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Systematic review: Interventions for alcohol use disorder in patients with cirrhosis or alcohol-associated hepatitis

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Summary

Background: Alcohol use is the most important factor in determining the prognosis of patients with alcohol-related cirrhosis and alcohol-associated hepatitis.

Aim: To conduct a systematic review of interventions for alcohol use disorder specific to patients with cirrhosis or alcohol-associated hepatitis.

Methods: We searched five databases between inception and November 2022. The primary outcomes were abstinence, hepatic decompensation and mortality. We included randomised and non-randomised studies. Risk of bias was assessed using validated tools. Where possible, meta-analysis was performed.

Results: Twenty-three studies met the inclusion criteria including six randomised trials and 17 non-randomised studies of interventions. These included 104,298 patients with a mean/median age range from 44 to 65, of whom 75% were male. Interventions included psychological therapy, pharmacological therapies, specialist clinics, patient education and low alcohol drinks. Baclofen was the only intervention to demonstrate a statistically significant impact on the primary outcomes in a randomised trial (abstinence OR: 6.3, 95% CI: 2.4–16.1). Three non-randomised studies reported reductions in episodes of hepatic decompensation that were significant in multivariate models. This was in response to psychological therapy, use of any pharmacotherapy, and use of any treatment. A meta-analysis of non-randomised studies that examined the impact of psychological therapies revealed statistically non-significant improvements in abstinence (4 studies, OR: 1.87, 95% CI: 0.38–9.23) and mortality (4 studies, OR: 0.47, 95% CI: 0.12–1.77).

Conclusions: Baclofen is the only intervention with randomised trial evidence for significant benefit in patients with cirrhosis. Non-randomised studies also point to non-pharmaceutical interventions possibly improving clinical outcomes.

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1 | INTRODUCTION

Alcohol is the leading risk factor for attributable burden of disease worldwide among people aged 15–49.[1] Alcohol use disorder (AUD) is a spectrum of illness characterised by an impaired ability to stop drinking alcohol despite adverse health, social or occupational consequences.[2] Alcohol-related liver disease is one such consequence. It is the leading cause of liver-related death in Europe and was responsible for more than 332,000 deaths globally in 2017.[3]

The most advanced stage of alcohol-related liver damage is cirrhosis where the liver is irreversibly scarred. For patients with cirrhosis, abstinence from alcohol is the only treatment which can halt liver disease progression. Patients who maintain abstinence from alcohol for 18 months are 50% more likely to be alive than those who continue to drink.[4] All patients with cirrhosis who continue to drink alcohol meet criteria for a diagnosis of AUD, since they continue drinking in the face of adverse health consequences.

It is important therefore that healthcare professionals have access to evidence-based interventions to support patients with cirrhosis in managing AUD, reducing their alcohol intake and ultimately achieving abstinence. Previous systematic reviews have examined the effectiveness of AUD interventions,[5–10] but were not specific to patients with cirrhosis. One previous systematic review explored psychological interventions in patients with liver disease and found that only a 2-year intervention combined with medical therapy was effective.[11] Helping patients with cirrhosis reduce their alcohol intake presents unique challenges. Approved drug treatments for AUD are either contraindicated in cirrhosis (disulfiram, naltrexone and nalmefene) or lack an evidence base for safety, dosing and effectiveness (acamprosate, baclofen).[12–14] These challenges create reluctance among prescribers and low uptake of treatments.[15] A retrospective study of 93,612 US veterans with cirrhosis found that only 1% had received behavioural and pharmacologic treatment for alcohol use disorder.[16]

There are also treatments that may be of particular relevance to patients with established cirrhosis and might not be as effective in other populations. Educational strategies, such as providing information about stages of liver disease[17,18] and the beneficial effect of abstinence, might be used as a mechanism of positive reinforcement. For patients with decompensated cirrhosis or alcohol-associated hepatitis, it could be important to stress the reversibility of symptoms such as ascites, jaundice, encephalopathy and sarcopaenia, and the potential for improved prognosis, if patients can achieve abstinence.

Finally, there is an opportunity to evaluate the impact of AUD interventions based on clinically important outcomes such as hepatic decompensation (ascites, bleeding, encephalopathy, etc) and mortality.

In this paper, we present a systematic review of the literature to understand the available interventions and their effectiveness specifically in patients with cirrhosis. We include patients with alcohol-associated hepatitis. A majority of patients with alcohol-associated hepatitis also have cirrhosis and the challenges and opportunities related to achieving abstinence are similar in both groups.[19]

2 | METHODS

The protocol was prospectively registered on PROSPERO (ref: CRD42022383530).[20] We closely followed the guidance in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21] in designing the protocol. Reviewing of abstracts, full-text reviews, selection of studies, data extraction and quality assessment were conducted independently by two authors (CO and OG), with disagreements resolved by discussion or by a third author.

