Application to add acamprosate to the the WHO Essential Medicines List for adults

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1. Summary statement of the proposal for inclusion.

In this application, we propose the addition of acamprosate oral formulation to the core list of the WHO Model List of Essential Medicines (EML), section 24.5 “Medicines for mental and behavioural disorders >> Medicines for disorders due to psychoactive substance use”, with the indication of maintenance treatment of adults with alcohol use disorder (AUD).
This proposal is based on the following elements:

A. Currently there is no medication available for the treatment of alcohol use disorder in the 22nd WHO EML. In the 2016 WHO mhGAP Intervention Guide, acamprosate is recommended as a medication to prevent relapse in alcohol dependence [1]. Despite this, globally, one in six people with AUD receive treatment and rates are even lower in low and lower-middle-income countries [2]. Globally, alcohol use was the seventh leading risk factor for premature death and disability in 2016, and was the leading risk factor among people aged 15-49 years [3].
B. Randomized controlled trials and meta-analytical evidence on the treatment of AUD found that acamprosate increases probability of abstinence [4–12]. Thus, many national guidelines include acamprosate as recommended pharmacotherapy in the treatment for moderate-severe AUD with a goal of achieving abstinence [13–17].
C. The cost of acamprosate oral tablets varies widely (28-day supply from $27 USD to $211 USD. Acamprosate would be cost effective depending on a willingness to pay higher than $6000 USD/QALY (for reference the UK NICE uses a reference of £20000-£30000/QALY)[16]. This underestimates cost effectiveness of acamprosate given that such analyses do not include the reduction of societal costs of harmful drinking (arrests, motor vehicle accidents, employment).

2. Relevant WHO technical department and focal point (if applicable).

- **Alcohol, Drugs and Addictive Behaviours Unit**
  - **https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours**
- **Mental Health and Substance Use**
  - **https://www.who.int/teams/mental-health-and-substance-use/overview**
- **Vladimir Poznyak**

3. Name of organization(s) consulted and/or supporting the application.

- Jessica Ristau, MD. University of California, San Francisco (UCSF). California, USA. Addiction Medicine specialist.
- Romany Redman, MD. USA. Internal Medicine - Pediatrics
- Casey Sautter, MD, MSc, FACOG. USA. Obstetrics and Gynecology
- Fátima Rodriguez, MD. Compañeros en Salud - PIH México, Mexico. Primary care physician and Mental Health Coordinator

4. International Nonproprietary Name (INN) and Anatomical Therapeutic Chemical (ATC) code of the medicine.

Category: 24.5. Medicines for disorders due to psychoactive substance use

https://www.whocc.no/atc_ddd_index/?code=N07BB03
INN: Acamprosate
ATC code : N07BB03 (WHO) https://www.whocc.no/atc_ddd_index/?code=N07BB03
DDD 2
U g
Adm.R O
Wikipedia: https://en.wikipedia.org/wiki/Acamprosate
DrugBank : https://go.drugbank.com/drugs/DB00659

5. Dose forms(s) and strength(s)proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

PO: Acamprosate 333 mg oral tablet

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We are requesting the addition of Acamprosate as an individual medicine.

7. Treatment details (requirements for diagnosis, treatment and monitoring).

AUD is diagnosed if a patient meets two or more criteria as per the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[18]. Pharmacologic assistance–along with psychosocial support as part of a comprehensive treatment plan–is recommended in promotion of alcohol cessation or reduction in alcohol consumption in patients who meet the diagnosis of moderate to severe AUD (meeting four or more of the DSM-V criteria)[13–15,18].

Acamprosate is available as a 333 mg tablet, and the recommended dosage regimen is two tablets (666 mg) three times per day. Acamprosate is more effective if initiated after detoxification is completed, but its pharmacokinetics are not altered by co-administration with alcohol or benzodiazepines and can therefore be safely used prior to alcohol cessation and during relapse [19–21].

Steady-state plasma concentrations of acamprosate are reached within five days [20]. Safety and effectiveness have been evaluated for durations of treatment up to a year [19]. Discontinuation may be considered once the patient has stable abstinence from alcohol, diminished craving and plan for ongoing recovery, or if the patient is not adhering to the medication regimen [19]. There is no evidence of tolerance, dependence, withdrawal, or rebound drinking when treatment is ceased [20].

Acamprosate is not metabolized in the liver and is excreted unchanged in the urine. The pharmacokinetics of acamprosate are not altered in patients with mild-to-moderate hepatic insufficiency, indicating that no dosage adjustments are necessary. However, there is risk of accumulation of acamprosate with prolonged administration of therapeutic doses in renally impaired patients and the use of acamprosate is contraindicated in patients with severe renal impairment (creatinine clearance 30 ml/min), and a dosage adjustment to one 333 mg tablet three times per day is recommended in patients with moderate renal impairment (creatinine clearance 30-50 ml/min) [20].

The most common adverse effect of acamprosate is diarrhea which is usually mild and self limited but in some patients can be severe and persistent [19]. Other less common adverse effects are suicidal ideation (infrequent but requires discontinuation), other gastrointestinal

symptoms (intestinal cramps, flatulence, nausea), headache, dizziness, increased or decreased libido, insomnia, anxiety, muscle weakness, itchiness [19].

