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Title of article: Effectiveness of baclofen for the treatment of alcohol use disorder in patients with alcoholic liver disease: a narrative literature review

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Article summary (160 characters): Alcoholic liver disease (ALD) linked to alcohol use disorder (AUD) is a significant health issue. Our review explores the efficacy of baclofen, a potential treatment for this indication.

Keywords: Alcohol use disorder; alcoholic liver disease; baclofen; effectiveness; abstinence

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Abstract

Background
Alcohol use disorder (AUD) is linked to alcoholic liver disease (ALD), which contributes greatly to the global burden of disease. Baclofen has been studied in patients with these concurrent disorders. However, due to limited research, baclofen is only used off-label.

Aim
To determine the effectiveness of baclofen for the treatment of AUD and ALD.

Methods
MEDLINE, Scopus and The Cochrane Library were searched using the terms [(("alcohol use disorder" OR "alcohol dependence") AND ("alcoholic liver disease" OR "cirrhosis")) AND ("baclofen")]. Additional papers were retrieved from the reference lists of relevant studies.

Results
We identified seventy-one studies and retrieved two from reference searching. Ten studies meeting inclusion and exclusion criteria were retained for review, four of which were randomised controlled trials (RCTs). Retrospective and prospective cohort studies were also included, along with one Markov model. The literature defined baclofen's effectiveness in terms of abstinence, alcohol consumption, hospitalisations, cost-effectiveness, mortality rates, and side effects. While controlled evidence is limited, baclofen was found to promote abstinence, whilst also reducing drinking levels, long-term mortality, and days spent in hospital. Additionally, the drug had a favourable cost-effectiveness profile. However, acute confusion and overdoses have been reported, particularly with high dosages.

Conclusion
Our findings support the efficacy and use of baclofen to treat AUD and ALD. The risk of serious adverse events remains a concern, requiring vigilant prescribing and reporting from healthcare professionals. RCTs and studies with larger sample sizes are required to support these initial findings and confirm the viability of baclofen.

Introduction

Alcohol use disorder (AUD) is a condition characterised by harmful alcohol intake [1]. AUD commonly results in alcoholic liver disease (ALD), which includes alcoholic hepatitis and liver cirrhosis [2]. Each year, AUD-associated ALD is responsible for half a million deaths worldwide [3]. Its prevalence is increasing, particularly amongst young adults [4]. When ALD patients continue to drink, hepatic decompensation occurs more rapidly, resulting in higher mortality rates [2]. This is particularly true for those with comorbid conditions such as hepatitis C virus (HCV) [5]. Hence, finding an effective method to reduce alcohol usage in these individuals remains a major priority in healthcare. Current research indicates the need for pharmacological interventions in particular [3].

Many medications used in AUD treatment, such as naltrexone, acamprosate and disulfiram [6,7], are contraindicated in patients with ALD due to an increased risk of hepatotoxicity and hepatic encephalopathy [7]. Baclofen represents a potential treatment for these individuals, given its minimal liver metabolism and primarily renal excretion [8].

To understand the proposed mechanism of action of baclofen, the biopsychosocial origins of AUD must first be explained. AUD is often associated with mental health disorders such as depression and post-traumatic stress disorder (PTSD) [9,10]. From a chemical perspective, chronic alcohol use triggers downregulation of inhibitory gamma-aminobutyric acid (GABA)-$_B$ receptors. This results in disinhibition of the dopaminergic pathway, which is responsible for reinforcing alcohol consumption and modulating drinking behaviour [11]. Baclofen combats this by stimulating GABA receptors on dopaminergic and glutaminergic neurons in the central tegmental area [11,12]. The resultant increase in inhibitory GABA normalises dopamine release, thus reducing alcohol cravings [11].

