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Cost-effectiveness of alcohol use treatments in patients with alcohol-related cirrhosis

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Background & Aims: Alcohol use treatment such as medication-assisted therapies (MATs) and counseling are available and effective in promoting alcohol abstinence. We sought to explore the cost-effectiveness of different alcohol use treatments among patients with compensated alcohol-related cirrhosis (AC).

Methods: We simulated a cohort of patients with compensated AC receiving care from a hepatology clinic over their lifetimes. We estimated costs (in 2017 US$) and benefits in terms of quality-adjusted life years (QALYs) gained from healthcare and societal perspectives. Transition probabilities, costs, and health utility weights were taken from the literature. Treatment effects of FDA-approved MATs (acamprosate and naltrexone) and non-FDA approved MATs (baclofen, gabapentin, and topiramate) and counseling were based on a study of employer-insured patients with AC. We calculated incremental cost-effectiveness ratios (ICERs) and performed one-way and probabilistic sensitivity analyses to understand the impact of parameter uncertainty.

Results: Compared to a do-nothing scenario, MATs and counseling were found to be cost-saving from a healthcare perspective, which means that they provide more benefits with less costs than no intervention. Compared to other interventions, acamprosate and naltrexone cost the least and provide the most QALYs. If the effectiveness of MATs and counseling decreased, these interventions would still be cost-effective based on the commonly used $100,000 per QALY gained threshold. Several sensitivity and scenario analyses showed that our main findings are robust.

Conclusions: Among patients with compensated AC, MATs and counseling are extremely cost-effective, and in some cases cost-saving, interventions to prevent decompensation and improve health. Health policies (*e.g.* payer reimbursement) should emphasize and appropriately compensate for these interventions.

Lay summary: Alcohol use treatments, including physician counseling and medication-assisted therapies (MATs), improve the outcomes of patients with compensated alcohol-related cirrhosis, though use and access have remained suboptimal. In this study, we found that counseling and MATs are extremely cost-effective, and in some cases cost-saving, interventions to help patients with alcohol-related cirrhosis abstain from alcohol and improve their health. Wider use of these interventions should be encouraged.

Introduction

Despite optimal management of their liver disease, patients with alcohol-related cirrhosis (AC) can rapidly decline with continued alcohol intake.[1] Alcohol consumption among patients with AC leads to jaundice, variceal bleeding, ascites, and hepatic encephalopathy – the signature symptoms of decompensated cirrhosis which may require liver transplantation.[2] Patients with AC can also develop acute alcoholic hepatitis and hepatocellular carcinoma (HCC) that are, along with decompensated cirrhosis, costly to treat and significantly increase the risk of death.[3] In the US, death rates from AC rose between 2009-2016, particularly among adults aged 25-34 years, who experienced double-digit annual increases in that time period.[4] Concurrently, AC has become the leading cause of liver transplantation in the US.[5]

Alcohol abstinence is associated with increased survival among patients with AC,[6] and various treatment modalities are available to promote abstinence and prevent relapse. Medication-assisted therapy (MAT) involves the daily intake of drugs, such as acamprosate and naltrexone, which the FDA has approved to increase alcohol aversiveness or reduce alcohol cravings.[7] Disulfiram, another FDA-approved MAT for alcohol use disorder (AUD), is highly hepatotoxic and should not be used in patients with AC. Baclofen, gabapentin, and topiramate are also used to treat AUD, though they have not been approved by the FDA for this use in the US.[1] Psychosocial interventions, such as clinician counseling with cognitive behavioral therapy or motivational enhancement therapy, have also been shown to be effective in promoting abstinence.[1,8]

While clinical trials have demonstrated the effectiveness of alcohol use treatments, little to no studies have focused on

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patients with alcohol-related liver disease (ALD) such as AC.[9] To date, only baclofen has been tested in patients with AC,[10] which has led experts to conditionally recommend its use while calling for additional studies.[11,12] Thus, optimal treatment of patients with co-occurring AUD and ALD remains to be defined and is often locally determined.[13] Recent observational studies, however, have shown that patients with AC who received MATs or counseling exhibit marked reductions in the rate of decompensation,[14,15] a key clinical objective in the treatment of ALD. Unfortunately, fewer than 10% of patients with AC receive either counselling or MAT at 1 year after their diagnosis, and these interventions are frequently poorly reimbursed.[14]

Increased use of alcohol use treatments among patients with AC is likely to be a good investment because of the significant costs that AC and its complications exact on healthcare systems, patients and their families, and society at large. To explore the value of these interventions on the compensated AC patient population, we conducted a cost-effectiveness analysis (CEA) comparing MATs and counseling with each other and to a do-nothing approach. CEA is a widely-used economic evaluation method that compares the costs and benefits of interventions designed to improve health.[16] One of CEA's advantages is its ability to quantify changes in an intervention's efficiency when different assumptions about its effectiveness and costs are made. CEA is therefore well-suited to explore the efficiency of alcohol use treatments in patients with AC because of uncertainties around their effectiveness and costs.