Acamprosate is FDA pregnancy category C and should be avoided in pregnant women unless benefits are felt to outweigh risks [19].

Table 1. Excerpts from national and international guidelines on the pharmacological treatment of alcohol use disorder. AUD = alcohol use disorder

Source	Year	Excerpt
WHO mhGAP evidence	2012	"Acamprosate, disulfiram or naltrexone should be offered as part of treatment to reduce relapse to heavy alcohol use in alcohol dependent patients. The decision to use acamprosate, disulfiram or naltrexone should be made taking into consideration patient preferences and availability." [22]
The American Psychiatric Association [APA] (USA)	2018	"APA recommends(1B) that naltrexone or acamprosate be offered to patients with moderate to severe alcohol use disorder who have a goal of reducing alcohol consumption or achieving abstinence, prefer pharmacotherapy or have not responded to nonpharmacological treatments alone, and have no contraindications to the use of these medications"[23]
VA/DoD (Department of Veterans Affairs Department of Defense) (USA)	2021	"For patients with moderate-severe alcohol use disorder, we suggest *(as opposed to recommend for naltrexone)* offering one of the following medications: • Acamprosate • Disulfiram" [24]
New York State Department of Health AIDS Institute (USA)	2020	"Clinicians should recommend pharmacologic treatment for individuals with moderate-to-severe AUD." [25] "Clinicians should recommend oral acamprosate or oral or injectable extended-release (XR) naltrexone as the preferred medications for treating AUD."[25]
Australian Department of Health	2021	"Acamprosate is recommended to help maintain abstinence from alcohol in patients with moderate to severe AUD." [26]
National Institute for Health and Care Excellence [NICE] (United Kingdom)	2011	"After a successful withdrawal for people with moderate and severe alcohol dependence, consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention…" [27]
British Columbia Centre on Substance Use, B.C. Ministry of Health and B.C.	2019	"Adult patients with moderate to severe AUD should be offered naltrexone or acamprosate as a first-line pharmacotherapy to support achievement of patient-identified treatment goals."[28]

Ministry of Mental Health and Addictions (Canada)		
Centre for Effective Practice (Canada)	2019	“Generally, naltrexone oral and acamprosate are the recommended first line options” [29]
Ministry of Health & Family Welfare (Government of India)	2017	“All patients with alcohol dependence should be offered long term management.” Naltrexone, acamprosate and disulfiram are listed in the table of medications used in long term management of alcohol dependence. [30]
Federal Ministry of Health (Nigeria)	2019	“Acamprosate, disulfiram or naltrexone should be offered as part of treatment to reduce relapse to alcohol use in alcohol dependent patients.” [31]

8. Information supporting the public health relevance.

An analysis of 195 countries and territories found that in 2016, 2.8 million deaths were attributable to alcohol use[3]. Alcohol use was the seventh leading risk factor for premature death and disability and was the leading risk factor in the age group 15-49. Alcohol consumption was shown to have a strong association with risk of cancer, injuries, and communicable disease[3]. These findings are consistent with the WHO Global Status Report on Alcohol and Health where alcohol consumption is recognized as an indicator of the Sustainable Development Goals due to its direct impact on maternal and child health, infectious diseases, noncommunicable diseases, and mental health, injuries, and poisonings[32]. The report highlights that the harmful use of alcohol resulted in 132.6 million disability-adjusted life years (DALYs) in 2016–or 5.1% of total DALYs that year. Importantly, the treatment coverage for alcohol dependence in 2016 was close to zero in low- or lower-middle-income countries, although the level of treatment coverage in most countries is not known[32]. During the COVID-19 pandemic, U.S. respondents to a cross-sectional survey reported consuming more drinks per day (+29%), exceeding recommended drinking limits more often (+20%), and more binge drinking days (+21%) when compared to February 2020, suggesting that need for treatment is increasing[33].

9. Review of harms and benefits

9.1 Summary of evidence of comparative effectiveness

Acamprosate (calcium acetylhomotaurinate) is a synthetic compound with a chemical structure similar to the neurotransmitter GABA, the chief inhibitory neurotransmitter, and the amino acid neuromodulator taurine. Acamprosate acts to normalize dysregulation in the neurochemical systems implicated in the biological mechanisms of alcohol dependence and it has been hypothesized that acamprosate promotes abstinence by minimizing some of the physiological changes produced by chronic heavy ethanol exposure and withdrawal that underlie symptoms associated with relapse [20].

Acamprosate was first approved in 1989 in Europe–and subsequently in the United States in 2004–to maintain abstinence from alcohol in conjunction with psychosocial interventions. Prior to United States FDA approval, thirteen European single or double-blind, placebo-controlled, randomized clinical trials between 1990 and 2002 evaluated acamprosate–along with psychosocial interventions–in people (N=4000) who met DSM III criteria for alcohol dependence and had undergone a detoxification process [4] . Analysis of these studies showed that acamprosate raised the percentage of patients that did not ingest alcohol during the study (abstinence rate; figure 1) with a number needed to treat (NNT) of 10 and, moreover, doubled the days of cumulative abstinence (cumulative abstinence duration; figure 2) from alcohol not only during the treatment phase but also in the follow-up period[4] . Another meta-analysis at the time showed that the beneficial effects of acamprosate on abstinence lasted up to 12 months [5].