The search strategy was developed in collaboration with a librarian at the University of Cambridge Clinical School Library and with a patient and public involvement panel. Elements of the search strategy were influenced by other systematic reviews in related topics.[11,17,22] The searches were optimised using techniques described by Bramer et al.[23] An example search is provided in Appendix S1. The search included four main domains: terms for study type, terms for alcohol use, terms for liver disease and terms for interventions. Filters for study type were taken from those developed for systematic reviews by the Scottish Intercollegiate Guidelines Network.[24]

The following databases were searched from inception to 15th November 2022: Medline (via Ovid), EMBASE (via Ovid), Psychinfo (via ProQuest), CINAHL (via EBSCOhost), Web of Science Core Collection and The Cochrane Central Register of Controlled Trials (CENTRAL). Grey Literature was searched via ScanMedicine[25] looking for relevant unpublished clinical trials or cohort studies. Hand searching was undertaken of reference lists of key papers and included studies as well as major guidelines. Forward searching to identify papers that cited those included in the review was also undertaken.

All search results were stored in Endnote X20 (Thomson Reuters).[26] All reasonable efforts were made to obtain full-text copies of manuscripts and any relevant missing data, including contacting the corresponding authors.

Studies were included if they measured the impact of an intervention aimed at reducing alcohol intake in adult patients of any age with a clinical diagnosis of cirrhosis or alcohol-associated hepatitis. We excluded patients who had received a liver transplant. Since the objective was to capture a broad spectrum of available evidence, we included randomised controlled trials (RCTs) and non-randomised studies of interventions (NRSIs). We excluded review articles and case reports. We included only studies with full text available in English. Diagnosis of cirrhosis or alcohol-associated hepatitis included clinical diagnosis, radiological evidence, histological evidence, or diagnosis based on elastography. Studies with mixed populations that included an identifiable sub-group of patients with cirrhosis or alcohol-associated hepatitis were also included. In those cases, only data specific to patients with cirrhosis or alcohol-associated hepatitis was included in the review. Any

intervention aimed at reducing future alcohol intake was included. Search terms were selected to identify psychological therapies, pharmacological therapies, mobile applications, or other technologies, follow-up clinics or services, educational interventions and biofeedback. We excluded studies where the intervention was intended to improve liver disease through a mechanism other than alcohol reduction.

The primary outcomes were abstinence, hepatic decompensation and mortality. These outcomes were selected in discussion with the patient and public involvement panel and after a scoping review of the data. Each outcome was recorded as defined by the reporting authors. All other reported outcomes from included studies were recorded as secondary outcomes. We also recorded whether studies reported on clinical outcomes (mortality, hospitalisation, hepatic decompensation), alcohol intake outcomes (abstinence, reduction in alcohol, craving) or both outcome categories. For studies that reported post liver transplant outcomes, only the pre-transplant outcomes were recorded.

2.1 | Data reporting and analysis

We report the interventions assessed, outcome measures and impact detected. The narrative synthesis focuses on the interventions that were found to have a statistically significant impact ($p < 0.05$) on the primary outcomes on univariate analysis and in multivariate models. The impact of interventions on all reported outcomes from included studies is included as Table S1.

Where possible and appropriate, meta-analysis was used to estimate the pooled odds ratio (OR) for the primary outcomes using Review Manager version 5.1 (The Nordic Cochrane Centre). The Mantel–Haenszel estimator was used to calculate ORs. Statistical heterogeneity was assessed by visual inspection of data and by using the Higgins I^2 value. Due to high levels of heterogeneity, a random-effects model was used to pool data.

Risk of bias in RCTs was evaluated using the Cochrane Collaboration Tool.[27] The quality of NRSIs was evaluated using the Newcastle–Ottawa Scale (NOS)[28] a validated and recommended tool. Scores in the NOS are assigned for selection criteria, comparability and outcome. A maximum score of nine reflects the highest quality. To assess for reporting bias, we compared the outcomes specified in trial protocols with the outcomes reported in the corresponding study publications. We also compared the outcomes reported in the methods and results sections of the study publications.

2.2 | Patient and public involvement

A panel of six patients with lived experience of AUD and alcohol-related cirrhosis advised on the design of this study. Input included developing search terms and selection of the primary outcomes. The panel was also influential in the interpretation of the findings and in the content of the discussion.

3 | RESULTS

The searches returned 16,255 results. After duplicates were removed there were 12,003 unique records. An additional two records were added after reviewing the reference lists of relevant review articles. One hundred and forty-six articles were reviewed in full text and 23 studies were eligible for inclusion in the review[16,29–50] (Figure 1). One study reported on two distinct cohorts[42] (a retrospective cohort with prospective validation) which were treated as separate populations.