Materials and methods

Overview

We used a Markov simulation model to project the lifetime costs and health benefits of different alcohol use treatments for a hypothetical cohort of patients with compensated AC. Data on transition probabilities, costs, and health utilities were taken from published peer-reviewed and gray literature (see supplementary information for additional details on parameter estimations and other assumptions). Since no human participants were involved in this study, no ethical approval was sought.

In addition to a do-nothing approach, the scenarios we modeled are (1) acamprosate and naltrexone, which are FDA-approved MATs; (2) baclofen, gabapentin, and topiramate, which are non-FDA-approved MATs; and (3) counseling (we chose to label this scenario "counseling" to disambiguate from the use of the word "therapy" in MAT), which involves weekly

Table 1. Values for model inputs.

Variable	Base	Range	Mean (SD)	Distribution	[Ref.]
Annual transition probabilities					
Decompensation among compensated AC patients	0.25	0.1875–0.3125	0.25 (0.0313)	Beta	17 *
HCC development among compensated AC patients	0.0019	0.0011–0.003	0.0021 (0.0005)	Beta	18
Death among compensated AC patients	0.06	0.03–0.1	0.065 (0.0175)	Beta	19
HCC development among decompensated AC patients	0.007	0.0053–0.0088	0.0071 (0.0009)	Beta	18
Transplantation among decompensated AC patients	0.0778	0.0523–0.0903	0.0713 (0.0095)	Beta	5,20 †
Death among decompensated AC patients	0.31	0.2325–0.3875	0.31 (0.0388)	Beta	17
Transplantation among HCC patients	0.09	0.0769–0.0998	0.0884 (0.0057)	Beta	21,22 †
Death among HCC patients	0.055	0.041–0.069	0.055 (0.007)	Beta	18
Death within the 1st year of liver transplantation	0.09	0.08–0.09	0.085 (0.0025)	Beta	5
Death after the 1st year of liver transplantation	0.03	0.03–0.0325	0.0313 (0.0006)	Beta	5
Intervention treatment effects					
Relative risk of decompensation among AC patients who receive acamprosate and naltrexone	0.78	0.72–0.84	0.78 (0.03)	Beta	14 ‡
Relative risk of decompensation among AC patients who receive baclofen, gabapentin, and topiramate	0.82	0.795–0.845	0.82 (0.01)	Beta	14 ‡
Relative risk of decompensation among AC patients who receive counseling	0.89	0.87–0.91	0.89 (0.01)	Beta	14 ‡
Annual costs (in 2017 US$)¶					
Intervention costs					
Acamprosate and naltrexone	1,419	1,064–1,774	1,419 (178)	Gamma	23,24
Baclofen, gabapentin, and topiramate	657	493–822	658 (82)	Gamma	23,24
Individual alcohol cessation counseling	1,154	334–1,974	1,154 (410)	Gamma	25
Medical management costs					
Compensated AC treatment	5,739	4,304–7,173	5,739 (717)	Gamma	26
Decompensated AC treatment	23,493	23,115–23,871	23,493 (189)	Gamma	27
Hepatocellular carcinoma treatment	52,661	51,813–53,509	52,661 (424)	Gamma	27
Liver transplantation and treatment	293,566	220,175–366,958	293,567 (36,696)	Gamma	28
Routine care for liver transplant patients after 1st year	61,400	220,175–366,958	61,400 (7,675)	Gamma	28
Annual health utilities					
Compensated AC	0.83	0.62–1	0.81 (0.1)	Beta	29
Decompensated AC	0.65	0.48–0.81	0.65 (0.08)	Beta	29
Hepatocellular carcinoma	0.25	0.18–0.31	0.25 (0.03)	Beta	29
Transplantation <12 months	0.77	0.58–0.96	0.72 (0.07)	Beta	30
Transplantation ≥12 months	0.78	0.59–0.98	0.75 (0.08)	Beta	30

AC, alcohol-related cirrhosis; HCC, hepatocellular carcinoma.
*Range determined by authors.
†Values calculated by authors using the references listed.
‡Results from the referenced study were re-analyzed and used as inputs to the model.
¶Only intervention and medical management costs are included here; see Supporting Information for other cost inputs.

individual therapy with a licensed counselor. We grouped FDA- and non-FDA-approved MATs together because estimates of the effectiveness of these drugs on the AC population combined them into these categories due to low rates of overall use of these medications, particularly in the US.[14,15] All interventions are assumed to be provided over 12 weeks. We assumed that patients in all 4 scenarios are receiving medical treatment for their ALD.

We considered both societal and healthcare perspectives in the analysis. The Impact Inventory (Table S1) lists all the health and non-health costs and effects that were included in each perspective.[16] We discounted future benefits and costs to their present value using a 3% rate in the base case analysis.[16]

Markov model

A truncated schematic of the Markov cohort model is presented in Fig. 1. The model simulates a cohort of 54-year-old patients with compensated AC, which is the median age reported in the literature.[5,31] We varied the age of the population between 25–65 in the sensitivity analysis based on a recent study[4] that reported significant increases in AC among young adults in the US. The model, which uses an annual cycle and lifetime time horizon, was programmed in TreeAge Pro 2019 (TreeAge Software Inc., Williamstown, MA).