Figure 1: Bouza Meta-Analysis. Acamprosate versus placebo on abstinence rate [4]

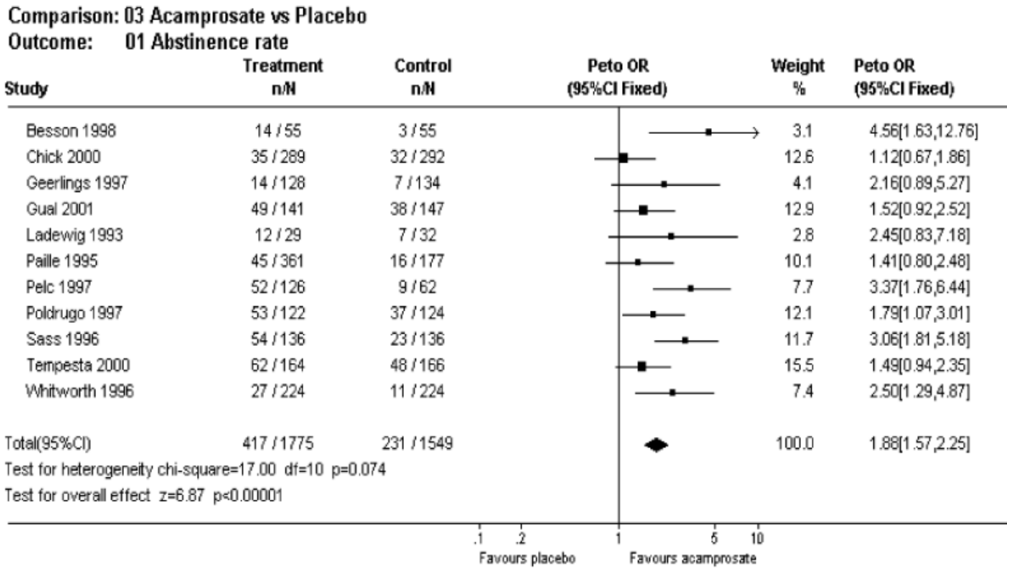
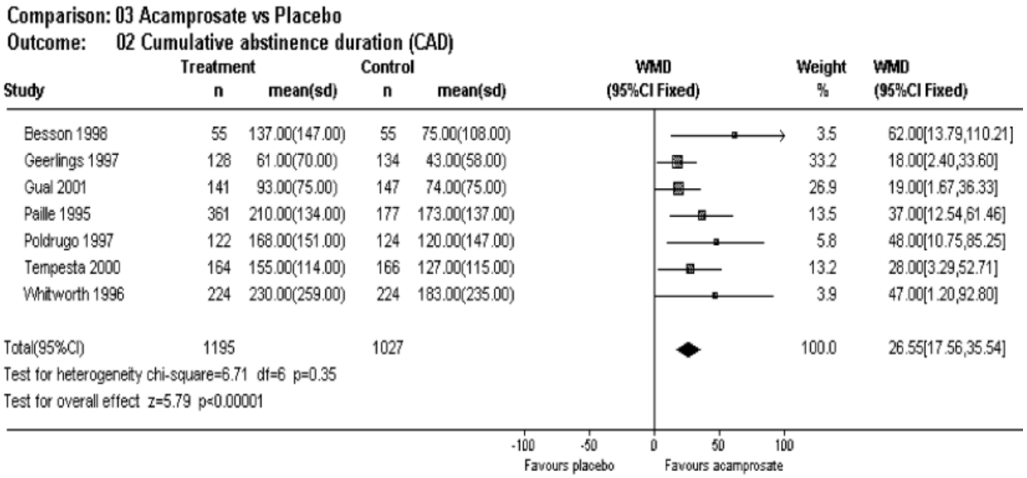


Figure 2: Bouza Meta-Analysis. Acamprosate versus placebo on cumulative abstinence duration [4]



Others analyzed randomized, placebo-controlled trials of acamprosate (which included unreported results) through 2004 (aforementioned studies from Europe and one each from the United States, Brazil, and South Korea; N=5280) [6]. Treatment with acamprosate was again found to reduce the risk of having a first drink to 84% of the risk with a placebo (Risk reduction (RR)=0.84, 95% Confidence Interval (CI), 0.78–0.91; figure 3) with a NNT of 7.7 to prevent one additional incidence of drinking (95% CI, 5.6–13.0). Acamprosate also reduced the risk of returning to heavy drinking compared to placebo (RR=0.82, 95% CI, 0.73–0.92; figure 4) with a NNT of 8.6 (95% CI, 5.7–18.7) although this effect disappeared within the subgroup of non-abstinent patients.