3.1 | Characteristics of included studies

The study population included 104,298 patients with a mean/median age range from 44 to 65, of whom 75% were male. Of these, 1033 patients had alcohol-associated hepatitis and 296 patients were on the waiting list for liver transplant. The study population was dominated by two, large, retrospective, database-derived cohorts which included a combined 101,735 patients with cirrhosis. The remaining 21 studies included 2563 patients. There were six RCTs that enrolled 293 patients (Table 1). Study populations were heterogeneous including patients listed, or under consideration, for liver transplantation, inpatients, outpatients and database-derived populations. With two exceptions, all of the non-database-derived studies were conducted in specialist liver centres.

3.2 | Randomised studies

The interventions assessed in RCTs were: baclofen, faecal microbiota transplant (FMT), motivational enhancement therapy, educational sessions, a text-message-based intervention and 6 months of integrated co-located psychological therapy. Two RCTs reported on both clinical outcomes and alcohol intake outcomes.[29,30] The remaining four studies reported only on alcohol intake outcomes.[31–34]

Baclofen was the only intervention to demonstrate a statistically significant impact on the primary outcomes in univariate analyses, showing improvements in abstinence rates (OR: 6.3, 95% CI: 2.4–16.1).[29] The remaining interventions did not find any statistically significant effects on our primary outcomes. The impact of interventions on univariate analysis for all reported outcomes is provided in Table S1.

Two randomised studies employed multivariate models in their analysis (Table 3). Only baclofen was found to have a statistically significant impact in reducing rates of alcohol lapse (HR: 0.2, 95% CI: 0.1–0.9) and relapse (HR: 0.4, 95% CI: 0.2–0.8). None of the RCTs reported a significant impact on the primary outcomes in multivariate models.

3.3 | Non-randomised studies of interventions

Ten NRSIs examined the impact of psychological treatments or alcohol rehabilitation[16,35,36,39–43,45,49] (Table 2). For the purpose

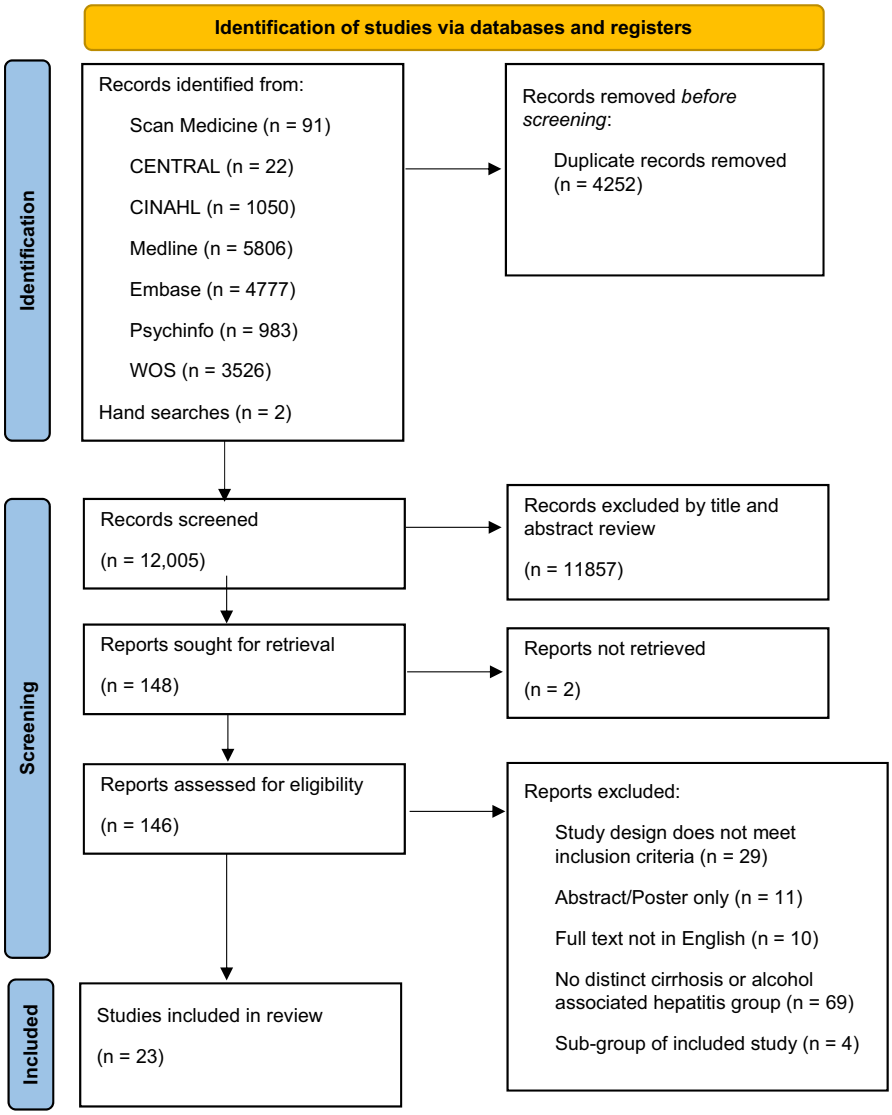

FIGURE 1 PRISMA diagram.

