

REVIEW

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Safety and Efficacy of Acamprosate for the Treatment of Alcohol Dependence

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Abstract: Acamprosate (calcium acetylhomotaurine) is an amino acid modulator that has displayed efficacy in some clinical trials in reducing craving and promoting abstinence in alcohol dependent patients following detoxification. While acamprosate is safe and generally well-tolerated, not all studies have demonstrated clinical efficacy that is superior to placebo. In addition, the precise neurochemical mechanisms of action of acamprosate have still not yet been identified. In this review, we summarize current clinical data on the safety, efficacy, and pharmacokinetic properties of acamprosate, as well theories on its potential mechanism of action. We also discuss tolerability and patient preference issues and conclude with a discussion of the place of acamprosate in addiction medicine and therapy.

Keywords: acamprosate, alcoholism, dependence, craving, amino acid, glutamate, pharmacotherapy

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Introduction

Recent global estimates from the World Health Organization reveal that most individuals either abstain from (58%) or have never consumed alcohol (45%) in their lifetime.¹ Despite these global abstinence rates, consumption of alcoholic beverages is a common practice in most parts of the world, and approximately 6.13 liters of pure alcohol is consumed each year for every person age 15 years or older. Thus, while most people either abstain from or drink alcohol at moderate levels, about 11.5% of drinkers report regular heavy drinking episodes.¹ In the United States, just over half (51.8%) of the population ages 12 and older regularly consumes alcohol with approximately a quarter (22.8%) reporting binge drinking (5 or more drinks in an episode) and 6.2% reporting heavy drinking (5 or more drinks per episode more than 5 days a week) in the last 30 days.² While global estimates of alcohol dependence vary, 12.5% of individuals (17.4% of men and 8% of women) in the United States will meet criteria for alcohol dependence in their lifetime.¹ Not surprisingly, for the United States and most countries around the world, harmful alcohol use remains a significant cause of chronic disease and injury.³ According to the World Health Organization, nearly 4% of all deaths in the world, equivalent to approximately 2.5 million a year, are caused by harmful alcohol use.¹ In the United States, excessive alcohol use accounts for 79,000 premature deaths annually.⁴ In addition to the devastating effects on users, the estimated economic burden in the United States due to alcohol use and its associated losses in productivity, health-care costs, criminal justice costs, and other effects is \$223.5 billion, around \$746 dollars per each US citizen.⁴ Of this, approximately 11% (\$24.6 billion) is due to health-care related expenses with treatment for alcohol abuse and dependence being the largest contributor (43.4%). These statistics highlight both the devastating impact excessive alcohol has on both users and society and reveal the importance of employing effective strategies for preventing excessive alcohol use and treating individuals currently diagnosed with alcohol use disorders.

Alcoholism is a complex behavioral disorder characterized by excessive and compulsive drinking, chronic relapse and impaired control over intake, tolerance to the effects of alcohol, presence of withdrawal symptoms, and impaired social and

occupational functioning.^{5,6} As with most substance use disorders, the mainstay treatments for alcohol use disorders are self-help social support groups, 12-step programs, cognitive-behavioral therapies, or some combination of these. While meta-analyses show traditional therapeutic approaches to be more effective than voluntary abstinence or moderation of drinking,^{7,8} research shows that even with treatment many individuals (estimates range from 20%–80%) will eventually relapse.⁹ Given the low success rates of even the best therapeutic interventions, researchers and clinicians have long sought pharmacological adjuncts for the treatment of alcoholism. While multiple drug types have been prescribed off-label for alcohol dependence,¹⁰ there are currently only three FDA approved pharmacological treatments: disulfiram, naltrexone, and acamprosate.

In this review we will provide a brief overview of the mechanisms of action and efficacy of disulfiram and naltrexone, followed by a more detailed discussion of acamprosate. We will also review clinical trials that have assessed the efficacy of acamprosate in promoting abstinence and reducing alcohol craving and relapse. We will confine this review to trials that primarily focused on the efficacy of acamprosate itself. Clinical trials examining combinations of acamprosate with other pharmacological agents or specific psychotherapeutic or cognitive-behavioral approaches will not be reviewed and can be found elsewhere in recent meta-analyses.^{11,12} As will be discussed, acamprosate offers several advantages over these other two medications, although various trials with negative findings have demonstrated that acamprosate may not be efficacious for all treatment outcomes.