Currently indicated for spasticity, baclofen is yet to be approved by Australian regulatory authorities for the treatment of AUD and ALD [9,13]. It is only prescribed "off-label", a term that describes medications used outside of their registered indication [14,15]. This is primarily due to an inconsistent literature base and lack of research into baclofen for AUD ALD [3,8,9,13,16,17,18,19]. Furthermore, many available studies quantify baclofen's effectiveness in terms of abstinence, offering minimal insight into alcohol consumption, hospitalisations, and costs [3,13,18]. To determine the drug's viability more broadly, it is necessary to consider these additional measures [20].

To the best of our knowledge, our narrative review is the first to assess the effectiveness of baclofen across various outcomes. We aimed to determine its viability for AUD ALD patients by investigating its impact on abstinence, alcohol consumption, hospitalisations, cost-effectiveness, mortality rates, and adverse events.

Methods

MEDLINE, Scopus, and The Cochrane Library were searched for relevant published studies on 2021 March 30. The following terms were used: [((("alcohol use disorder" OR "alcohol dependence") AND ("alcoholic liver disease" OR "cirrhosis")) AND ("baclofen")]. Reference lists were then analysed for additional sources. A supplementary search was also conducted on Google Scholar using the same terms. Inclusion criteria were as follows: original studies involving patients with both AUD and ALD, published between the years 2007 and 2020. We excluded non-English studies, reviews, and summaries of previous articles.

Results

Our initial search retrieved 71 studies, with a further two taken from reference lists and Google Scholar. Abstract and full-text screening identified 10 of these studies eligible for review with regards to inclusion and exclusion criteria. This process was conducted by a single investigator.

From these studies, we selected four randomised controlled trials (RCTs) including one post-hoc analysis. In addition, two prospective cohort studies, two retrospective cohort studies, and one retrospective case-series study with follow-up questionnaire were chosen. An original research article involving Markov modelling was also selected (Table 1). Of these, seven investigated abstinence [5,8,18,19,21-23]. Effectiveness was also assessed in terms of total alcohol consumption (n = 3), hospitalisation rates (n = 1), cost versus benefits (n = 1), mortality (n = 1), and side effects (n = 5).

Achievement of alcohol abstinence
Seven studies assessed the effectiveness of baclofen in terms of alcohol abstinence (Table 1) [5,8,18,19,21-23]. Classically defined as total cessation of alcohol use, abstinence is taken as the gold standard for AUD treatment in the context of liver disease [3].

Both a single RCT and a retrospective cohort study investigated alcohol abstinence in AUD ALD patients specifically [8,21]. In these studies, AUD ALD patients received 30 mg/day of baclofen for three months and 12 months, respectively [8,21]. Addolorato *et al* using a double blind RCT study design in 84 patients, demonstrated that 71% achieved and maintained total abstinence, compared to 29% of those prescribed placebo by 12 weeks [8]. In the retrospective cohort study, Yamini *et al.* [21] defined abstinence as a desire to abstain. from alcohol. Out of 35 patients, 97% achieved abstinence and improvements in liver function tests (LFTs) within 1 year. LFTs are a commonly utilised biomarker of hepatic function [21].

Abstinence rates were considered in two studies involving patients with AUD, ALD, and co-morbid HCV. This included a post-hoc analysis of 24 patients from the Addolorato *et al*. RCT [8] and a double blind, placebo controlled RCT with 180 participants [5,18]. In both studies, participants were prescribed 30 mg/day of baclofen for three months. However, results were conflicting [5,18]. Leggio *et al.* [5] demonstrated that 83.3% of patients receiving baclofen achieved total alcohol abstinence, compared to 25% in the placebo cohort. Treatment also led to an overall improvement in LFTs with increased albumin values and a reduced international normalised ratio (INR) [5]. However, Hauser *et al.* [18], who defined abstinence as no heavy drinking between weeks four and 12 of the study, demonstrated no significant difference in days abstinent between placebo and treatment groups.