of this analysis, these psychological therapies were grouped together and considered to have a class effect.[51,52] The specific components and definitions of each intervention are reported in Table S2. Seven studies examined the impact of pharmacological interventions (acamprosate,[48] baclofen,[38,48] naltrexone,[37] any pharmacotherapy[16,45,50] and FMT[47]). Other interventions assessed in only one study were as follows: specialist multidisciplinary clinic,[46] general outpatient clinic attendance[44] and low-alcohol drink use.[35]

Two studies assessed the overall impact of any intervention.[16,45] Only one study specifically examined combined psychological therapy and pharmacotherapy.[53]

A majority of studies compared the intervention to no treatment or to standard of care. In one case, standard of care explicitly included the use of corticosteroids.[47] In several studies, patients in the control arms had access to some form of alcohol treatment or support. Two studies did not report a control group,[37,38] one compared hospital admissions for participants over a 6-month period before and after entering a specialist clinic[46] and one study compared acamprosate with baclofen.[48]

Six NRSIs reported exclusively on clinical outcomes[16,37,45,46,49,50] and four reported exclusively on alcohol intake outcomes.[35,38–40] The remaining seven studies reported both outcome categories.[36,41–44,47,48]

Many interventions were found to have a statistically significant benefit on univariate analysis in at least one primary outcome measure (Table S1). Six NRSIs with control groups reported multivariate analysis (Table 3). The statistical methods and covariates included in these analyses are reported in Table S3. Three studies reported statistically significant reductions in episodes of hepatic decompensation on multivariate analysis.[16,45,50] This was in response to psychological therapy,[45] use of any pharmacotherapy for AUD[45,50] and use of any AUD treatment.[16,45] In addition, one study examining psychological therapy and reporting two cohorts demonstrated improvements in hospital readmissions and alcohol relapse at 30 days, as well as mortality over a median follow-up of 2.8 and 1.3 years.[42] Conversely, Kalaitzakis et al reported that psychological treatment was independently associated with increased mortality during follow-up.[41] The authors note, however, that liver transplant was included as a combined outcome with mortality and that their local

TABLE 1 Characteristics of randomised studies.

Study	Country	Setting	Specialist centre	Age	Male	*n*	Intervention	Comparison	Outcome categories	Follow up (months)
Addolorato 2007[29]	Italy	IP/OP	Yes	49	73%	84	Baclofen	Placebo	Alcohol intake Clinical	3
Bajaj 2021[30]	USA	OP	Yes	65	100%	20	Faecal transplant	Placebo	Alcohol intake Clinical	6
DeMartini 2018[31]	USA	LTA	Yes	51	73%	15	Text-message intervention	Standard care	Alcohol intake	2
Proeschold Bell 2020[32]	USA	OP	Yes	NR	NR	58	Psychological therapy	SBIRT only	Alcohol intake	12
Sussman 2005[33]	USA	OP	Yes	44	75%	25	Educational sessions	Standard care	Alcohol intake	3
Weinrieb 2011[34]	USA	LTA	Yes	49	84%	91	Motivational therapy	Standard care	Alcohol intake	24

Note: Age and follow up = mean or median.

Abbreviations: IP, inpatients; LTA, liver transplant assessments; NR, not reported; OP, outpatients; SBIRT, screening, brief intervention & referral to treatment.

protocol required patients undergoing transplantation to engage with psychological therapy.

3.4 | Meta-analysis of primary outcomes

In keeping with guidance from the Cochrane Collaboration, we did not combine RCTs and NRSIs in meta-analysis. Moreover, no studies conducted in a population of patients awaiting liver transplant were included in meta-analysis since this patient population was considered to have distinct characteristics which differ significantly from non-transplant listed patients. Thus, meta-analysis of RCT data was not possible since no two studies examined similar treatments in comparable populations.

We were able to conduct a meta-analysis of NSRIs which examined the impact of psychological therapies and reported on the primary outcomes of abstinence and mortality. Five cohorts reported in four studies provided data on abstinence in a comparable format (Figure 2A). The pooled OR for abstinence was 1.87 (95% CI: 0.38–9.23). Five cohorts from four studies reported on mortality for psychological therapies and were combined in a meta-analysis (Figure 2B). The pooled OR for mortality was OR: 0.47 (95% CI: 0.12–1.77). Insufficient data on comparable studies existed for meta-analysis of outcome data related to hepatic decompensation.

