Acamprosate calcium

Essential medicine status

Section: 24. Medicines for mental and behavioural disorders > 24.5. Medicines for disorders due to psychoactive substance use > 24.5.1. Medicines for alcohol use disorders

ATC codes: N07BB03

Indication	Disorders due to use of alcohol ICD11 code: 6C40
INN	Acamprosate
Medicine type	Chemical agent
List type	Core
Formulations	**Oral > Solid > tablet:** 333 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents.
Wikipedia	Acamprosate calcium
DrugBank	Acamprosate calcium (Acamprosate)

Expert Committee recommendation

The Expert Committee noted the public health importance of treatment of alcohol dependence and harmful use of alcohol from a medical, social and economic perspective. Currently, only one in six people globally with alcohol use disorder receives treatment and rates are even lower in low- and lower middle-income countries. The Committee recognized the need to identify and address the various factors that increase alcohol consumption and influence its effects, as well as the need to develop and implement appropriate policies to decrease the harmful use of alcohol. The Committee considered that the availability of pharmacotherapies for the treatment of alcohol use disorder should be seen as part of this complex strategy of interventions. The Committee noted that evidence from several randomized clinical trials (6 to 12 months follow-up) was available, indicating acamprosate efficacy on abstinence rates compared with placebo. The magnitude of treatment effects appeared to be moderate, but the Committee considered the impact at the population level would be significant. Post-treatment follow-up studies have shown that the effects of acamprosate are maintained for up to 1 year after the last dose. Psychosocial interventions, such motivation enhancement and cognitive behavioural treatment improve the likelihood that people treated with acamprosate meet their goals for recovery. The Committee noted that acamprosate was generally well tolerated and its use did not require specialized supervision meaning acamprosate can be effectively and safely used in primary care and other community settings. The Committee noted that in head-to-head trials that compared acamprosate with naltrexone, no statistically significant difference was found between the two medications for some outcomes (e.g. return to any drinking). The Committee noted that acamprosate was one of the medicines recommended in the WHO mhGAP guidelines for treatment of alcohol use disorder and was also recommended in other international guidelines. The Committee considered that the availability of different medicines for alcohol use disorder would provide valuable options and choice for patients and clinicians. It could also facilitate increased market competition, reduce costs and improve affordable access for national health systems. The Committee therefore recommended the inclusion of acamprosate on the core list of the EML for the treatment of alcohol use disorder in adults.

Background

Medicines for treatment of alcohol use disorders have not previously been evaluated for inclusion in the EML.

Public health relevance

Globally in 2016, alcohol use was the seventh leading risk factor for premature death and disability and was the leading risk factor in people aged 15 to 49 years. Worldwide, 2.8 million deaths were attributable to alcohol use. Alcohol consumption was shown to have a strong association with a higher risk of cancer, injuries and communicable disease (1). The 2018 WHO Global status report on alcohol and health recognized that the harmful use of alcohol directly affects numerous targets of the Sustainable Development Goals including those for maternal and child health, infectious diseases, noncommunicable diseases, mental health, injuries and poisonings (2). Globally in 2016, estimates suggest that the harmful use of alcohol was responsible for 3 million deaths and caused 132.6 million disability-adjusted life years (DALYs) or 5.1% of total DALYs that year. The age-standardized burden of disease and injury associated with alcohol use varied geographically across WHO regions and was highest in the African region, where it was responsible for 70.6 deaths and 3044 DALYs per 100 000 people (2). During the COVID-19 pandemic, a cross-sectional survey in the United States found that respondents reported consuming more drinks per day, more binge drinking and more alcohol consumption beyond recommended drinking limits than before the introduction of stay-at-home orders (3).