Pharmacological treatments for alcohol dependence

Disulfiram

Disulfiram was the first drug approved for the treatment of alcoholism. Approved in 1951,¹³ disulfiram has been the primary pharmacological treatment for alcoholism until the last three decades. Disulfiram inhibits the enzyme acetaldehyde dehydrogenase (ALDH) from converting acetaldehyde, an intermediate in the metabolism of alcohol, to acetate. The result is an accumulation of acetaldehyde, which produces an aversive reaction characterized by nausea,



vomiting, diarrhea, breathing trouble, skin flushing, dizziness, hypotension, and tachycardia.^{14,15} Thus, disulfiram is largely a deterrent and its effectiveness results from the patient's avoidance of intentional side effects from the alcohol-disulfiram interaction.¹⁶ Not surprisingly, disulfiram has shown potential in maintaining abstinence and reducing relapse, but its effectiveness requires supervision due to a high rate of medication noncompliance.^{14,15} The utility of disulfiram is further decreased due to its various contraindications with drugs metabolized by cytochrome p450 enzymes including imipramine, warfarin, phenytoin, various benzodiazepines, omeprazole, and others.¹⁷ Furthermore, disulfiram is known to produce other unintentional side effects including various types of neuritis, hepatotoxicity, fulminant hepatitis, confusion, and psychosis.^{13,17} More severe adverse effects of disulfiram include myocardial infarction, congestive heart failure, respiratory depression, and rarely, death.¹⁶ Disulfiram is not recommended for individuals with a history of psychosis, cardiovascular disease, pulmonary disease, previous renal failure, diabetes, or those over the age of 60.¹⁶ Thus, despite over 60 years as an approved medication, disulfiram is not recommended as a first-line treatment for alcohol dependence.¹⁸

Naltrexone

Naltrexone was FDA approved in 1994 for prevention of relapse in alcohol dependent patients.¹⁹ Naltrexone is a broad spectrum opioid receptor antagonist, with preferential binding to the μ receptor subtype. The reinforcing effects of alcohol appear to be mediated by the endogenous opioid system as well as a number of other neurotransmitter receptors including type A γ -aminobutyric acid (GABA_A) receptors, glutamate receptors particularly the N-methyl-D-aspartate (NMDA) subtype, the type 3 serotonin (5-HT₃) receptor, nicotinic acetylcholine receptors, and others.²⁰ While these systems are all capable of modulating the reinforcing effects of alcohol, alcohol-induced increases in endogenous opioid transmission is thought to be a primary mediator of alcohol reinforcement.²¹ These endogenous opioids, such as β -endorphin and enkephalin, bind primarily to μ opioid receptors located on GABAergic interneurons within the mid-brain ventral tegmental area (VTA). This results in the disinhibition of dopaminergic cell firing which leads

to increased dopamine (DA) release in the nucleus accumbens (NAcc) of the ventral forebrain.^{21,22} The ability of naltrexone to antagonize μ opioid receptors ultimately decreases DA release in the NAcc, thus dampening the reinforcing and rewarding effects of alcohol.²³

Clinical trials have revealed gastrointestinal side effects of naltrexone including decreased appetite, nausea, vomiting, diarrhea, and abdominal pain.^{24,25} Sleep related side effects include daytime sleepiness, drowsiness, fatigue, somnolence, and insomnia.²⁴ Additional side effects include blurred vision, decreased libido, depression, dizziness, and nightmares.²⁴ Unlike disulfiram, naltrexone is generally considered to have an overall safe and tolerable profile. However, naltrexone has been reported to lead to hepatocellular toxicity and is contraindicated in individuals with hepatic insufficiency,²¹ a common complication in alcohol dependence. While these complications can limit naltrexone efficacy and compliance, a long-lasting depot injection form of naltrexone was recently approved and may increase patient compliance.²⁶