3.5 | Quality assessment

Risk of bias of RCTs and NRSIs is reported (Tables 4 and 5). The nature of the interventions meant that blinding of patients and investigators was challenging or impossible. Some studies provided little or no details on the randomisation process. Studies also suffered from high rates of patient drop out in the pre-randomisation and post-randomisation phases. Four of the studies had small numbers or were pilot studies examining feasibility and safety.

For NRSIs, the overall quality of the studies was good with all studies scoring 6–9 on the NOS. The most common weakness identified was the lack of consideration for confounding factors that might influence the reported outcomes. Some reported multivariate analysis such as Cox regression, but none of the studies employed risk-matched cohorts.

3.6 | Publication and reporting bias

Grey literature searching identified two potential study protocols which were relevant to the review and completed but had not been reported. Analysis of outcomes stated in the protocols and methods sections for included studies revealed consistency between intended and reported outcomes with only minor deviations.

4 | DISCUSSION

Our primary outcomes of interest were abstinence, hepatic decompensation and mortality. We identified six RCTs which met the inclusion criteria, of which two suffered from a very high risk of bias. Studies examined a wide range of interventions. Notably absent from the literature was the testing of complex or combined interventions. Also absent were studies specifically examining peer support or group therapies. Despite the widespread availability of mobile applications designed to support and monitor abstinence,[54] these have not been studied in patients with cirrhosis. For the non-database-derived evidence, the vast majority of included patients were recruited from tertiary centres with

TABLE 2 Characteristics of non-randomised studies.

Study	Country	Setting	Specialist Centre	Age	Male	*n*	Intervention	Comparison	Outcome categories	Follow up (months)
Altamirano (2012)[35]	Spain	LTA	Yes	49	88%	90	Low-alcohol drinks Previous psychological therapy	No low-alcohol drinks No previous psychological therapy	Alcohol intake	6
Andersen (2013)[36]	Denmark	IP	Yes	55	71%	33	Psychological Therapy	No treatment	Alcohol intake Clinical	10
Ayyala (2022)[37]	USA	IP/OP	No	54	87%	47	Naltrexone	None	Clinical	24
Barrault (2017)[38]	France	IP/OP	Yes	55	77%	65	Baclofen	None	Alcohol intake	12
Bjornsson (2020)[39]	Iceland	IP	Yes	56	72%	158	Psychological Therapy	No treatment	Alcohol intake	12
Erim (2016)[40]	Germany	LTA	Yes	53	61%	100	Psychological Therapy	Treatment dropouts	Alcohol intake	6
Kalaitzakis (2008)[41]	Sweden	IP/OP	Yes	58	70%	87	Psychological therapy	No treatment	Alcohol intake Clinical	19
Kamath (2020)[42]	USA	IP	Yes	48	67%	135	Psychological therapy	No treatment	Alcohol intake Clinical	31
Kamath (2020)[42]	USA	IP	Yes	50	58%	159	Psychological therapy	No treatment	Alcohol intake Clinical	16
Lopez-Pelayo (2019)[43]	Spain	IP	Yes	49	67%	120	Psychological Therapy	Treatment dropouts	Alcohol intake Clinical	24
Majc (2018)[44]	Slovenia	OP	No	59	80%	199	Attending OP clinic	Admissions only	Alcohol intake Clinical	60
Mellinger (2019)[45]	USA	Database	No	55	68%	66,053	Any psychological therapy. Any pharmacotherapy Either psychological or pharmacotherapy.	No treatment	Clinical	12
Mellinger (2021)[46]	USA	OP	Yes	47	45%	51	Multi-disciplinary clinic	None	Clinical	6
Philips (2022)[47]	India	IP	Yes	47	100%	61	Faecal Transplant	Corticosteroids	Alcohol intake Clinical	36
Rogal (2020)[16]	USA	Database	No	59	98%	35,682	Any psychological therapy Any pharmacotherapy Either psychological therapy or pharmacotherapy. Both psychological therapy and pharmacotherapy.	No treatment	Clinical	6
Tyson (2022)[48]	UK	IP/OP	Yes	53	65%	92	Acamprosate	Baclofen	Alcohol intake Clinical	36
Vannier (2022)[49]	USA	Database	No	NR	NR	467	Any psychological therapy	No treatment	Clinical	46
Vannier (2022)[50]	USA	Database	No	NR	NR	406	Any pharmacotherapy	No treatment	Clinical	120

Note: Age and follow-up = mean or median. Kamath et al describe two cohorts treated separately in this review.