In our model, all patients start at the compensated AC state, and those who are in one of the intervention arms (Fig. 1) receive a 12-week intervention only once in their lifetime. After receiving the intervention, the cohort then progress through the various ALD health states, namely decompensated AC, HCC, liver transplantation, and death. We did not model alcoholic hepatitis as a separate state, and patients with this clinical syndrome are assumed to be in either the compensated or decompensated AC states. Because of the significant difference in mortality between the first and succeeding years post-transplantation,[5] we separated out the transplantation states into <12 months and ≥12 months (not shown in Fig. 1 for simplicity). We assumed that patients in all ALD states cannot transition back to less-severe health states, though in reality some patients with AC may return and experience the same state again (*e.g.* recurrent cirrhosis in a post-transplant patient or re-compensation in a previously decompensated patient who stops drinking).

Data and sources

Transition probabilities

Annual transition probabilities were estimated based on previously published rates and probabilities in peer-reviewed literature (Table 1). Natural history and disease progression probabilities were taken from cohort studies and reviews on ALD development.[17,19] The probability of HCC development from compensated and decompensated cirrhosis and the probability of death from HCC are based on large population-based cohort studies of Danish patients.[17,18] For death after transplantation, we relied on a recent analysis of cohort data from the United Network for Organ Sharing database.[5] We calculated the probability of transplantation among patients with decompensated cirrhosis and HCC using waitlist rates reported from previous studies[20,21] and liver transplant rates from the Organ Procurement and Transplantation Network annual reports (see supplementary information for more details).[22,32]

The same annual transition probabilities are used in all 4 scenarios; the main difference between the scenarios is the treatment effect applied to the yearly rate of decompensation among patients with AC. To estimate treatment effects, we relied on the unpublished corrected results of a retrospective cohort

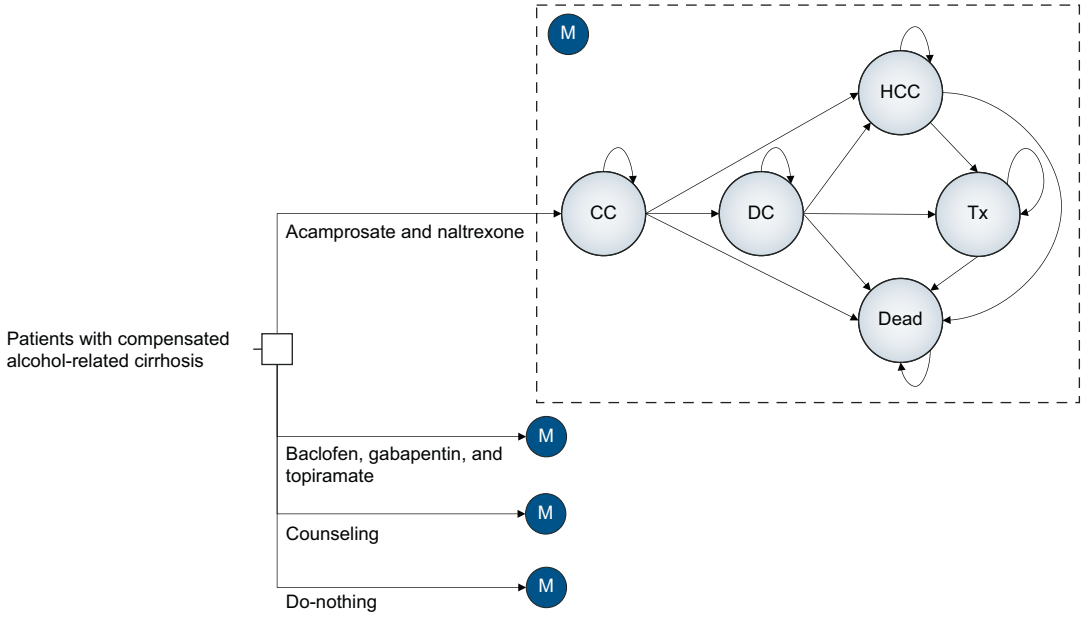

Fig. 1. Markov cohort model schematic. Root of the schematic shows the four decision alternatives or scenarios – acamprosate or naltrexone, baclofen, gabapentin, and topiramate, counseling, and do-nothing. The shaded circle denotes the common Markov node, and the ovals are the ALD states the simulated cohort progresses through. Each health state is associated with a cost and health utility. Arrows represent transitions and are associated with an annual probability. ALD, alcohol-related liver disease; CC, compensated alcohol-related cirrhosis; DC, decompensated alcohol-related cirrhosis; HCC, hepatocellular carcinoma; Tx, transplantation.