Figure 3: Rösner Meta-Analysis. Acamprosate versus placebo relative risk of first drink. [6]

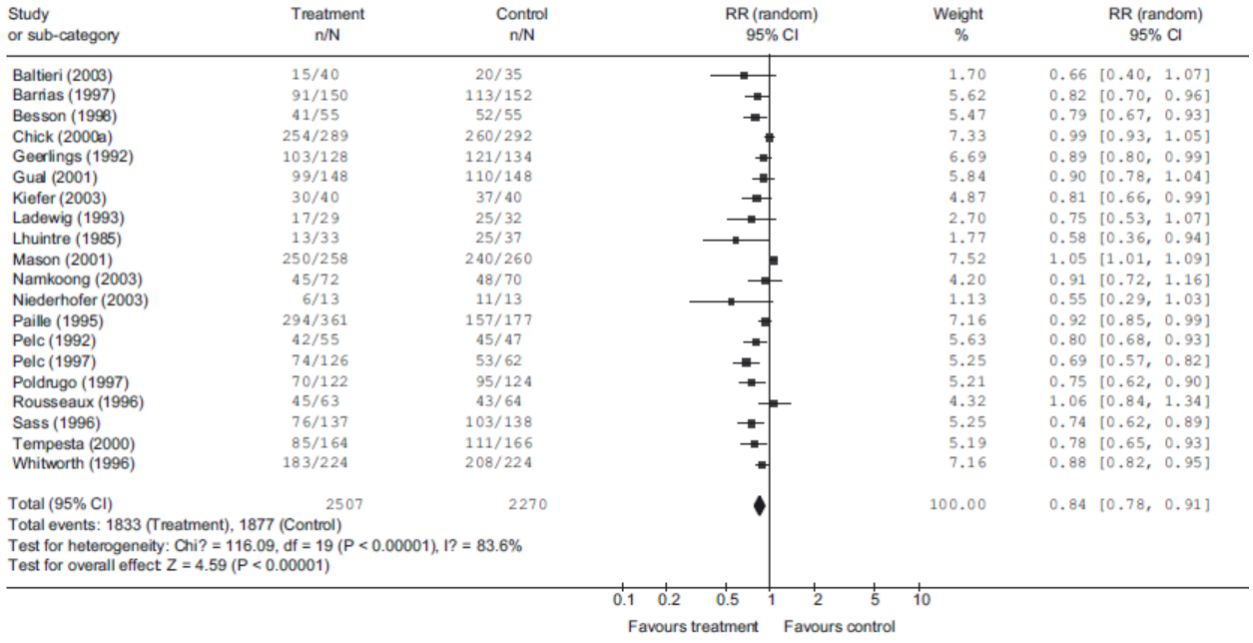
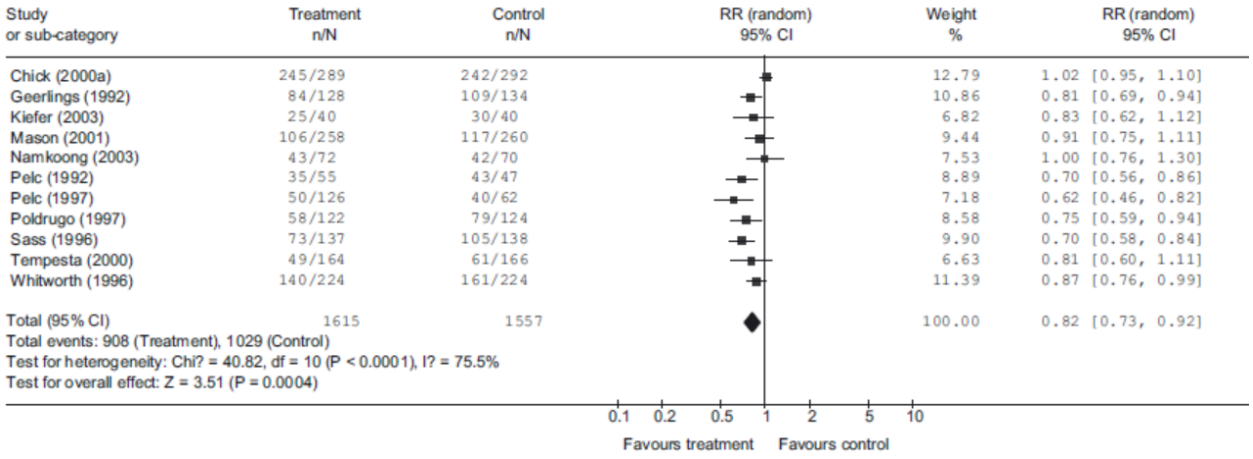


Figure 4: Rösner Meta-Analysis. Acamprosate versus placebo relative risk of relapse to heavy drinking [6]



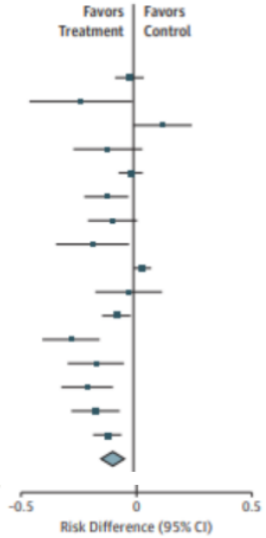
The largest trial to date on the use of acamprosate for the treatment of alcohol dependence (based on DSM IV criteria), the Combined Pharmacotherapies and Behavioral Interventions (COMBINE) trial, took place across 11 U.S. academic sites and compared effectiveness of acamprosate with placebo and naltrexone (N=1383) (Anton et al. 2006). Sponsored by the National Institute on Alcohol Abuse and Alcoholism (NIAAA), this multisite, randomized, controlled study observed 16 weeks of treatment and followed subjects one year after treatment ended. Participants (majority white men; “ethnic minorities” comprised 23%) were randomly assigned into groups after 4-21 days of abstinence. Groups included naltrexone, acamprosate, both, or neither with or without combined behavioral intervention (CBI; provided by behavioral health specialist). All groups received medical management sessions focused on enhancing medication adherence and abstinence. This study did not find additional benefit of acamprosate in increasing abstinence either as monotherapy or in combination with naltrexone. However, all treatment groups experienced a large increase in percent days abstinent–from 25 prestudy to 73 during treatment–and all groups receiving pills–whether placebo or active drug–had improvement in abstinent days compared to the CBI only group. The strong placebo effect in this trial may have made it difficult to detect any additional effect of acamprosate. Additionally, this study began treatment after four days of abstinence whereas most positive studies of acamprosate had a longer pretreatment abstinence period (Anton et al. 2006).