Two additional studies investigated AUD patients both with and without cirrhosis suggesting ALD [19,22]. Barrault *et al.* [19] used a prospective cohort study design involving 100 AUD patients, 65 with cirrhosis and 35 with alcohol dependence only. Participants were treated with a mean daily dose of 40 mg of baclofen over 12 months. At the conclusion of the study, 44% were abstinent [19]. Owens *et al.* [22] also used a prospective cohort design involving 219 AUD patients, which included 82 participants with cirrhosis, 50 with ALD but no cirrhosis, and 87 with abnormal LFTs [22]. These patients were instead treated for three months with a variable dose, up to 30 mg of baclofen three times daily, based on tolerability. Of patients in the original cohort, 186 and 113 were evaluated at three months and 12

months, respectively. The proportion of eligible patients reporting complete abstinence at three and 12 months was 55% and 53%, respectively [22].

Reducing alcohol consumption
Three studies evaluated baclofen's overall effect on alcohol consumption, defined as any change in participant alcohol usage from baseline (Table 1) [9,19,22]. Heydtmann *et al.* [9] conducted a two-part study consisting of a retrospective case series, followed by standardised questionnaire. The latter was mailed to 46 AUD ALD patients receiving baclofen, who were asked questions pertaining to their drinking levels. 19 participants returned the survey, with statistical analysis revealing an average reduction in mean alcohol use from 240 g/day to 144 g/day (p = 0.009) [9].

Two prospective cohort studies similarly concluded that baclofen decreased patient alcohol consumption [19,22]. Furthermore, their data were supported by positive changes in biomarkers of alcohol consumption [22], including reduced gamma-glutamyl transferase (GGT) and mean corpuscular volume (MCV) [19,22]. GGT is an enzyme released from hepatocytes in response to alcohol-related damage, while MCV measures average red blood cell (RBC) size [24,25]. A raised MCV may indicate macrocytosis, which often occurs in the setting of alcohol abuse [26]. Barrault *et al.* [19] correlated decreases in these biomarkers with improved liver health and reduced drinking.

Hospitalisation rates
Heydtmann *et al.* [9] also investigated the impact of baclofen on hospitalisation rates through a retrospective case series. In this initial study, 53 AUD ALD patients were treated with varying dosages, tailored according to their individual responses (median dose of 60 mg/day) [9]. Hospitalisation rates and hospital stay duration before and after treatment were compared [9]. Reductions in both outcomes were demonstrated, with patients spending an average of 19.1 days in the hospital per year, compared to 25.48 days prior to commencement of baclofen (p=0.59) [9]. However, this change was not considered statistically significant.

Cost-effectiveness
Avancena *et a*l. [4] explored the effectiveness of various AUD ALD treatments from a cost-benefit perspective (Table 1). Several strategies were compared including providing counselling, offering no intervention, and prescribing AUD medications such as baclofen. This was represented in a schematic diagram, known as a Markov model [27]. This demonstrated the impact of these interventions on ALD progression in hypothetical patients of all ages. Six stages of disease were considered, beginning with compensated alcoholic cirrhosis, followed by decompensated alcoholic cirrhosis, hepatocellular carcinoma, liver transplantation, and death. Transition to each stage was associated with monetary costs and benefits to society and the patient, estimated from previous cost-effective analyses into alcohol-related cirrhosis [4]. For example, baclofen was found to be more cost-saving than a no intervention approach, due to its positive impacts on patient health and disease progression. Despite treatment expenses and ongoing physician fees, baclofen offered long-term benefits to both the hospital system and the individual. These included reduced burden on healthcare services and improved lifetime productivity. The latter was approximated using published data of time spent on alcohol use treatments multiplied by average daily wages [4].