Benefits

A 2004 systematic review and meta-analysis evaluated the efficacy and safety of acamprosate and naltrexone in the treatment of alcohol dependence. The study included 13 randomized-controlled trials (4000 participants) of acamprosate in people who met the Diagnostic and statistical manual of mental disorders, third edition (DSM-III) criteria for alcohol dependence and who had undergone a detoxification process (4). A meta-analysis of 12 of the 13 studies showed that acamprosate was associated with an increased rate of continuous abstinence compared with placebo (Peto odds ratio (OR 1.88, 95% confidence interval (CI) 1.57 to 2.25; number needed to treat (NNT) = 10). Acamprosate was also associated with a doubling of the days of cumulative abstinence based on seven studies that measured this outcome. Another 2004 systematic review and meta-analysis of 17 randomized controlled trials (4087 participants) evaluated the efficacy of acamprosate for maintenance of abstinence in alcohol-dependent individuals (5). Participants treated with acamprosate compared with placebo had significantly higher continuous abstinence rates at 6 months (36.1% versus 23.4%, relative benefit (RB) 1.47, 95% CI 1.29 to 1.69). The pooled difference in success rates for continuous abstinence at 12 months between acamprosate and placebo was 13.3% (95% CI 7.8% to 18.7%; NNT = 8). A 2008 meta-analysis compared the efficacy profiles of acamprosate and naltrexone. The analysis included 21 randomized controlled trials (5280 participants) that evaluated the efficacy and safety of acamprosate compared with placebo (6). Treatment with acamprosate reduced the risk of having a first drink by 84% compared with placebo (risk ratio (RR) 0.84, 95% CI 0.78 to 0.91; NNT to prevent one additional incidence of drinking = 8). Acamprosate was also associated with a reduced the risk of returning to heavy drinking compared with placebo (RR 0.82, 95% CI 0.73 to 0.92; NNT = 9). However, acamprosate did not significantly reduce the risk of heavy drinking among the subgroup of non-abstinent participants (RR 0.98, 95% CI 0.94 to 1.02). A 2010 Cochrane systematic review of 24 randomized controlled trials (6915 participants) evaluated the effectiveness and tolerability of acamprosate in comparison with placebo and other pharmacological agents (7). Acamprosate significantly reduced the risk for the primary outcome of return to any drinking (RR 0.86, 95% CI 0.81 to 0.91; NNT for an additional beneficial outcome = 10) compared with placebo. Sensitivity analyses to assess the effect of the funding source/sponsorship of the trials found that partially industry-supported trials had the highest magnitude of effect (RR 0.84, 95% CI 0.78 to 0.89), while fully industry-supported trials had the lowest magnitude of benefit (RR 0.88, 95% CI 0.80 to 0.97). For the outcome of cumulative abstinence duration, a statistically significant difference was found between acamprosate and placebo groups favouring acamprosate (mean difference (MD) 10.9, 95% CI 5.08 to 16.8). A 2013 meta-analysis of 64 randomized, placebo-controlled trials conducted between 1970 and 2009 that evaluated the efficacy of naltrexone and acamprosate included 16 randomized controlled trials (4349 participants) comparing acamprosate with placebo and three randomized controlled trials (1210 participants) comparing naltrexone, acamprosate and placebo (8). Outcome measures included aggregate measures of abstinence and heavy drinking. For abstinence outcomes, acamprosate showed a significantly larger effect size than naltrexone (Hedges g 0.36, 95% CI 0.25 to 0.47 for acamprosate versus Hedges g 0.12, 95% CI 0.05 to 0.18 for naltrexone). The NNT for one additional case of abstinence was 8. For heavy drinking outcomes, naltrexone (Hedges g 0.19, 95% CI 0.12 to 0.25) showed a larger effect than acamprosate (Hedges g 0.07, 95% CI –0.08 to 0.22), however the difference was not statistically significant. The NNT to prevent one additional case of return to heavy drinking was 9. A 2014 meta-analysis of 123 studies (22 803 participants) evaluated the benefits and harms of pharmacotherapy for alcohol use disorders and included 27 randomized controlled trials (7519 participants) comparing acamprosate and placebo (9). As in previous studies, acamprosate was associated with improvements in consumption outcomes compared with placebo. The risk difference (RD) for acamprosate for return to any drinking was –0.09 (95% CI –0.14 to –0.04; NNT = 12). Acamprosate did not reduce the risk of return to heavy drinking (RD –0.01, 95% CI –0.04 to 0.03). A 2015 meta-analysis of 22 randomized controlled

trials (5236 participants) evaluated the efficacy of acamprosate in the treatment of alcohol dependence and examined the variance in outcomes in Europe versus other countries (10). A significantly reduced risk of individuals returning to any drinking at 6 months follow-up was observed in the acamprosate group compared with placebo (RR 0.83, 95% CI 0.78 to 0.89). No difference in risk reduction was observed between European studies and studies outside of Europe. A 2020 network meta-analysis of 64 randomized controlled trials compared interventions used in primary care for patients with alcohol dependency who recently underwent detoxification (11). Acamprosate was associated with increased probability of abstinence up to 12 months following detoxification compared with placebo (OR 1.86, 95% CI 1.49 to 2.33, corresponding to an absolute probability of 38%). A 2022 systematic review and network meta-analysis of pharmacotherapies for alcohol use disorders included 35 randomized controlled trials comparing acamprosate with placebo (12). Acamprosate significantly improved both total abstinence (rate ratio 1.33, 95% CI 1.15 to 1.54) and reduce heavy drinking (rate ratio 0.78, 95% CI 0.70 to 0.86). The combined pharmacotherapies and behavioural interventions study (COMBINE) was a multicentre, randomized controlled trial that compared the effectiveness of acamprosate with placebo and naltrexone (1383 participants). Patients received 16 weeks of treatment and were followed for 1 year after treatment completion (13). Participants were randomly assigned after 4 to 21 days of abstinence to receive either acamprosate, naltrexone, acamprosate in combination with naltrexone, or placebo, with or without a combined behavioural intervention. All treatment groups experienced an increase in percentage of days abstinent, from 25% pre-study to 73% during treatment. All groups receiving medicines or placebo showed improvements in abstinent days compared with the group who only received combined behavioural intervention. 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 4 days of abstinence whereas most positive studies of acamprosate had a longer pretreatment abstinence period.