Subsequently, a Cochrane review in 2010 found that acamprosate significantly reduces the risk of any drinking (RR=0.86, 95% CI, 0.81–0.91) with a NNT 9.09 (95% CI, 6.66–14.28) compared to placebo[34] . This review also showed that results in industry-sponsored trials (RR=0.88, 95% CI, 0.80–0.97) did not differ from those of non-profit funded trials (RR=0.88, 95% CI, 0.81–0.96). A meta-analysis of English-language randomized, placebo-controlled trials through 2009–including the COMBINE study–continued to find improved abstinence outcomes (abstinence rate, percent days abstinent, and time to first drink) with acamprosate. Specifically, the analysis finds that 8 people would need to be treated with acamprosate to achieve an additional case of abstinence (NNT=7.5) and that the medication is more effective when participants are detoxified and abstinent when treatment begins. Effects of acamprosate were not significant for relapse to heavy drinking or reducing cravings[7]

A 2014 meta-analysis of 27 studies on acamprosate (N=7519) found the NNT to prevent return to any drinking was 12 (95% CI, 8–26; risk difference, -0.09; 95% CI, -0.14 to -0.04; figure 5) but also did not find an effect of acamprosate on the return to heavy drinking [9].

Figure 5: Jonas Meta-Analysis. Acamprosate versus placebo on return to any drinking [9]

Source	Duration, wk	Risk of Bias	Treatment Group Events, No.	Treatment Group No Events, No.	Control Group Events, No.	Control Group No Events, No.	Risk Difference (95% CI)	Weight, %
Acamprosate								
Anton et al,[30] 2006	16	Low	244	59	254	55	-0.02 (-0.08 to 0.04)	7.73
Baltieri et al,[47] 2004	12	Med	15	25	21	14	-0.22 (-0.45 to -0.00)	3.21
Berger et al,[46] 2013	12	Med	48	3	40	9	0.12 (-0.00 to 0.25)	5.61
Besson et al,[48] 1998	51	Med	41	14	47	8	-0.11 (-0.26 to 0.04)	4.94
Chick et al,[49] 2000	24	Med	254	35	260	32	-0.01 (-0.06 to 0.04)	8.01
Geerlings et al,[51] 1997	26	Med	96	32	116	18	-0.12 (-0.21 to -0.02)	6.66
Gual et al,[45] 2001	26	Med	92	49	109	38	-0.09 (-0.19 to 0.02)	6.28
Kiefer et al,[39] 2003	12	Low	30	10	37	3	-0.17 (-0.33 to -0.02)	4.68
Mason et al,[37] 2006	24	Low	328	13	240	20	0.04 (0.00 to 0.08)	8.34
Morley et al,[38] 2006	12	Low	44	11	50	11	-0.02 (-0.16 to 0.12)	5.08
Paille et al,[52] 1995	51	Med	294	67	157	20	-0.07 (-0.13 to -0.01)	7.74
Pelc et al,[53] 1997	13	Med	74	52	53	9	-0.27 (-0.39 to -0.14)	5.72
Poldrugo et al,[54] 1997	26	Med	63	59	84	40	-0.16 (-0.28 to -0.04)	5.78
Sass et al,[28] 1996	48	Med	75	61	102	34	-0.20 (-0.31 to -0.09)	6.11
Tempesta et al,[55] 2000	26	Med	87	77	115	51	-0.16 (-0.27 to -0.06)	6.35
Whitworth et al,[56] 1996	52	Med	183	41	208	16	-0.11 (-0.17 to -0.05)	7.76
Subtotal: I^2=80.8%; P<.001							-0.09 (-0.14 to -0.04)	100.00



Similarly, a 2015 meta-analysis of randomized controlled trials for acamprosate use in alcohol dependence (based on DSM IV criteria) analyzed 18 European studies, two from the United States, one from South Korea, and one from Australia (N=2649 in acamprosate group and N=2587 in placebo group). This similarly found significantly reduced risk of individuals returning to any drinking at 6 months follow-up in the acamprosate group (RR=0.83, 95% CI, 0.78–0.89). They further analyzed whether there was a difference in risk reduction between European studies and studies outside of Europe and found no difference (Donoghue 2015).