Mortality
Rogal *et al*. [7] considered the efficacy of baclofen in terms of mortality (Table 1). This retrospective cohort study examined various alcohol use disorder treatments amongst 35 682 veterans with both AUD and cirrhosis [7]. Of these, 0.4% received pharmacotherapy, 2% of which were prescribed baclofen specifically, representing 703 patients. All forms of pharmacotherapy decreased long-term mortality and hepatic decompensation. However, baclofen had no impact on short-term mortality, defined as death occurring less than 90 days after presentation to a hospital [28].

Side effects
The possible side effects of baclofen were evaluated in five studies (Table 1) [8,9,19,22,23]. Barrault *et al*. [19] and Addolorato *et al.* [8] specifically investigated low dose baclofen for AUD ALD (30 mg/day and 40 mg/day, respectively). Only minor side effects were reported, including drowsiness and vertigo. Importantly, no renal or hepatic complications were demonstrated [8,19].

Heydtmann *et al*. [9], Owens *et al.* [22] and Morley *et al.* [23] used higher doses of baclofen (60 mg/day, 90 mg/day and 75 mg/day, respectively). In the prospective cohort study by Owens *et al*. [22], one patient developed acute confusion [22]. Morely *et al*. [23] employed an RCT study design with 104 AUD ALD patients assigned to 75 mg/day of baclofen, 30 mg/day, or placebo for 12 weeks. In the 75 mg/day group, one participant attempted to overdose with baclofen, which can be toxic in extreme doses [25]. Others experienced more significant side effects than the low-dose and placebo cohorts, with reports of debilitating sedation and shortness of breath [23].

In contrast to these findings, Heydtmann *et al.* [9] found no serious adverse events amongst 53 AUD ALD patients prescribed high dose baclofen (60 mg/day). Instead, participants self-reported a high level of satisfaction with the drug and overall treatment experience [9]. Only minor and transient side effects were noted, including fatigue (n=8), decreased libido (n=1), dizziness (n=3), and unsteadiness (n=3). In all cases, these symptoms resolved upon dose reduction [9].

Discussion

Most importantly, baclofen was found to promote alcohol abstinence amongst AUD ALD patients [5,8,18,19,21-23], thus indicating effectiveness. This is supported by a RCT conducted by Addolorato *et al.* [8], representing level one evidence [29]. However, in this trial, abstinence was self-reported, with no objective biomarkers used to monitor ongoing drinking [8]. This method likely introduced measurement bias secondary to human reporting error. Yamini *et al.* [21] also used self-reporting measures to determine abstinence, producing similar effects. A further issue with the RCT by Addolorato *et al.* [8] was that patients received treatment for three months only. Following participants for a longer period and assessing for relapse may have yielded less favourable, but more realistic, findings [8]. The prospective cohort study by Barrault *et al.* [19] used a more longitudinal assessment of baclofen's impact [19]. Patients were treated for 12 months and achieved similar levels of abstinence, suggesting long-term effectiveness [19]. However, only 35% of participants in this study were diagnosed with both AUD and ALD, with the remaining 65% suffering from AUD only [19]. As no distinctions were made between outcomes amongst the AUD ALD patients versus the AUD only patients, the effectiveness of baclofen for AUD ALD specifically remained unclear [19].

Similar methodological flaws were noted in the prospective cohort study by Owens *et al.* [22]. Although most AUD patients achieved abstinence, only 132 of the 219 participants were diagnosed with co-morbid ALD. Therefore, the exact proportion of abstinent AUD ALD patients was also unknown. In addition, all patients received adjunctive counselling sessions, such that the impact of baclofen alone could not be ascertained [30,31].