Abbreviations: IP, inpatients; LTA, liver transplant assessments; NR-not reported; OP, outpatients; P, prospective; R, retrospective.

TABLE 3 Multivariate analysis in all studies.

Interventions	Outcome	Study	Effect size	*p* value/ 95% CI
RCTs				
Baclofen	Lapse	Addolorato (2007)[29]	HR: 0.2	0.1–0.9
	Relapse	Addolorato (2007)[29]	HR: 0.4	0.2–0.8
MET	Drinking	Weinrieb (2011)[34]	NR	Not significant
NRSIs				
Any psychological therapy	Hepatic decompensation	Mellinger (2019)[45]	HR: 0.89	<0.035+001
	Hepatic decompensation	Vannier (2022)[49]	HR: 0.62	0.34–1.07
	Hospital readmission	Kamath (2020)[42]	AOR: 0.16	0.04–0.65
	Hospital readmission	Kamath (2020)[42]	AOR: 0.3	0.09–0.98
	Relapse	Kamath (2020)[42]	AOR: 0.11	0.02–0.53
	Relapse	Kamath (2020)[42]	AOR: 0.09	0.01–0.73
	Mortality	Kamath (2020)[42]	AHR: 0.2	0.05–0.56
	Mortality	Kamath (2020)[42]	0.2	0.01–0.94
	Mortality or liver transplant	Kalaitzakis (2008)[41]	Beta co-efficient: 3.96	0.035+
Any pharmacotherapy	Hepatic decompensation	Vannier (2022)[50]	HR: 0.38	0.25–0.57
	Hepatic decompensation	Mellinger (2019)[45]	HR: 0.65	<0.001
Any AUD Tx	Mortality	Rogal (2020)[16]	AOR: 0.79	0.57–1.08
	Hepatic decompensation	Rogal (2020)[16]	AOR: 0.63	0.52–0.76
	Hepatic decompensation	Mellinger (2019)[45]	HR: 0.85	<0.001

Note: "+" denotes that psychological therapy was associated with increased mortality. *p*-values are provided where 95% CI was unavailable.
Abbreviations: AOR, adjusted odds ratio; HR, hazard ratio; NR, not reported.

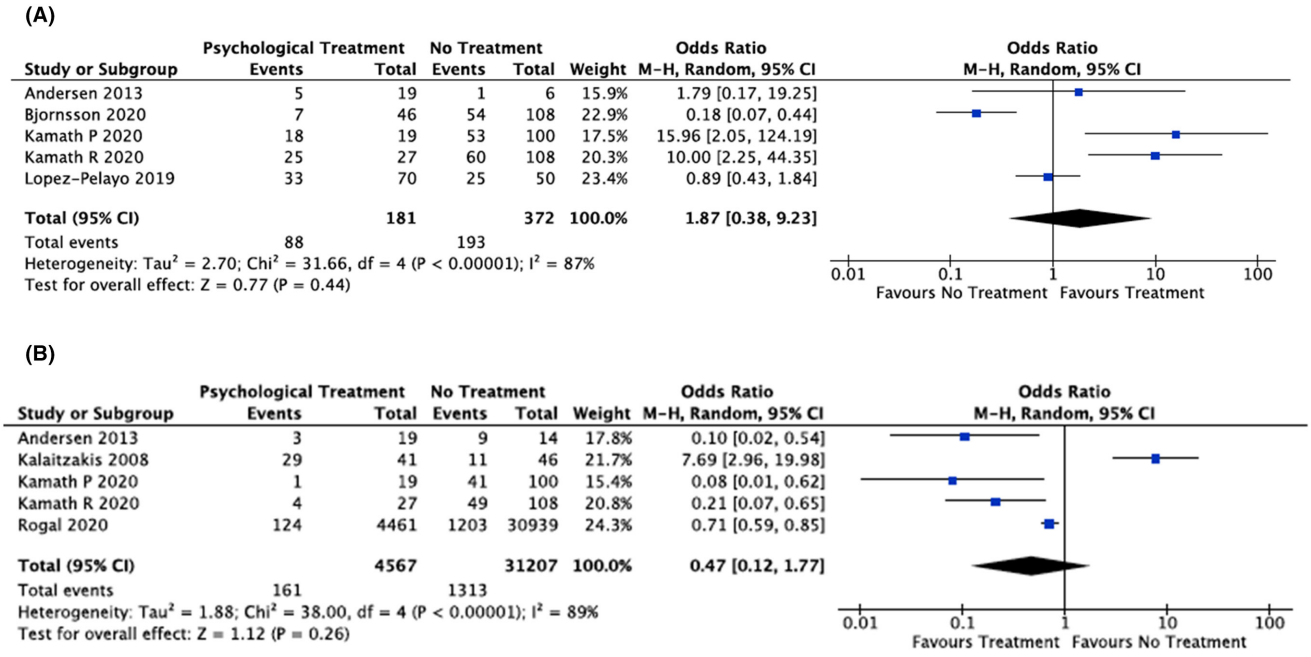

FIGURE 2 Meta-analysis. (A) Abstinence. Pooled OR indicates higher rates of abstinence in treated group. (B) Mortality. Pooled OR indicates a lower rate of death in treated group.

specialist interests in hepatology and/or alcohol use disorder. This is important when considering the applicability of the findings to other settings.