study that compared the rate of decompensation between patients with AC who received different alcohol use treatments *vs.* those who did not receive an intervention.[14] The resulting relative risks, which are similar to those reported in a more recent study,[15] were used as model inputs (Table 1). While our treatment effectiveness estimates are based on observational, real-world data, we do use a large sample of patients with AC and employer-sponsored insurance followed over time, and our estimates reflect real-life effectiveness of alcohol use treatments in the AC population. These estimates also reflect other realities of clinical practice, such as the fact that women are significantly less likely to be provided MAT or counseling than men.[14]

Unlike other CEAs, we could not rely on data from trials such as the COMBINE Study[33] or published systematic reviews[34] that evaluate the effect of alcohol use treatments on abstinence and/or relapse because these studies do not focus on patients with AC. In some cases, patients with AC have been deliberately excluded from trials because certain treatments can worsen ALD.[9] Because of the uncertainty around our treatment effectiveness estimates, we conducted several sensitivity analyses to explore the impact on our results.

Costs

Healthcare costs include healthcare service delivery (*e.g.* physician and facility fees) and drug costs (Table 1). The routine costs of care for compensated and decompensated AC were based on a previously-published CEA[26] and a study on the costs of treating US veterans with cirrhosis,[27] respectively. All costs associated with liver transplantation are based on a claims-based analysis of a commercially-insured population in the US.[28] The costs of alcohol use treatments were based on 2 previous CEAs[23,25] that provided detailed cost estimates and whose drug costs we updated using public sources.[24] As mentioned previously, we assumed in the base case that all patients receive alcohol use treatments once in their lifetime, so alcohol use treatment costs were only applied once (we vary this assumption in the sensitivity analysis).

For the societal perspective, we included lifetime productivity and health and consumption costs. We also valued and included time costs or foregone productivity of patients using published estimates of time spent on alcohol use treatments and ALD treatments multiplied by average daily wages (see supplementary information). All costs are in 2017 US dollars (US$).

Health outcomes and utilities

We measured health outcomes from each scenario in terms of quality-adjusted life years (QALYs) gained. A QALY represents a year that a person is alive weighted by that person's health-related quality of life.[35] QALYs, which have their limitations, are a preferred measure of health in CEAs because they combine quantity and quality of life in one metric and provide a common and consistent metric that can be used to compare different treatments and their efficiency.[36]

The weights used to calculate QALYs are based on health utilities that typically range from 1 (a year in perfect health) to 0 (death). We took health utility estimates for the various states in the model from the literature (Table 1).[29,30] Very few preference-based measures of health-related quality of life have been published specifically on patients with ALD; we thus had to rely on available estimates, which include studies that have been done on other chronic liver diseases (*e.g.* infectious hepatitis). We address uncertainty in utility estimates in the sensitivity analysis.

Analysis

Cost-effectiveness

The summary metric of CEAs is the incremental cost-effectiveness ratio (ICER), defined as the cost per unit of health outcome gained. The ICER is calculated by dividing the incremental costs by the incremental benefits of 2 scenarios. We present ICERs from the healthcare and societal perspectives by comparing each intervention scenario (*i.e.* acamprosate and naltrexone, baclofen, gabapentin, and topiramate, and counseling) to the do-nothing scenario. As is usually done in CEAs, we arranged the interventions by increasing costs and calculated ICERs while comparing each intervention to the next costlier option.

An intervention is typically considered cost-effective if its ICER is equal to or below a context-specific cost-effectiveness threshold. The cost-effectiveness threshold represents a decisionmaker's willingness to pay for an additional unit of health benefit such as QALYs. The threshold can also be seen as a measure of opportunity cost, or the amount of health that is displaced by additional spending in the health sector.[36] In this study, we consider an intervention to be cost-effective if its ICER is <$100,000 per QALY gained, a commonly-used threshold in the US.[36] We evaluate a lower threshold of $50,000 per QALY in sensitivity analysis.

Sensitivity analyses

Sensitivity analyses explore how different assumptions and parameter uncertainty may affect the conclusions about the cost-effectiveness of alcohol use treatments; in this study, we conducted 3 types. The first sensitivity analysis is a one-way sensitivity analysis where each transition probability, cost input, and health utility are varied one at a time from their lowest to highest value (while keeping other parameters at their base value) to understand how extreme values affect the cost-effectiveness of each intervention. Where data were available, low and high values were based on ranges in the literature; for select parameters, the authors determined reasonable bounds which were 25% above and below a given value.

The second sensitivity analysis is called scenario analysis where we vary certain assumptions in the model; specifically, we vary the number of times patients receive alcohol use treatments. In the base case analysis, we assumed that alcohol use treatments costs were only applied in the first year, and treatment effects lasted over the lifetime of the cohort. We varied this assumption by calculating ICERs where alcohol use treatment costs were applied each year over 5 and 10 years.