Acamprosate

Mechanism of action

Acamprosate (calcium acetylhomotaurine) is derived from and structurally similar to the endogenous biochemical homotaurine, a nonspecific GABA receptor agonist.²⁷ Not surprisingly, when studies first revealed the ability of acamprosate to attenuate alcohol-seeking in both rats²⁸ and humans,²⁹ acamprosate was hypothesized to act primarily as a GABA_A receptor agonist given its structural similarity to taurine and the ability of the GABA_A antagonist bicuculline to reverse its effects. However, with the findings that acamprosate reduced excitatory post-synaptic potentials in the presence of excitatory neurotransmitters in vitro and decreased neocortical neuronal excitability in vivo,³⁰ subsequent interest shifted to the potential ant glutamatergic activity of acamprosate. While a complete understanding of the molecular targets and mechanism(s) of acamprosate and mechanism of action are still lacking,³¹ numerous lines of evidence suggest that acamprosate primarily exerts its effects by modulating glutamatergic, and not GABAergic, transmission.^{31,32} Radioligand binding data has revealed that acamprosate indirectly interacts with the spermidine-, glutamate-, and/or



dizocilpine-sensitive binding site of the NMDA receptor and functions as a partial coagonist or modulator of the receptor.^{33–35} As a partial coagonist, the functions of acamprosate appear to be dependent on endogenous polyamine activity such that in the presence of high concentrations, acamprosate functions as an antagonist but in low concentrations functions as an agonist. The modulating actions of acamprosate at the NMDA receptor has generally been accepted as the primary therapeutic mechanism.³⁶ In addition to NMDA receptor interaction, acamprosate has also been reported to bind to and display antagonistic activity at group I metabotropic glutamate receptors (mGluR1 and mGluR5), particularly mGluR5.^{35,37} However, later work revealed that acamprosate did not bind to mGluR5 receptors.³⁸ Finally, acamprosate also increases the release of the inhibitory neurotransmitter taurine in the nucleus accumbens,³⁹ further adding to its inhibitory effects on neurotransmission.

Currently, most theorists believe that decreased glutamatergic transmission through a combination of the aforementioned effects underlies the therapeutic action of acamprosate.⁴⁰ Furthermore, through modulation rather than complete antagonism of excitatory signaling, acamprosate is able to avoid the side effects commonly associated with other glutamate antagonists, therefore, increasing patient compliance. As mentioned previously, a primary mechanism of alcohol dependence in the brain is through the inhibition of NMDA receptors.⁴¹ With repeated excessive alcohol intake, the brain compensates with an upregulation, clustering, and increased sensitivity of NMDA receptors.⁴¹ Following the removal of alcohol, these changes produce a hyperexcitable state associated with withdrawal symptoms such as behavioral agitation, autonomic instability, anxiety, insomnia, delirium tremens, increased risk for epilepsy and seizures, excitotoxicity, and is also thought to contribute to alcohol craving and relapse.⁴² Thus, through a combination of its allosteric modulation at NMDA receptors and evoked release of taurine, acamprosate functions as a counterbalancing agent in the presence of high extracellular glutamate levels, restoring homeostasis to the glutamatergic synapse.⁴⁰

Metabolism, pharmacokinetics, and safety

Acamprosate is available in 333 mg enteric-coated tablets equivalent to 300 mg of acamprosate.

Typically, acamprosate is given orally three times daily in two 333 mg tablets. Acamprosate is absorbed through the paracellular route in the gastrointestinal tract, and plasma concentrations are detectable 48 hours after dosing. The terminal half-life is approximately 20 to 33 hours following oral administration. Acamprosate is not metabolized by liver enzymes and is excreted primarily by the kidneys.⁴³ Approximately 88% of the drug is eliminated in fecal matter, and 11%, in urine. Thus, acamprosate has extremely poor bioavailability in humans at 11% on an empty stomach with a 20%, but clinically insignificant, reduction when taken with food. Therefore, large doses are required to achieve therapeutic effects.