Moreover, the literature was contradictory regarding baclofen's efficacy for AUD ALD patients with HCV [5,18]. Whilst a double blind, placebo-controlled RCT of only 24 participants by Leggio *et al.* [5] reported high abstinence rates, a larger study of similar design by Hauser *et al.* [18] found no significant difference between placebo and treatment groups [5,18]. These conflicting findings are likely due to differences in patient characteristics, how baseline drinking was defined, and AUD severity. The study by Hauser *et al.* [18] included veterans with lower levels of baseline drinking than seen in other publications [5,18]. Prior to treatment, participants were consuming an average of 7.65 drinks per day in the placebo group, versus 7.12 drinks per day in the baclofen group [18]. It is possible that these patients experienced fewer consequences from their drinking, and thus felt less inclined to commit to treatment. In contrast, Leggio *et al.* [5] included patients drinking 16 and 21 alcoholic beverages per day in the placebo and baclofen cohorts respectively [5]. Hauser *et al.* [18] also focused exclusively on war veterans, who were predominantly male and suffering from PTSD [18]. Therefore, these findings may not be generalisable or comparable to a wider patient group with fewer psychiatric co-morbidities [18].

Three studies described decreased drinking levels from baseline with baclofen administration, which is another measure of effectiveness [9,19,22]. Heydtmann *et al.* [9] used a standard questionnaire to gauge patient alcohol use, potentially introducing recall bias. Retrospective reporting of alcohol consumption is likely to be inaccurate, with over or under-estimation common [9]. An element of social desirability bias may also be present due to the nature of the survey and its sensitive subject matter. This refers to the tendency of individuals to respond in a manner that will be perceived well by others [32]. It is also possible that only those with favourable outcomes returned the questionnaire, thus positively inflating the results [32]. In addition, the researchers noted a low response rate of 41% [9]. As just 19 out

9

of 53 participants returned the survey, external validity is limited [9]. Furthermore, and most importantly, the results were not reported as statistically significant (p = 0.59).

Barrault *et al.* [19] and Owens *et al.* [22] also concluded that baclofen reduced participant alcohol usage, as indicated by decreases in GGT and MCV [19,22]. However, it is difficult to determine if these results were solely caused by lower drinking levels [22]. Although indicative of improvements in liver function, such surrogate measures lack specificity in relation to alcohol [22]. For example, GGT may be affected by factors unrelated to drinking, including medication use and viral hepatitis [24]. Similarly, a raised MCV can occur secondary to vitamin B12 deficiency [26]. Using more specific methods, such as blood/breath alcohol concentration, would allow this distinction to be made [22]. In future, combining the survey approach of Heydtmann *et al*. [9] with more objective biomarker data could overcome the limitations of each individual technique.

Heydtmann *et al.* [9] also conducted a retrospective case series in which baclofen was reported to reduce hospitalisation rates [9]. In this instance, the relatively small sample size of 53 participants represents a potential drawback, which likely limits the generalisability of results. However, it could also be argued that this sample was highly representative of AUD ALD patients in general. Data were gathered directly from hospital records, thus simulating a real-world experience [9]. Furthermore, patients with comorbid psychiatric conditions were not excluded, which is important given the high prevalence of mental health disorders in this population [9,26].

In terms of cost-effectiveness, an article by Avancena *et al*. [4] concluded that baclofen provides societal and health-care benefits [4]. However, the Markov model used to predict these outcomes assumed participants were already seeking care and wanted to improve their health [4]. Similar findings may not apply to patients unable or unwilling to commit to treatment over the long-term [4]. Moreover, it should be noted that this model was heavily simplified and did not account for all aspects of the patient ALD AUD experience. For example, the costs of alcohol withdrawal were not considered in the analysis, such that the benefits of baclofen treatment may be overestimated [4].

Interestingly, Avancena *et al*. [4] included data from patients aged 25 to 65, in contrast to other included studies that focused predominantly on middle-aged individuals [5,8,19,21,22]. Thus, the study provides a new insight into baclofen for younger patients in the context of increasing prevalence of ALD within this age group[4].