The third type of sensitivity analysis we conducted is probabilistic sensitivity analysis (PSA), where all parameters are varied simultaneously over 10,000 independent trials. We used predetermined distributions for each parameter input (Table 1). To understand the efficiency of alcohol use treatments across different ages, we varied the age group of the cohort from 25 to

Table 2. Base case results from societal and healthcare perspectives.

	Societal perspective				Healthcare perspective				
Intervention	**QALYs gained***	**Cost**	**ICER compared to do-nothing**	**ICER compared to the next most expensive, undominated option**	**Intervention**	**QALYs gained***	**Cost**	**ICER compared to do-nothing**	**ICER compared to the next most expensive undominated option**
Acamprosate and naltrexone	6.12	278,794	Cost-saving	n.a.	Acamprosate and naltrexone	6.12	249,055	Cost-saving	n.a.
Baclofen, gabapentin, and topiramate	6.05	282,007	Cost-saving	Dominated†	Baclofen, gabapentin, and topiramate	6.05	250,712	Cost-saving	Dominated†
Do-nothing	5.79	284,583	n.a.	Dominated†	Counseling	5.94	255,044	Cost-saving	Dominated†
Counseling	5.94	285,135	3,724	Dominated†	Do-nothing	5.79	259,101	n.a.	Dominated†

This table shows the results for the base-case analysis only. Interventions are arranged by increasing costs. ICERs are calculated by dividing incremental costs by incremental QALYs between two interventions. "Cost-saving" (or "dominant") refers to an intervention that incurs less costs and produces more QALYs compared to its comparator; cost-saving interventions are preferred because they outperform their comparator in both costs and benefits. "Dominated" refers to an intervention that incurs more costs and produces less QALYs compared to its comparator; dominated interventions are rejected because their cost-effectiveness is inferior to their comparator. All costs are in 2017 US$, rounded to the nearest dollar, and have been discounted at 3% to the present.
ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
*Refers to lifetime QALYs and are discounted at 3% to present value.
†Compared to acamprosate and naltrexone.

65 years conducting separate PSAs. Using the simulation results, we generated cost-effectiveness acceptability curves to plot the probability that each scenario is cost-effective over a range of reasonable cost-effectiveness thresholds.[37]

Results

Base case

The results of the base case analysis are shown in Table 2. Compared to a do-nothing scenario, all 3 alcohol use treatments were cost-saving from a healthcare perspective; this means that the total costs of receiving MATs or counseling is less than not receiving them while producing more QALYs.

From a societal perspective, acamprosate and naltrexone and baclofen, gabapentin, and topiramate are also cost-saving when compared to a do-nothing scenario. On the other hand, counseling costs more but produces more QALYs compared to a do-nothing scenario, with an ICER of $3,724 QALY (Table 2). This ICER is significantly less than the $100,000 per QALY gained threshold we use to assess cost-effectiveness.

After arranging the interventions based on increasing costs, we calculated ICERs while comparing each scenario to the next most costly option. As shown in Table 2, baclofen, gabapentin, and topiramate, counseling, and a do-nothing scenario were dominated by acamprosate and naltrexone from healthcare and societal perspectives; this means that baclofen, gabapentin, and topiramate, counseling, and a do-nothing scenario are costlier and provide less QALYs than acamprosate and naltrexone. All-in-all, we found that only acamprosate and naltrexone are not dominated by any other intervention we evaluated.

Sensitivity analysis

One-way sensitivity analysis

The one-way sensitivity analysis found that all 3 intervention scenarios – acamprosate and naltrexone, baclofen, gabapentin, and topiramate, and counseling – remained cost-saving when compared to a do-nothing scenario from a healthcare perspective, even after extreme values of each parameter were used in the model.

We show the partial results of the one-way sensitivity analysis for acamprosate and naltrexone in Fig. 2, which shows how the net monetary benefit of the intervention changes as the parameter values are varied between their lowest and highest values in the model. The net monetary benefit is intended to combine the costs and health benefits into a single monetary value and is calculated by multiplying the QALYs gained by a cost-effectiveness threshold (*e.g.* $100,000 per QALY gained), and then subtracting from the product the total costs of the intervention. We find that the net monetary benefit of acamprosate and naltrexone remains positive even when we use the most extreme values of any parameter, which means that the benefits of the intervention (when monetized) outweigh its costs. When we use a $50,000 per QALY gained threshold (Fig. 3) we find similar results.