Since its availability in Europe starting in 1989, pharmacovigilance data from over 1.5 million patients has revealed no serious health risks from acamprosate use.⁴⁴ In addition, acamprosate does not possess an abuse potential.⁴⁵ The most common side effect reported in clinical studies was diarrhea, which was generally mild and occurred primarily only in the first 4 weeks of treatment.^{44,46} As reported in a Cochrane meta-analysis, other less common side effects include abdominal pain, constipation, nausea, vomiting, headache, pruritis, vertigo, and other minor side effects.⁴⁷ Since acamprosate is not metabolized in the liver, it appears safe for all individuals with varying degrees of hepatic insufficiency. Furthermore, acamprosate does not appear to pharmacokinetically interact with alcohol or other drugs such as imipramine, desipramine, disulfiram, diazepam, nordiazepam, or naltrexone when given concomitantly, nor does it appear to be contraindicated with any other medications metabolized by the liver.⁴³ Because acamprosate is excreted by the kidneys, however, it is contraindicated in people with renal impairment. For individuals with low to moderate renal impairments, the acamprosate dose is typically cut in half (one 333 mg tablet 3 times a day). Those with severe renal impairment should not be given acamprosate. Acamprosate is also contraindicated for individuals with previously reported acamprosate calcium sensitivity.^{43,46,48}

Efficacy

The most comprehensive review of the safety profile of acamprosate suggests that acamprosate is generally considered to have an excellent safety and tolerability profile.⁴⁶ Acamprosate has been approved for



the treatment of alcohol dependence in Europe since 1989, while the US Food and Drug Administration (FDA) has only recently approved the use of acamprosate for alcohol dependence in 2004.¹¹ The New Drug Application (NDA) for acamprosate submitted by Lipha SA (Lyon, France) to the FDA was initially denied in 2002; the FDA indicated that the data submitted did not adequately establish the safety and efficacy of acamprosate.⁴⁹ The revised NDA that was approved in 2004 included an additional trial as well as additional pharmacokinetic analyses.⁴⁸ Acamprosate is now widely marketed in the United States for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation. The approval of acamprosate by the FDA was largely based on three randomized, double-blind, placebo-controlled European clinical trials. The three studies evaluated the efficacy of acamprosate in combination with psychosocial interventions, and all three trials found higher abstinence rates and cumulative abstinence duration with acamprosate versus placebo.^{50–52} There have also been a host of other studies conducted on the safety, efficacy, and tolerability of acamprosate in alcohol dependence^{29,50–68} (see Table 1). According to several meta-analyses (Table 2), acamprosate is statistically superior to placebo in maintaining abstinence.^{47,69–74} A meta-analysis of 17 randomized, placebo-controlled, double-blind trials conducted by Mann and colleagues showed a statistically significant benefit of acamprosate over placebo in the primary outcome measure of continuous abstinence at 6 months.⁶⁹ Mason and Leherter also showed a positive effect of acamprosate in their meta-analysis of 22 randomized and controlled clinical trials.⁷⁴ They found that acamprosate was associated with significant improvements in the rate of abstinence as well as in days of cumulative abstinence. The three pivotal European studies used by the FDA for approval of acamprosate were later reanalyzed and revealed that the rate of complete abstinence, percent days abstinent, and time to first drink were significantly higher with acamprosate versus placebo therefore supporting the FDA decision.⁷¹

A recent Cochrane review of 24 randomized controlled trials, most of which were conducted in Europe, though two studies were conducted in the United States, evaluated the efficacy of acamprosate for the maintenance of abstinence in alcohol-dependent patients.⁴⁷