In a retrospective cohort study by Rogal I. [7], baclofen was additionally found to reduce long-term mortality and hepatic decompensation amongst veterans [7]. These conclusions were drawn from a sample of 703 participants, so external validity was relatively high [7]. However, the exclusive focus on veterans may have reduced the study's generalisability. Moreover, it was unclear exactly why these patients had been prescribed baclofen. The cohort generally scored low on the Alcohol Use Disorders Identification Test – Consumption (AUDIT-C) screening tool, indicating reduced AUD severity prior to treatment [7]. In addition, 59% had been diagnosed with a concurrent chronic pain condition. Based on these factors, researchers hypothesised that patients were receiving baclofen for pain rather than for AUD ALD [7]. If true, treatment outcomes would have been affected significantly, and potentially underestimated. However, this theory could not be confirmed due to a lack of detail from the study regarding indications [7].

Finally, results concerning baclofen's side effect profile were conflicting. Complications occurred only in trials involving higher doses of baclofen (60 mg/day and 75 mg/day), representing a dose-related adverse drug reaction profile [22,29]. However, this was contrary to the findings of Heydtmann *et al*. [9]. In this retrospective case series, patients also received 60 mg/day, but did not experience the same severe side effects. This may be explained by differences in methodology between the studies. For example, in Heydtmann *et al.* [9], patients experiencing minor discomfort were permitted to reduce their dosage. This method of tailoring was designed to ensure satisfaction and minimise consequences [9]. Patients were not given this option in the studies by Owens *et al*. [22] and Morely *et al.* [23], potentially leading to adverse events such as acute confusion and attempted overdose, respectively.

The overdose raised concerns about the efficacy and safety of baclofen, particularly for those with suicidal tendencies. We suggest additional research into its abuse potential given the incidence of depression amongst ALD AUD patients.

Conclusion
Our review aimed to determine the viability of baclofen as a potential treatment for AUD and ALD [1]. We found that it promotes alcohol abstinence, the primary goal of ALD management and an important measure of effectiveness [5,8,18,19,21-23]. However, it was associated with an overdose and other minor side effects. Furthermore, our conclusions were limited predominantly by heterogeneity in the literature and a shortage ofRCTs. Additional clinical trials are required to confirm previous findings and determine its safety for high-risk groups.

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Table 1. Summary of articles selected for review

Ref	Title	Study design	Measures of effectiveness and safety	Sample size (N)	Intervention group/s	Control group/s	Patient characteristics	Results
[3]	Impact of alcohol use disorder treatments on clinical outcomes among patients with cirrhosis	Retrospective cohort	Short-term mortality, long-term mortality	5,088	Veterans with AUD and liver cirrhosis receiving behavioural therapy versus pharmacotherapy versus both	-	• Median age of 58.7 years • Included patients with mood disorders, anxiety disorders, schizophrenia, PTSD, other addictions	Baclofen was not associated with short-term mortality when controlling for other factors
[4]	Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis	Double blind, placebo-controlled RCT	Alcohol abstinence, LFTs, side effects	84	AUD patients with liver cirrhosis receiving 30 mg/day baclofen, over three months	AUD patients with liver cirrhosis receiving placebo, over three months	• Median age of 49.5 years • Median alcohol abuse duration of 22.0 years • Excluded patients with abnormal renal function, hepatorenal syndrome, malignant disease, psychiatric conditions, metabolic diseases, hepatic encephalopathy or other addictions	Baclofen was more effective than placebo for achieving and maintaining abstinence and improving LFTs; baclofen was generally more effective in patients with advanced liver cirrhosis; no significant side effects
[6]	Tailored dose baclofen in patients with alcoholic liver disease: a case	Retrospective case series with questionnaire	Hospitalisation rates, days spent in hospital, side effects, alcohol	53 with 19 questionnaire responses	AUD patients with ALD receiving median highest dose of 60 mg/day baclofen,	-	• Median age of 50.12 years • Included patients with psychiatric conditions and	Baclofen was effective in reducing hospitalisation rates and days spent in hospital; no