We found that the utility of compensated AC, the probability of death among patients with compensated AC, and the post-transplantation utility are the most influential parameters on the net monetary benefit of acamprosate and naltrexone (Fig. 1). The treatment effectiveness of acamprosate and naltrexone was the ninth most-influential parameter; only when the treatment effectiveness decreased by 24% (or a change in the relative risk of decompensation from 0.78 to 0.968) did the ICER of acamprosate

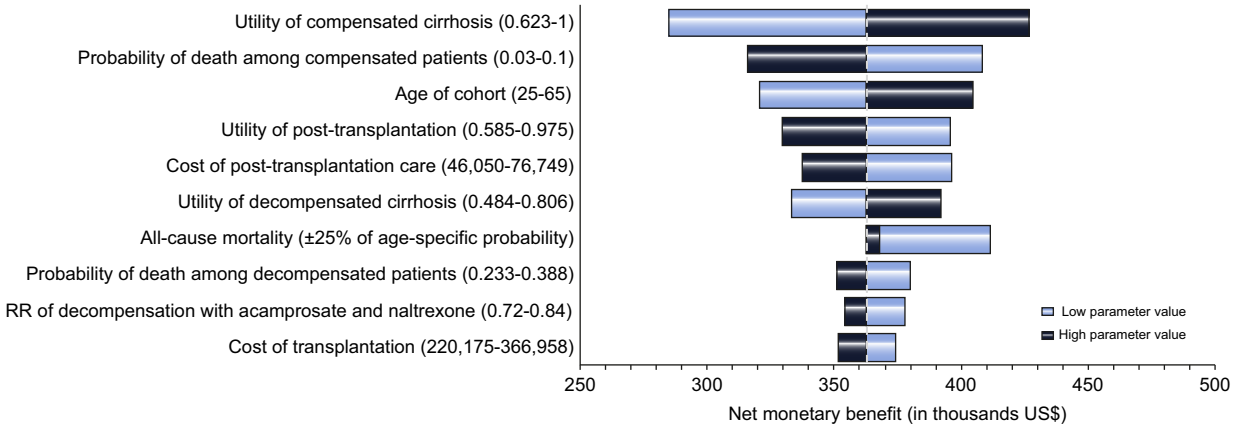

Fig. 2. Net monetary benefit of acamprosate and naltrexone using a $100,000 per QALY gained threshold. This tornado diagram shows how the net monetary benefit of acamprosate and naltrexone from a healthcare perspective changes when parameters in the model are varied from their lowest to highest estimated value while keeping the other parameters constant. The net monetary benefit is intended to combine the costs and health benefits into a single monetary value and is calculated by subtracting the costs of an intervention from the product of its QALYs and a cost-effectiveness threshold, which in this case was $100,000 per QALY gained. Only the top 10 most influential parameters are included. The results show that acamprosate and naltrexone have a positive net monetary benefit even when the most extreme values of any parameter are used in the model, which means that the benefits of the intervention outweigh its costs. QALY, quality-adjusted life year; RR, relative risk.

and naltrexone exceed the $100,000 per QALY gained threshold. Similarly, the treatment effectiveness of baclofen, gabapentin, and topiramate and counseling needed to decrease by 17% (or a change in a relative risk of decompensation from 0.82 to 0.9628) and 9% (or a change in a relative risk of decompensation from 0.89 to 0.9663), respectively, before their ICERs crossed the same cost-effectiveness threshold.

From a societal perspective, we found that acamprosate and naltrexone no longer becomes cost-saving when (1) the probability of death among patients with compensated AC exceeded 0.033 and (2) the age of the patient cohort exceeded 61 (see Fig. S1).

Scenario analysis

After varying the duration in which patients receive MATs and counseling, we found that all 3 intervention scenarios are cost-saving from a healthcare perspective compared to a do-nothing scenario even when these interventions are received annually for 5 or 10 years over the lifetime of patients with compensated AC (Table S5).

Probabilistic sensitivity analysis

The average results of the PSA are shown in Table S6. The cost-effectiveness acceptability curve in Fig. 4 plots the probability that each intervention would be preferred at various cost-effectiveness thresholds from a healthcare perspective. Our analysis suggests that acamprosate and naltrexone are most likely to be the optimal choice at any cost-effectiveness threshold, followed by baclofen, gabapentin, and topiramate.

We also conducted PSAs while varying the cohort age to 25, 35, 45, and 65 years, and the results are shown in the Tables S7 and S8. We found that all 3 interventions remain cost-saving