From the RCT data, only baclofen was shown to have a positive impact on the primary outcomes (abstinence OR: 6.3, 95% CI: 2.4–16.1, $p < 0.001$). Despite this finding in a high-quality

placebo-controlled RCT and supporting data on the effectiveness and safety of baclofen in patients with cirrhosis, it has not yet been universally adopted or licensed for this indication. Further evidence for the use of baclofen in patients with liver disease supports its role in this population but was excluded from this review either because data on patients with cirrhosis was not clearly reported[55] or because the report fell out with the timeframe of our searches.[56]

This review highlights that other pharmacological interventions lack the evidence base required to be included in national and international guidelines and therefore clinical practice. Despite the lack of RCT data for agents such as acamprosate and naltrexone, which are widely used, there are signals from the NRSIs included in the review that any pharmacological intervention could be effective in promoting abstinence, reducing episodes of hepatic decompensation and potentially decreasing mortality.

Psychological therapies are challenging to evaluate in this population. Two confounding effects are recognised. The first is that attendance at psychological treatment and rehabilitation may be a marker of more severe dependency and thus predicts future alcohol use. This observation is reported in three of the studies included in this review.[35,39,41] Second, in the case of patients with cirrhosis, it could be that patients with advanced disease become too unwell to either consume alcohol or engage with alcohol therapies. Meta-analysis from this review failed to demonstrate a statistically significant benefit from psychological therapies on either mortality or abstinence. This might be attributed to the aforementioned phenomena, or to the heterogeneity of interventions and populations combined in the meta-analysis.

The included studies variably reported on outcomes related to alcohol use and/or clinical outcomes. In this population, the impact of AUD treatments on mortality and episodes of hepatic decompensation is particularly important. Large-scale retrospective analyses of usual practice included in this review indicate that AUD interventions can independently impact clinical endpoints. Linking treatments for AUD to improved clinical endpoints in patients with cirrhosis would create a powerful case for better funding and utilisation of these treatments. Well-designed, multi-centre RCTs with propensity-matched cohorts, powered to detect impacts on mortality and hepatic decompensation, are needed.

This review is the first to examine interventions for AUD specifically in patients with alcohol-related cirrhosis and alcohol-associated hepatitis. The 2016 review by Khan et al[11] examined only psychological interventions in patients with variable stages of liver disease. Elfeki et al[57] have also recently published their review of simultaneous management of AUD and liver disease. These reviews overlap with our analysis but included studies which we have excluded either because a diagnosis of cirrhosis was not specified, or because the study examined a post-liver transplant population. Nevertheless, both of those reviews confirm the usefulness of AUD interventions in patients with varying degrees of alcohol-related liver disease.

This review adopted a comprehensive search strategy, clear inclusion criteria and robust methodology following closely Cochrane Collaboration guidelines. The search strategy emphasised sensitivity over specificity, so it is unlikely that important evidence was missed. An advisory panel of patients with lived experience of cirrhosis and AUD helped form the protocol for the review and aided in the analysis of the results. Patient involvement in research ensures that the work is relevant and provides unique insights into the findings which could be missed by clinicians or researchers.[58]

Interpretation of this review is limited by a number of potential factors. A low number of RCTs was found, many of which had a high risk of bias or included low numbers of patients. Feedback from the patient advisory panel helped identify that few studies controlled for important social and economic factors, which are known to influence alcohol intake and therefore other outcomes in this cohort. Specifically, studies did not control for co-existing mental illness, socioeconomic status and perceived social support.[59,60] Where studies did include control groups, they were often not contemporaneous, or the control group also benefited from an alternative form of addiction treatment. Most often, alcohol use was recorded either by record review or by patient history, methods which are known to have significant weakness. By taking a broad approach to inclusion criteria for interventions, we limited the ability to compare studies. Our decision only to include studies

TABLE 4 Quality assessment of randomised studies.

