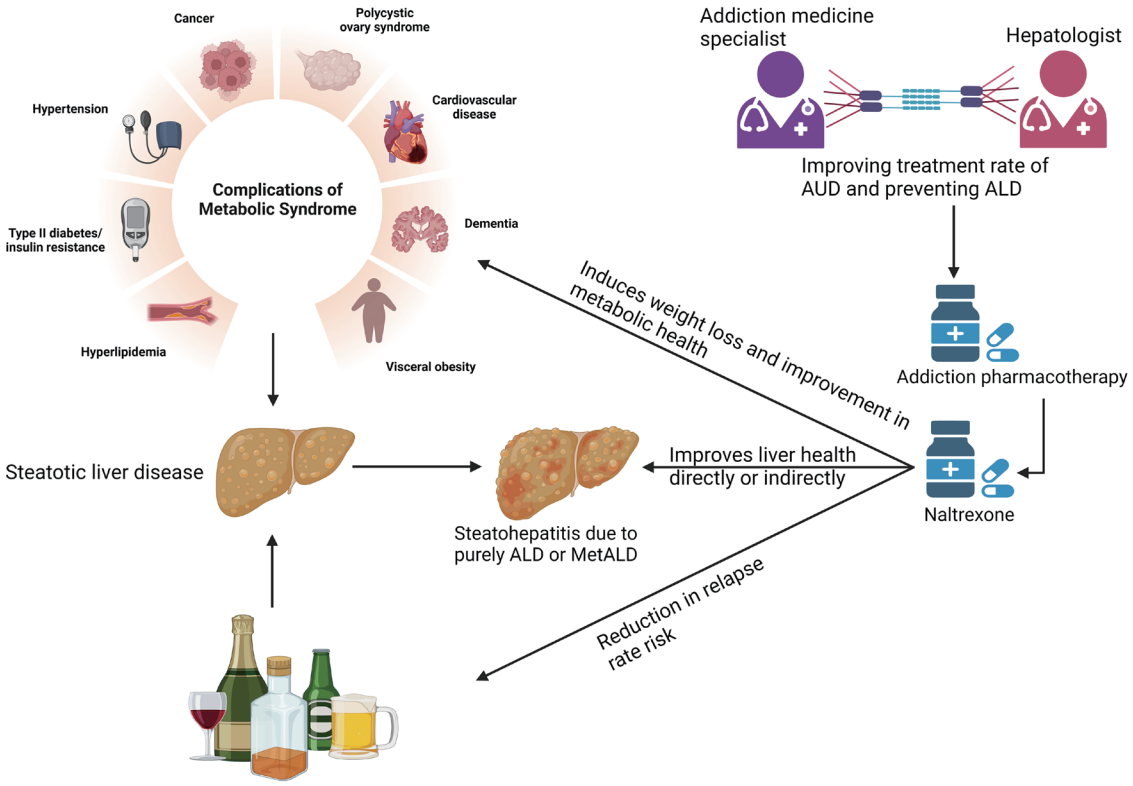

Fig. 1. A proposed model for improving management of ALD. Intensive multidisciplinary treatment of AUD alongside follow-up and management of ALD is proposed to improve liver disease-related morbimortality. AUD, alcohol use disorder; ALD, alcohol-associated liver disease; MetALD, metabolic dysfunction associated steatotic liver disease with concurrent increased alcohol intake.