A network meta-analysis of randomized controlled trials comparing interventions that could be used in primary care for patients with alcohol dependency who recently underwent detoxification found that acamprosate was associated with increased probability of abstinence (odds ratio (OR)=1.86, 95% CI, 1.49–2.33, corresponding to an absolute probability of 38%) up to twelve months following detoxification [11]. Most recently a network meta-analysis of placebo controlled, randomized trials including 35 studies assessing acamprosate found that acamprosate improved both total abstinence (RR=1.33; 95% CI, 1.15– 1.54) and reduced heavy drinking (RR=0.78; 95% CI, 0.70–0.86) [12]

9.2 Search strategy and identified studies

PubMed database search conducted November 2022 with the following terms: (Alcohol use disorder) AND (acamprosate); (Alcohol use disorder) AND (acamprosate) – filter clinical trial, RCT, or meta-analysis; (Guidelines[Title]) AND (alcohol use disorder). To supplement the search, we additionally hand searched relevant randomized controlled trials from reference lists of identified systematic reviews, meta-analyses, and guidelines included in this review.

10. Comparative cost-effectiveness

A. Modeling studies

Several modeling studies have looked at the cost–effectiveness of acamprosate. A model based on German healthcare system perspective and data from an RCT of acamprosate versus placebo which retrospectively applied costing demonstrated net savings with acamprosate [35]. Another German study looked at lifetime cost effectiveness and found that adjunctive acamprosate with standard counseling compared to counseling alone resulted in more life years gained (15.9 versus 14.6) and lower costs [36]. Another model based study based on the Belgian health payers' perspective also showed cost savings with acamprosate [37]. A modeling study using a hypothetical cohort and Scottish health service estimates found that acamprosate resulted in net savings compared to standard care [38].

B. Prospective cohort

A prospective study of costs from the perspective of German health insurance found that adjunctive acamprosate (with psychosocial rehabilitation support) resulted in higher abstinence and lower costs than psychosocial rehabilitation support alone [39].