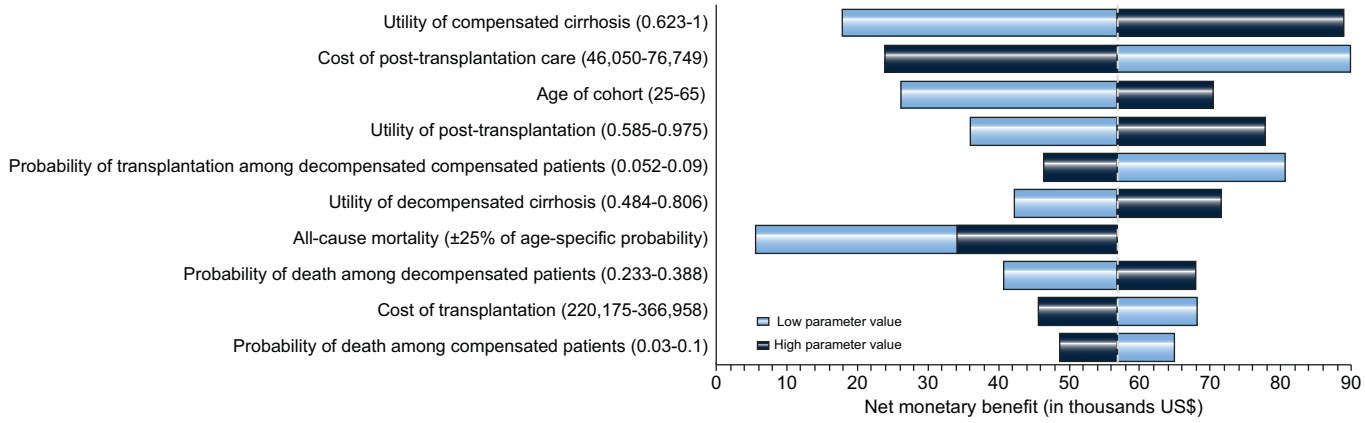

Fig. 3. Net monetary benefit of acamprosate and naltrexone using a $50,000 per QALY gained threshold. This tornado diagram shows how the net monetary benefit of acamprosate and naltrexone from a healthcare perspective changes when parameters in the model are varied from their lowest to highest estimated value while keeping the other parameters constant. The net monetary benefit is calculated by subtracting the costs of an intervention from the product of its QALYs and a cost-effectiveness threshold, which in this case was $50,000 per QALY gained. Only the top 10 most influential parameters are included. The results show that acamprosate and naltrexone have a positive net monetary benefit even when the most extreme values of any parameter are used in the model, which means that the benefits of the intervention outweigh its costs. QALY, quality-adjusted life year; RR, relative risk.

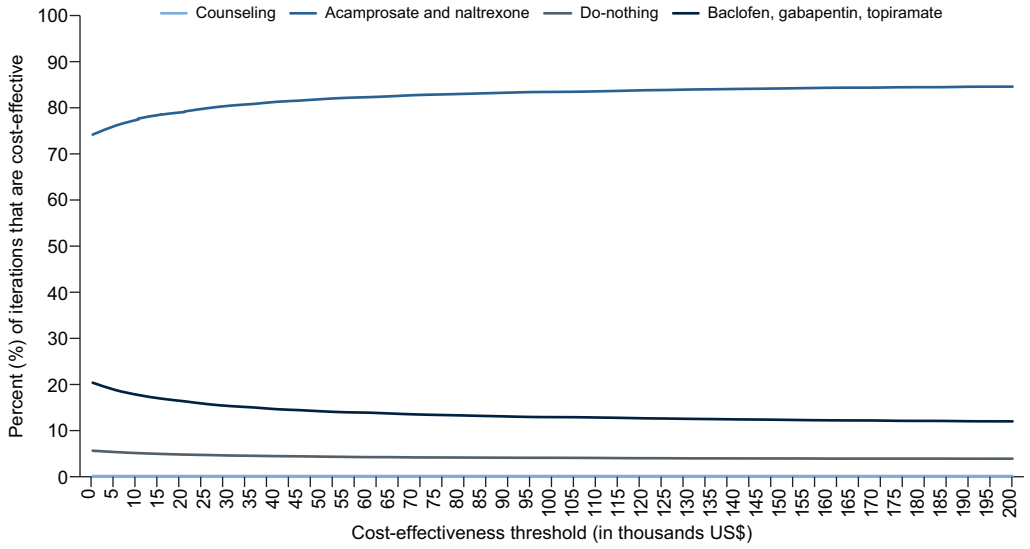

Fig. 4. Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves summarize the results of probabilistic sensitivity analyses. The curves plot the probability that each scenario is cost-effective over a range of cost-effectiveness thresholds. The figure shows that acamprosate and naltrexone are most likely to be cost-effective compared to any other alternative over all threshold values explored.

from a healthcare perspective when compared to a do-nothing scenario. While counseling and non-FDA-approved MAT are cost-saving across all ages from a healthcare perspective, they cost more and produce more QALYs than the no-intervention scenario from a societal perspective.

Discussions

This CEA found that short-term MATs and counseling are extremely cost-effective – and often cost-saving – alcohol use treatments for patients with AC across all ages when compared to no intervention. Among the interventions studied, only acamprosate and naltrexone and baclofen, gabapentin, and topiramate were found to be cost-saving from both healthcare and societal perspectives. Counseling, though dominated by acamprosate and naltrexone, was also cost-effective across all patient ages when compared to a no-intervention scenario. Our results remained robust after various assumptions were modified and parameter uncertainty was taken into account.