depicting the effects on liver health and treatment of alcohol addiction, naltrexone might be the most beneficial for treating both AUD and ALD. It is worth noting that all US Food and Drug Administration (FDA) approved drugs, including naltrexone, acamprosate, and disulfiram, have not been investigated in trials with liver cirrhosis patients, and therefore, pharmacological evidence in this group is limited. This could contribute to the under-treatment of AUD in people with ALD. Nonetheless, carefully weighted tailored medicine is important in certain cases, best achieved within multidisciplinary settings. Naltrexone is contraindicated for patients with acute hepatitis or liver failure and for those using opioids. The AASLD recommends acamprosate in people with AUD and ALD since fewer cases of hepatic toxicity have been reported due to its metabolism outside the liver.[16] However, according to the above-mentioned study, acamprosate is associated with increased odds of ALD development. Furthermore, despite its association with increased odds of ALD development, compliance with acamprosate might be lower due to a frequent and complex dosing regimen, and secondly, dosage adjustments might be needed according to kidney function.[14] Moreover, in an RCT in patients with AUD and ALD (including compensated and decompensated cirrhosis) without hepatic encephalopathy, only baclofen is indicated, which was found to be safe and effective in inducing and maintaining abstinence after one year.[17] It must be highlighted that the above-mentioned results (summarized in Table 1) regarding associations with incident ALD development and related hepatic decompensation alongside liver-related mortality are based on two studies only. Lastly, in the above-mentioned meta-analysis investigating relapse rates,[13] 63 out of 70 studies provided data on race and sex, and in these studies, there was an overrepresentation of white male participants, meaning these results cannot be entirely extrapolated to every patient. Considering the available evidence so far and looking at FDA approved drugs only, we would argue that naltrexone is superior to acamprosate and disulfiram.

Studies in mouse models have shown that naltrexone can attenuate steatosis by reducing body weight and adipose tissue, improving hyperinsulinemia, improving the expression of lipid metabolism-related proteins, and decreasing liver inflammation and endoplasmic reticulum stress.[18–20] In this regard, naltrexone might hold promise for patients with a dual etiology for liver steatosis due to metabolic dysfunctions and AUD (Fig. 1). In fact, a significant weight reduction after 56 weeks in overweight and obese individuals treated with a combination of naltrexone/bupropion was shown in a phase-3 double-blind placebo-controlled randomized multicenter trial.[21] Effects were more pronounced in the group receiving higher concentrations of naltrexone (16 mg vs. 32 mg). Furthermore, a post-hoc analysis of four randomized controlled trials indicated that naltrexone/bupropion showed benefits to liver health, such as improvement in FIB-4 and alanine aminotransferase.[22]

Undertreatment of AUD

Preventing relapse and improving liver health through addiction pharmacotherapy seems obvious. However, as pointed out above, acamprosate is associated with adverse liver-related effects. Moreover, there is clear evidence that people with AUD are significantly undertreated with addiction

pharmacotherapies. A cross-sectional study investigated the prevalence of guideline-directed use of such drugs in people with AUD. Among adults with AUD, only 7.3% out of over 14 million people reported receiving any treatment in the past year and only 1.6% were actually using these drugs.[23] Living in big metropolitan areas, receiving treatment for mental health, and frequent visits to emergency departments were associated with receiving pharmacotherapy for AUD.[23] Another study reported that only 12%, 1%, and 0.45% received treatment for AUD in the form of behavioral therapy, both behavioral/pharmacotherapy and pharmacotherapy alone, respectively.[15] Astonishingly, this study included cirrhotic patients, which is a missed opportunity from the perspective of a hepatologist. Firstly, there is evidence demonstrating an improvement in liver health when treated with addiction pharmacotherapy, even in patients with liver cirrhosis. Secondly, ongoing cirrhosis and alcohol consumption will continue to burden the individual and eventually the healthcare system, especially when cirrhosis of the allograft occurs due to post-transplantation relapse.

Abstaining from alcohol is the strongest contributing factor in improving long-term outcomes for patients with ALD.[24] However, from the patients' perspective, consuming harmful amounts of alcohol and subsequent liver damage are not their main concerns. What impacts their quality of life are sleeping difficulties, anxiety, and fatigue, as concluded by a survey conducted among ALD patients.[25] The importance of coordination between different healthcare professionals, including medics and paramedics specialized in this field, is illustrated by this survey. This specific group of patients requires multidisciplinary healthcare facilities that offer tailored pharmacological and non-pharmacological treatments alongside lifestyle interventions to sustain long-lasting improved liver health. These multidisciplinary healthcare facilities should include a hepatologist to assess liver health by performing regular liver stiffness measurements and screening for cirrhosis and hepatocellular carcinoma. Equally important are addiction specialists who treat AUD (including anxiety and sleep disorders), and other team members pivotal in preventing relapse, such as social workers to investigate socio-economic status and related demographics, and peers who have overcome the alcohol use disorder.[26] As mentioned, there is a discrepancy between the reported amount of people being treated for AUD and the number of people who are actually compliant, which should also be addressed in this proposed multidisciplinary setting. Lastly, involving nutrition specialists to improve alcohol-induced sarcopenia and metabolic dysfunctions will improve liver health and educate these patients about a healthy lifestyle. In the end, liver health is not just the absence of metabolic dysfunctions and harmful amounts of alcohol but rather a projection of a healthy lifestyle.