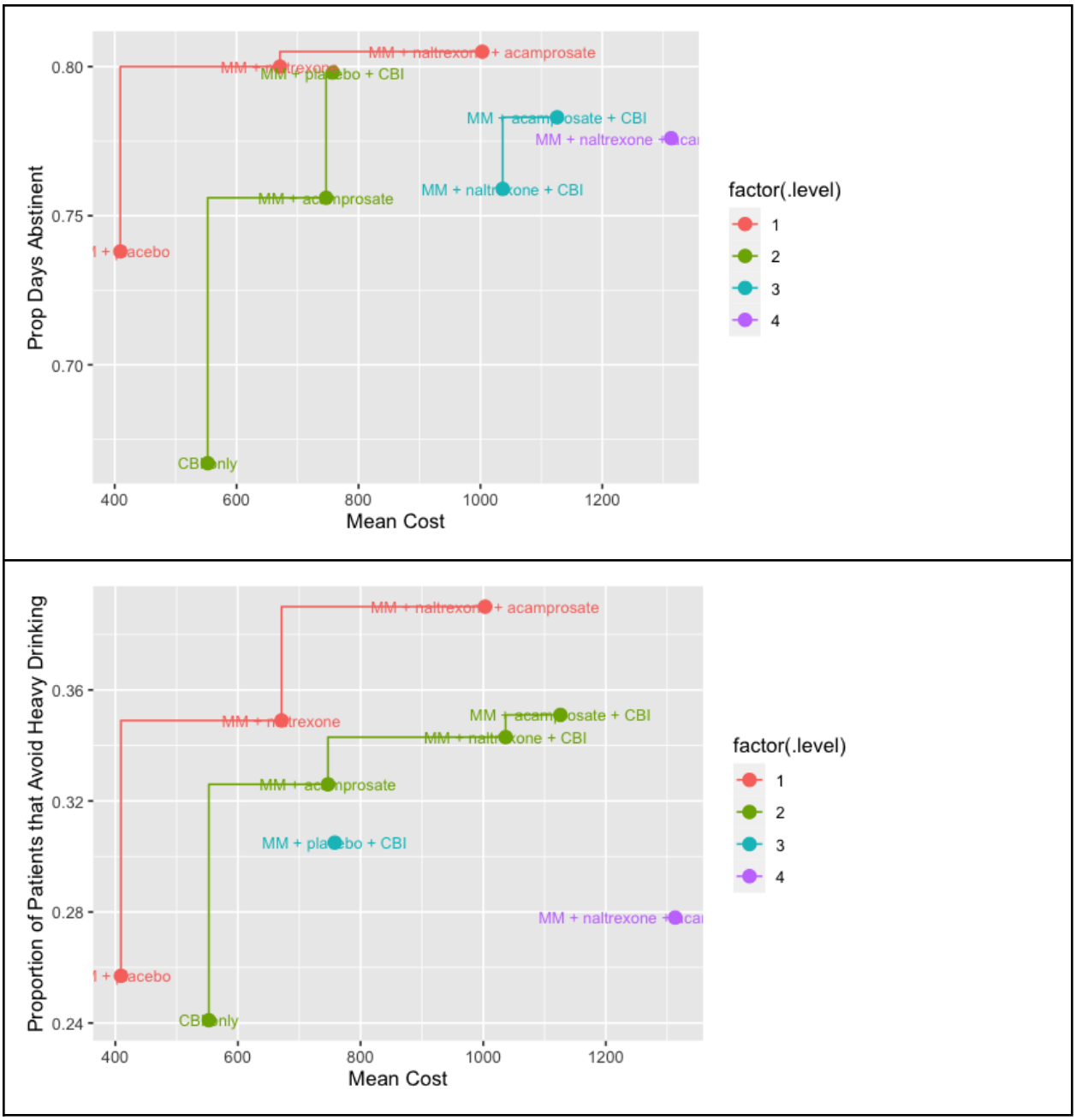
C. RCTs

The COMBINE study was a multicenter randomized clinical trial in the United States comparing the efficacy of combinations of behavioral and pharmacologic therapies for alcohol use disorder [8]. One derivative study estimated the costs and cost effectiveness of the nine treatment arms over the 16 week treatment period of the COMBINE trial [40]. Figure 10 shows the pareto frontier of cost versus effectiveness for three outcomes studied. Results of the analysis showed that three treatment arms are in the cost-effective choice set:

- Medical management and placebo ($409 per patient) - cheapest but less effective than the other two.
- Medical management and naltrexone ($671.16 per patient) - more expensive and more effective than above, but much lower cost per additional unit effectiveness than below (more value).
- Medical management and naltrexone and acamprosate ($1003.06 per patient) - most expensive of the set but most effective.

The choice of strategy depends on the willingness to pay for each incremental unit of effectiveness for a particular outcome. At willingness to pay greater than $200 to 800 (per additional patient avoiding heavy drinking or per additional good clinical outcome) the probability of most cost effective options is medical management and naltrexone, once willingness to pay increases beyond $800 medical management and naltrexone and acamprosate has the highest probability of being the most cost effective option [40].

Figure 10. Pareto frontier comparing various COMBINE treatment arms for outcomes a) proportion of days abstinent, b) proportion of patients that avoid heavy drinking, c) proportion of patients with good clinical outcome. Factor 1 represents most preferable options on the pareto frontier, factor 1 dominates factor 2, which dominates factor 3 etc.


Prop Days Abstinent
0.80
0.75
0.70
400
600
800
1000
1200
Mean Cost
MM + naltrexone + acamprosate
MM + placebo + CBI
MM + acamprosate + CBI
MM + naltrexone + CBI
MM + acamprosate
CB only
factor(.level)
1
2
3
4
Proportion of Patients that Avoid Heavy Drinking
0.36
0.32
0.28
0.24
400
600
800
1000
1200
Mean Cost
MM + naltrexone + acamprosate
MM + naltrexone
MM + acamprosate + CBI
MM + naltrexone + CBI
MM + acamprosate
MM + placebo + CBI
CB only
factor(.level)
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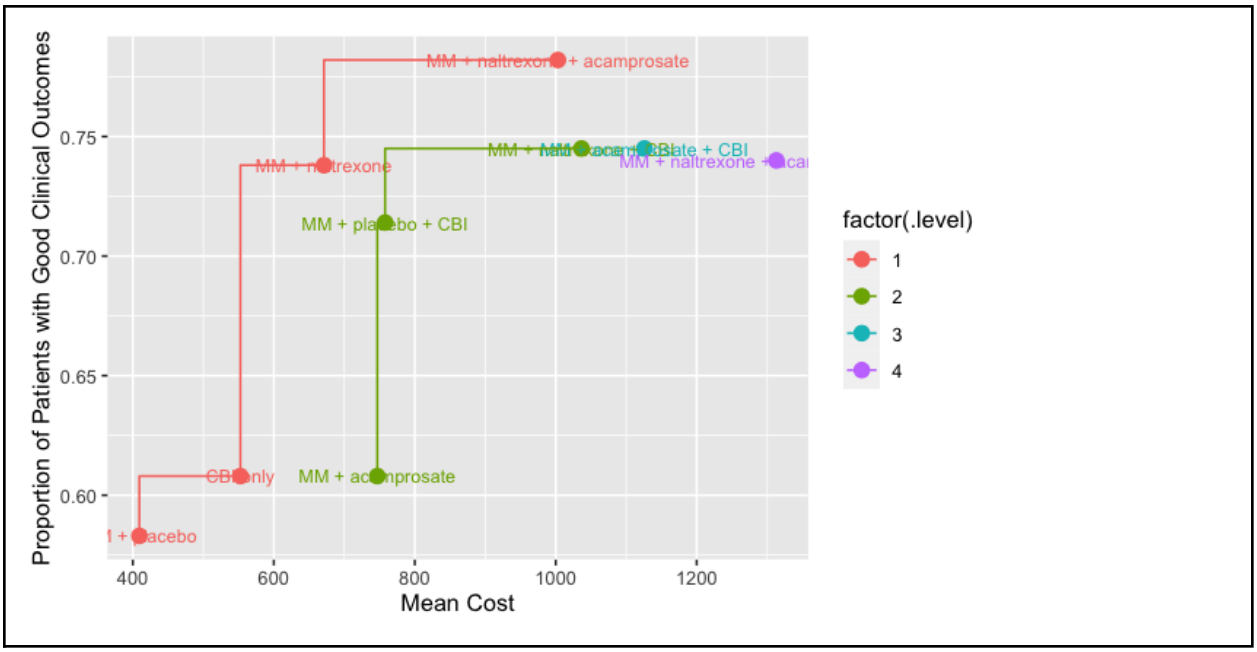

Cost effectiveness of behavioral treatments for alcohol use disorder was studied in 2 RCTs, neither of which had a placebo arm. One study showed a decline in total medical care post treatment for 3 of 3 treatment arms without significant differences[41]. The second RCT evaluated two behavioral treatments and showed similar and substantial savings of 5 times cost of treatment for both treatment arms in the form of reduced health care expenditures, social services and criminal justice services[42].