Harms

The application did not present a summary of evidence on the harms of acamprosate. The most common adverse effect of acamprosate is diarrhoea, which is usually mild and self-limiting, but in some patients can be severe and persistent. Other less common adverse effects are suicidal ideation (infrequent but requires discontinuation), other gastrointestinal symptoms (intestinal cramps, flatulence and nausea), headache, dizziness, increased or decreased libido, insomnia, anxiety, muscle weakness and itchiness (14). From the 2010 Cochrane systematic review, diarrhoea was the only adverse effect that occurred more frequently with acamprosate than placebo (risk difference 0.11, 95% CI 0.10 to 0.13; NNT for an additional case of diarrhoea = 10). The risk of drop-outs due to adverse events was significantly greater for acamprosate than placebo (RR 1.35, 95% CI 1.01 to 180), but the risk of drop-outs due to any cause was significantly lower with acamprosate (RR 0.91, 95% CI 0.83 to 0.99) (7). 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 patients with renal impairment and the use of acamprosate is contraindicated in patients with severe renal impairment. Dosage adjustment is recommended for patients with moderate renal impairment (15). Acamprosate is more effective if started after detoxification is completed, but its pharmacokinetics are not altered by co-administration with alcohol or benzodiazepines and can therefore be safely used before alcohol cessation and during relapse (14–16). Acamprosate should be avoided in pregnant women unless benefits are considered to outweigh potential risks (14).

Cost / cost effectiveness

A health technology assessment performed by the National Institute for Clinical Excellence (NICE) in the United Kingdom found that the the incremental cost–effectiveness ratio of acamprosate and naltrexone compared with standard care were both within the cost–effectiveness threshold of £20 000 to £30 000 per quality-adjusted life year (QALY) (18). The finding was robust for various scenarios evaluated in the one-way sensitivity analysis. Several modelling studies have evaluated the cost–effectiveness of acamprosate. A model from the perspective of the German health care system using data from a randomized controlled trial of acamprosate versus placebo which retrospectively applied costing demonstrated net savings with acamprosate (19). Another German study examined the lifetime cost–effectiveness of acamprosate and found that adjunctive acamprosate with standard counselling compared with counselling alone resulted in more life years gained (15.9 versus 14.6) and lower costs (20). Another model-based study from the Belgian health payers' perspective also showed cost savings with acamprosate (21). A modelling study using a hypothetical cohort and Scottish health service estimates found that acamprosate resulted in net savings compared with standard care (22). 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 (23). A 2007 prospective cost and cost–effectiveness study of the COMBINE study interventions found three of the nine interventions to be cost-effective from the treatment provider perspective: medical management plus placebo; medical management plus naltrexone; and medical management plus naltrexone and acamprosate.

Estimated treatment costs per patient were US$ 409, US$ 671 and US$ 1003, respectively, using 2007 costs (24). An additional cost study using data from COMBINE examined the effect of treatment arms on social costs of alcohol dependence and outcomes at 3 years (in terms of health care use, arrests and motor vehicle incidents in the United States) (25). Median social cost savings comparing medical management and placebo were: US$ 2547 for medical management plus acamprosate; US$ 2991 for medical management plus naltrexone; US$ 3871 for medical management plus acamprosate and naltrexone; and US$ 3277 for medical management plus acamprosate plus cognitive behavioural interventions. A substantial effect on cost differences was related to the outcomes of arrests and motor vehicle incidents (25).

WHO guidelines

The 2023 WHO Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders includes a strong recommendation that combined psychosocial and pharmacological interventions should be offered for adults with alcohol dependence (moderate certainty of evidence). Pharmacological treatments considered included acamprosate, disulfiram and naltrexone (17).

Availability

Acamprosate has regulatory approval globally for use in alcohol use disorder and is available in most countries in innovator and generic brands.

Other considerations

The WHO Department of Mental Health and Substance Use reviewed and provided comments on the application. The technical unit stated that the application to include acamprosate on the EML was timely and in line with guidance provided by WHO global policy frameworks and action plans.

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