While it is well-known that alcohol cessation reduces morbidity and mortality in patients with AC,[38] our findings demonstrate the value of alcohol use treatments in clinical settings, especially for younger patients. Current practice guidelines recommend screening and treating heavy alcohol use or AUD among patients with cirrhosis[11,12]; in practice, however, few patients with AC receive alcohol treatment. For example, in a privately insured cohort where 72% had mental health or substance abuse coverage, only 0.8% received a prescription for an FDA-approved relapse prevention medication; by the first year after AC diagnosis, only 10% had received a face-to-face visit with a mental health provider.[31] For patients on Medicaid, other non-private insurance, and those who receive care through the Veteran's Administration, rates are similarly low,[15,39] and substance use providers frequently struggle to obtain adequate reimbursement. Finally, medical care for patients with AC is often detached from AUD treatment, with hepatology providers frequently ill-equipped to manage complex AUD independently.[40] Our findings support the integration of medical and substance use care for patients with AC, which studies have shown is effective in reducing alcohol relapse, particularly after transplantation.[41,42]

It is important to note that MATs and counseling (*vs.* no intervention) were found to be cost-saving from a healthcare perspective across all patient ages. Rates of advanced ALD have risen most sharply among young people,[4] and these higher rates of advanced ALD come with a high price tag in both costs and mortality. When considering that many of these young people will have comorbid substance use and mental health disorders, the need for counselling and treatment is even more important.[43] That these interventions appear to be cost-saving in this age group makes the urgency of adequate insurance coverage expansion, linkage to care, and reimbursement rates for AUD treatment even more important.

Our study also adds to the literature on the cost-effectiveness of alcohol use treatments. Using results from the COMBINE study, Zarkin *et al.* (2008) and Dunlap *et al.* (2010) found that MAT (*i.e.* naltrexone or acamprosate) alone are cost-effective from provider and patient perspectives.[23,44] Both studies, however, only looked at short-term (12 week) and intermediate outcomes (*e.g.* days abstinent and patients avoiding heavy drinking). Kim *et al.* (2017) was the first to look at lifetime costs and benefits of counseling and MAT, and they estimated that MAT – when coupled with medical management – are cost-saving from healthcare and societal perspectives.[45]

Use of naltrexone in advanced liver disease is, however, not without controversy. Naltrexone, though approved by the FDA for alcohol relapse prevention, carries a black-box warning for hepatotoxicity based on studies showing elevated liver function tests and higher circulating levels of naltrexone and its active metabolite, 6B-naltrexol, in patients with AC.[46] A high degree of caution is warranted in prescribing naltrexone where side effects, including withdrawal symptoms and elevated liver function tests, are seen. Patients should undergo a thorough

informed consent before prescribing and should be closely monitored.

Relapse is a lifelong concern in patients with AUD, even after liver transplantation.[47] While studies have clearly shown that alcohol relapse increases mortality in advanced ALD, people with AUD experience a range of drinking patterns, with periods of lesser alcohol use or total abstinence and other periods of more moderate drinking that can lead to heavier drinking.[47] These differential ranges of drinking patterns over a lifetime can be challenging to model, but we varied our treatment effects as a way to incorporate uncertainty in adherence and risk of relapse. Future models can more explicitly and deliberately incorporate this as more data becomes available on the natural history of AUD in this population.

This study has several limitations. First, our costs and transition probabilities are based on disparate sources. Though most are specific to ALD, some were not due to a lack of available data on ALD specifically. However, we addressed parameter uncertainty in the sensitivity analyses by varying the ranges around the median values. Additional research is needed to empirically measure some of the parameter inputs used; specifically, our measure of treatment effectiveness was based on observational data, which introduces uncertainty in our cost-effectiveness estimates. Second, we only considered the impact of clinic-based counseling, and future CEAs can explore other types of psychosocial interventions, such as group therapy, community support networks (*e.g.* Alcoholics Anonymous), and telehealth AUD treatment. Third, the Markov model necessarily simplifies the clinical experience of patients with ALD and may exclude certain events that affect the estimation of intervention costs and health benefits. For example, we did not include the costs of alcohol withdrawal which are experienced by up to 50% of patients with AUD nor did we model the costs of comorbid substance use or mental health disorders which are experienced by a large fraction of patients with AC.[13] Finally, the generalizability of this study is limited to patients with AC who are already seeking care, and the impact of interventions will be necessarily modified by level of engagement in care.

In conclusion, alcohol use treatment, whether MATs or counseling, proved cost-effective for all patients with AC and even cost-saving for some. Our results support broader coverage and better reimbursement for alcohol use treatments, which improve care and prevent complications among patients with AC.

Abbreviations

AC, alcohol-related cirrhosis; ALD, alcohol-related liver disease; AUD, alcohol use disorder; CEA, cost-effectiveness analysis; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; MAT, medication-assisted therapy; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year

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Conflict of interest

The authors declare no conflicts of interest related to this research.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

ALVA and JLM conceived and designed the study, collected and analyzed the data, prepared the manuscript. NM and SEU collected and analyzed data and prepared the manuscript. DWH designed the study, analyzed the data, prepared the manuscript, and provided oversight throughout the study. All authors have approved the final submitted version. ALVA is the guarantor or the study.

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Data availability statement

All input parameters that were used in the simulation model to generate results presented here are reported in the main text and Supplementary Material.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.12.004.

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