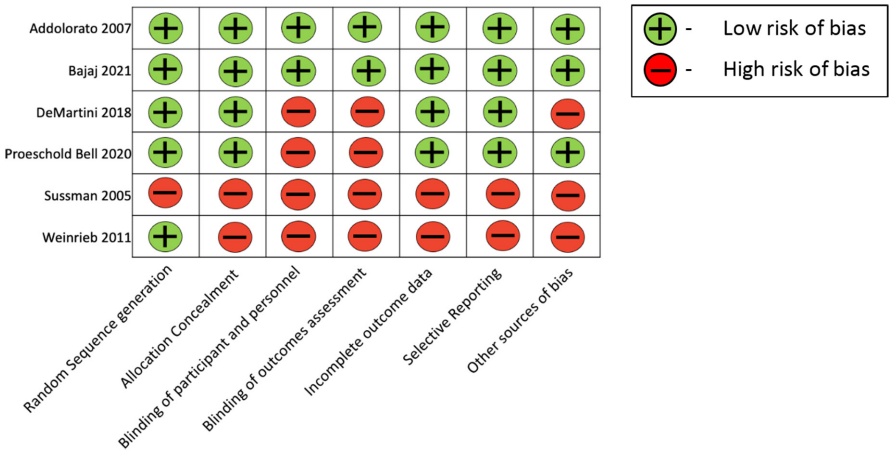

TABLE 5 Quality assessment of non-randomised studies.

Study	Selection	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Demonstration outcome of interest not present at start of study	Comparability	Study controls for abstinence duration	Study controls for additional factor	Outcome	Assessment of outcome	Length of follow-up	Adequacy of cohort follow-up	Score
Altamirano (2012)		+	+	+	–		+	+		+	+	+	8
Andersen (2013)		+	+	+	+		–	–		+	+	–	6
Ayyala (2022)		+	–	+	+		–	–		+	+	+	6
Barrault (2017)		+	+	+	+		+	–		+	+	+	8
Bjornsson (2020)		+	+	+	+		–	–		+	+	+	7
Erim (2016)		+	+	+	–		–	–		+	+	+	6
Kalaitzakis (2008)		+	+	+	+		+	+		+	+	+	9
Kamath (2020)		+	+	+	+		+	+		+	+	+	9
Kamath (2020)		+	+	+	+		+	+		+	+	+	9
Lopez-Pelayo (2019)		+	+	+	+		–	–		+	+	+	7
Majc (2018)		+	+	+	–		–	–		+	+	+	6
Mellinger (2019)		+	+	+	+		–	–		+	+	–	6
Mellinger (2021)		+	–	+	+		+	+		+	+	–	7
Philips (2022)		+	+	+	+		–	+		+	+	–	7
Rogal (2020)		+	+	+	+		–	+		+	+	+	8
Tyson (2021)		+	+	+	+		–	–		–	+	+	6
Vannier (Psych) (2022)		+	+	+	+		–	–		+	+	+	7
Vannier (Pharma) (2022)		+	+	+	+		–	–		+	+	+	7

Abbreviations: R, retrospective cohort; P, prospective cohort.

with full text in English may mean that important studies in other languages were missed.

5 | CONCLUSIONS

This review included the broadest possible range of interventions for AUD in patients with cirrhosis and alcohol-associated hepatitis. It describes the landscape of available evidence and could act as a starting point for the development of novel interventions. Although baclofen was the only intervention with RCT evidence for significant benefit in patients with cirrhosis, NRSIs also point to both pharmaceutical and non-pharmaceutical interventions improving clinical outcomes, in particular rates of hepatic decompensation. In parallel with establishing which therapies are beneficial in this patient group, it is also important to improve access to and uptake of effective interventions[61] and to recognise patient preferences.

AUTHOR CONTRIBUTIONS

Christopher Oldroyd, Caitlin Notley, Michael Allison and Graham Martin conceived of the study and designed the methods. Christopher Oldroyd and Olivia Greenham performed the searches and data collection. Christopher Oldroyd wrote the paper with collaborative input from all other authors. The work is part of a PhD thesis for Christopher Oldroyd with Michael Allison, Caitlin Notley and Graham Martin as supervisors. All authors approved the final verion of this manuscript.

AUTHORSHIP

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CONFLICT OF INTEREST STATEMENT

None of the authors have relevant personal or funding interests to declare. In full interests are as follows: Christopher Oldroyd has received research funding from the National Institute for Health and Care Research. Christopher Oldroyd is an employee of Cambridge University Hospitals NHS Foundation Trust. Graham Martin has served as a speaker for NHS Providers. Graham Martin has served as an advisory board member for the National Institute for Health and Care Excellence. Graham Martin has received research funding from the National Institute for Health and Care Research and the Health Foundation. Graham Martin is an employee of the University of Cambridge. Olivia Greenham has nothing to declare. Michael Allison has received research funding from GlaxoSmithKline. Michael Allison is an employee of Cambridge University Hospitals NHS Foundation Trust. Caitlin Notley is an employee of University of East Anglia. There was no additional team members undertaking analysis. There was no additional funding or support for writing.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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