	series with 2-year follow-up of hospitalisation		consumption		over two years		undisclosed medical comorbidities	significant side effects
[13]	The safety and efficacy of baclofen to reduce alcohol use in veterans with chronic hepatitis C	Double-blind, placebo-controlled RCT	Alcohol abstinence, alcohol consumption, side effects	180	Veterans with chronic hepatitis C and AUD receiving 30 mg/day baclofen, over 12 weeks	Veterans with chronic hepatitis C and AUD receiving placebo, over 12 weeks	• Mean age of 57.0 years • Excluded patients with metabolic disorders, other addictions • Included patients with post-traumatic stress disorder, depression, anxiety	No significant difference found between groups in terms of number of days abstinent and level of alcohol consumption; no significant side effects
[14]	One year of baclofen in 100 patients with or without cirrhosis	Prospective cohort	Alcohol abstinence, alcohol consumption, LFTs	100	AUD patients with or without liver cirrhosis receiving mean dose of 40 mg/day baclofen, over 12 months	-	• Median age of 53.0 years • Excluded patients with psychiatric conditions, hepatic encephalopathy, epilepsy or renal failure	Baclofen was effective for achieving alcohol abstinence, decreasing alcohol consumption, improving LFTs; no significant side effects
[16]	Utilization of baclofen in maintenance of alcohol abstinence in patients with alcohol dependence	Retrospective cohort	Alcohol abstinence, LFTs	35	AUD patients with alcoholic hepatitis and liver cirrhosis receiving 10 mg baclofen three times daily, over 12 months	-	Mean age of 50.5 years	Baclofen was effective in achieving and maintaining alcohol abstinence and improving LFTs

	and alcoholic hepatitis with or without cirrhosis						
[17]	Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with HCV infection	Double-blind, placebo-controlled RCT as a post-hoc analysis of [4]	Alcohol abstinence, LFTs	24	AUD patients with HCV and liver cirrhosis receiving 30 mg/day baclofen, over three months	AUD patients with HCV and liver cirrhosis receiving placebo, over three months	• Median age of 47.0 years • Median alcohol abuse duration of 19 years	Baclofen was more effective than placebo for achieving and maintaining abstinence and improving LFTs; no significant side effects
[18]	A prospective cohort study examining the effectiveness of baclofen in the maintenance of abstinence in alcohol use disorder patients attending a joint liver and alcohol treatment clinic	Prospective cohort	Alcohol abstinence, alcohol consumption, side effects	219	AUD patients with or without ALD receiving up to 30 mg baclofen three times daily, over three months	-	Median age of 48.0 years	For all patients, baclofen was effective for achieving alcohol abstinence and reducing alcohol consumption; no significant difference in results was found between cirrhotic and non-cirrhotic patients; acute confusion reported as a side effect

Ref								
[22]	Cost-effectiveness of alcohol use treatments in patients with alcohol-related cirrhosis	Markov modelling	Cost-effectiveness	-	Simulated AUD patients with liver cirrhosis receiving approved pharmacotherapy versus non-approved pharmacotherapy versus counselling	Simulated AUD patients with liver cirrhosis receiving no intervention	Patients 25 to 65 years	Baclofen was more cost-saving and cost-effective for society and the health-care system than a do-nothing approach
[25]	Baclofen in treatment of alcohol dependence with or without liver disease	Double-blind, placebo-controlled RCT	Side effects, alcohol abstinence	104	AUD patients with or without ALD receiving high-dose baclofen (75 mg/day) and low-dose baclofen (30 mg/day), over 12 weeks	AUD patients with or without ALD receiving placebo, over 12 weeks	• Median age of 48.2 years • Excluded patients with psychiatric conditions • Median alcohol abuse duration of 16.3 years	High-dose baclofen was associated with a larger number of side effects than low-dose baclofen, including shortness of breath and overdose

Ref, reference; LFTs, liver function tests; AUD, alcohol use disorder; RCT, randomised controlled trial; ALD, alcoholic liver disease; HCV, hepatitis C virus