Although historically alcohol has always been a major contributor to liver cirrhosis and LT, progress in this field has not evolved as rapidly as with other etiologies causing chronic liver disease. One reason is the conventional approach to treating and understanding this population, which has been discipline-focused, leading to fragmented treatment plans. Holistically addressing AUD treatment and integrating psychological and behavioral elements with biomedical aspects is necessary to provide the best care for these vulnerable patients. This specific setting is likely more effective in preventing alcohol relapse.[27,28] However, these strategies have not been put into practice yet as evidenced by a cohort of over 35,000 patients with ALD and cirrhosis, the majority did not receive treatment for AUD in the shape of pharmacotherapy or behavioral intervention.[15]

The cornerstone of treating people with AUD and concomitant ALD remains psychosocial treatment, which may consist of group therapies, individual therapies, family therapy, and support buddies comprising patients who have overcome addiction. Within these sessions, the main goal is behavioral change through cognitive-behavioral therapy and motivational interviewing. A review investigating abstinence in people with AUD and concurrent chronic liver diseases, focusing on psychosocial interventions, showed that no psychosocial intervention separately can achieve abstinence. However, combining integrated cognitive-behavioral therapy and intensive medical care yielded promising results in achieving and maintaining abstinence.[29] An explanation for this is that people who are unwilling to accept treatment for alcoholism may still attend medical appointments, increasing their engagement with healthcare professionals.[30] Again, psychosocial/behavioral therapies have not been extensively studied in people with AUD and ALD, since there is a lack of prospective studies on the effects of integrated care for people with AUD and ALD. These knowledge gaps could be addressed in the multidisciplinary setting we propose since it is arguable that people with AUD and concurrent ALD might consist of a distinct population with heavier drinking and little insight into their liver damaging-behavior, leading to refusal of referreals.[29] Therefore, we advocate for integrated models and tailored plans in which patients are treated (pharmacologically or behavioral) in a multidisciplinary setting by multiple specialists aiming for good liver health, without disregarding metabolic dysfunction (Fig. 1).

These settings will also open avenues for collaborative trials and research to address knowledge caveats and potentially reduce the global burden of liver disease and LT due to lifestyle-induced chronic liver disease.

Conclusions

In conclusion, AUD is common, and consequently, ALD (with or without concurrent MASLD) is a major etiology for liver transplantation. Pharmacological treatment of AUD, even among those with ALD, is not common, despite evidence that such therapy could improve liver morbidity and mortality directly or indirectly. Unfortunately, psychosocial behavioral treatment, the cornerstone of treating individuals with AUD and concomitant ALD, is still lacking. Therefore, multidisciplinary clinics involving close collaborations between hepatologists and addiction medicine specialists/psychiatrists alongside other important care providers are needed to address these pressing issues. Considering stigma and shame as barriers to seeking treatment and subsequent loss of follow-up, a one-stop-shop clinic for this population might be a solution to start with (Fig. 1).

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Conflict of interest

QP has been an Editorial Board Member of *Journal of Clinical and Translational Hepatology* since 2020. The other authors have no conflict of interests related to this publication.

Author contributions

JZ drafted the first version based on the available evidence. JL screened the available evidence and contributed to the first version. QP and IA critically conceptualized and finalized the final version. All authors have approved the final version of manuscript.

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