One cost effectiveness study that included pharmacologic therapies was a derivative study from the COMBINE study which examined the effect of treatment arms on social costs and outcomes at 3 years (in the form of health care use, arrests, and motor vehicle accidents in the US) [43]. The study showed median social cost savings compared to medical management and placebo at 3 yeast after randomization, with magnitude of savings greater than costs of the treatment for four arms of the study (but not mean reductions due to skew of data)[43]. Compared to medical management and placebo, cost reductions of

- Medical management and acamprosate: $2,547.31
- Medical management and naltrexone: $2,991.12
- Medical management and acamprosate and naltrexone: $3,871.26
- Medical management and acamprosate and CBI: $3,276.55

Importantly, the analysis showed that a substantial effect on cost differences were related to arrests and motor vehicle accident outcomes[43]. Limitations of the study were that it was wholly in the United States and did not examine outcomes related to social costs related to labor and employment.

NICE analysis of cost effectiveness by QALY

In their guideline NICE developed an economic model to evaluate cost effectiveness of pharmacologic therapies for prevention of relapse of people in recovery from alcohol dependence [16]. The model considered three treatment groups: (1) acamprosate and standard care; (2) naltrexone and standard care; and (3) standard care alone [16]. The outcome of interest was the QALY and the analysis accounted for costs for drug acquisition, lab tests, psychological interventions and outpatient primary and secondary care [16].

In the deterministic analysis they found that the incremental cost-effectiveness ratio (ICER) of acamprosate and naltrexone compared to standard care were both within the cost-effectiveness threshold of £20,000 to £30,000 per QALY currently set by NICE [16]. Naltrexone was extendedly dominated by acamprosate (lower ICER). The result that both options were cost effective by NICE criteria was robust under various scenarios evaluated in the one-way sensitivity analysis [16].

Table 2: 12-month mean costs and QALYs per 1000 patients and ICERs for pharmacological interventions used for relapse prevention in people in recovery from alcohol dependency (adapted from [16].

	QALYs per 1000 patients	Costs per 1000 patients	ICER vs Standard care	ICER vs naltrexone
Standard Care	656	£1,664,382	—	—
Naltrexone	680	£1,797,737	£5395 per QALY	—
Acamprosate	683	£1,802,982	£5043 per QALY	£1899 per QALY

The probabilistic analysis results were similar - with acamprosate being most probable to be most cost effective with willingness to pay above £6000 per QALY [16]. For thresholds of £20,000 to £30,000 per QALY the probability of acamprosate being the most cost-effective treatment option was 52 to 53% and or probability of naltrexone was 44 to 45%, respectively [16]. The meta-analysis was somewhat limited in that the majority of studies were relatively short term (3 to 6 months), had different definitions of relapse, and included different baseline psychological therapies [16].

Extrapolating this data to the global context is difficult based on differing costs of medication, consultations and varying estimates for willingness to pay. If we are to convert the ICER per QALY to US dollars (£5043 GBP equals $6006 USD) and using the WHO criterion of cost effectiveness as less than three times GDP per capita per QALY(there is substantial critique of such thresholds available at [44]), we could then transitively deduce that acamprosate would be cost effective in countries with GDP per capita greater than $2002. By reviewing World Bank Data [45] in 2015 we see that seven countries have missing GDP per capita data, 48 countries have GDP per capita below the threshold and 162 countries have GDP per capita where acamprosate may be considered cost effective.

10.1 Summary of costs

Acamprosate oral tablet

Table 3: Market availability and prices of Acamprosate oral tablet

	Availability Notes	Average Price (28d supply)
United States	Public: on 40 (of 53) medicaid formularies, preferred 27 (of 53), and need prior auth (8 of 53) [46]	VA-FSS[47] $211.47
	Private: available	Online search: average $92.79
Australia	On Pharmaceutical Benefits Scheme (PBS)	General patient charge $27.37 (DPMQ $56.94)
India	Not on Tamil Nadu EML	
	Private: available online search	Online search: average $29.6
United Kingdom	On formulary	General patient charge $ 11.64 (Net Ingredient Cost: median $30.07, mean $63.15)

11. Summary of regulatory status and market availability of the medicine.

Regulatory status of acamprosate oral tablet

Acamprosate is approved by the United States FDA for moderate to severe alcohol use disorder, specifically for maintenance of abstinence.

It is also approved in other countries such as Australia, France, India, Ireland, Japan and the United Kingdom.

Patent and Exclusivity

Acamprosate is no longer patent protected.

12. Availability of pharmacopoeial standards

Acamprosate is included in the United States Pharmacopoeia [48], and the British Pharmacopoeia [49] but not the International Pharmacopoeia.

13. References

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