The efficacy measures of the review were divided into primary and secondary outcomes. The primary outcomes included (1) return to any drinking and (2) cumulative duration of abstinence during the study. The secondary outcomes included (1) return to heavy drinking (typically defined as five or more standard drinks per occasion), (2) liver enzyme levels of gamma-glutamyl transpeptidase, and (3) side effects. The review found that the use of acamprosate as an adjunct to psychosocial treatment strategies had a statistically significant effect on both of the primary outcomes compared with placebo; it reduced the risk of returning to any drinking after detoxification by 86% and increased the sum of days a patient remained abstinent during the study by 11%. In addition, patients who received acamprosate had a 9% lower risk of returning to any drinking 3 to 12 months after discontinuing treatment in comparison with the placebo group. Acamprosate was not shown to have a significant effect on the secondary outcomes of returning to heavy drinking or levels of gamma-glutamyl transpeptidase compared with placebo. The most recent meta-analysis comparing acamprosate to naltrexone found that acamprosate is more effective than naltrexone in maintaining abstinence, while naltrexone reduces heavy drinking and craving to a greater extent than acamprosate.⁶⁶ The Cochrane review did not find significant differences in primary or secondary outcomes between groups receiving a combination of acamprosate and naltrexone with groups receiving placebo or acamprosate alone. Based on these reviews, acamprosate appears to be an effective form of alcohol treatment for supporting continuous abstinence after detoxification in alcohol dependent patients.^{47,75}

There have also been several studies that have failed to show a significant benefit of acamprosate over placebo in maintaining abstinence.^{50,58,61,64–68,76,77} The National Institute on Alcohol Abuse and Alcoholism Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) trial evaluated the effects of acamprosate, naltrexone, and behavioral therapies (alone or in combination) on maintaining abstinence in alcohol-dependent patients.⁶⁴ Interestingly, all groups receiving active drug or placebo pills showed improvements in the percentage of abstinent days. However, a significant effect of acamprosate on drinking compared with

Table 1. Summary of clinical trials on acamprosate in alcohol dependence.

Study (citation)	Trial description	Acamprosate dose (sample size)	Cumulative abstinence duration (mean # of days)	Adherence/ compliance
Lhuintre et al ²⁹	3 month randomized, double-blind, placebo-controlled	ABW (n = 33) Placebo (n = 37)	20 did not relapse 12 did not relapse	NR
Ladewig et al ⁵³	6 month randomized, double-blind, placebo-controlled, multi-center (3)	ABW (n = 29) Placebo (n = 32)		84.8% 92.2%
Paille et al ⁵⁰	12 month randomized, double-blind, placebo-controlled, multi-center; 6 month post-treatment recovery period on placebo	1300 mg/day (n = 188) 2000 mg/day (n = 173) Placebo (n = 177)	198 ± 133 (n.s.) 223 ± 134* 173 ± 126	47.3% 35.6% 54.8%
Roussaux et al ⁵⁴	3 month randomized, double-blind, placebo-controlled	ABW (n = 63) Placebo (n = 64)		
Sass et al ⁵²	12 month randomized, double-blind, placebo-controlled, multi-center; 12 month follow-up	ABW (n = 136) Placebo (n = 136)	224.62 ± 136.61* 162.03 ± 132.19	97% 94%
Whitworth et al ⁵⁵	12 month randomized, double-blind, placebo-controlled, multi-center (5)	ABW (n = 224) Placebo (n = 224)	138.8 ± 137.5* 103.8 ± 119.0	NR
Barrias et al ⁵⁶	12 month randomized, double-blind, placebo-controlled, multi-center (9), 6 month follow-up	ABW (n = 150) Placebo (n = 152)		94.4% 92.8%
Geerlings et al ⁵⁷	6 month randomized, double-blind, placebo-controlled, multi-center (22), 6 month follow-up	ABW (n = 128) Placebo (n = 134)	61 ± 70* 43 ± 58	86% 88%
Pelc et al ⁵¹	3 month randomized, double-blind, parallel placebo-controlled, multi-center (11)	1332 mg/day (n = 63) 1998 mg/day (n = 63) Placebo (n = 62)	51.9 ± 4.69* 56.6 ± 4.25* 34.3 ± 4.29	More than 95% of pills issued were not returned
Chick et al ⁵⁸	6 month randomized, double-blind, placebo-controlled, multi-center (20), 4 week follow-up	1998 mg/day (n = 289) Placebo (n = 292)	77 (n.s.) 81	27% 28%
Tempesta et al ⁵⁹	6 month randomized, double-blind, placebo-controlled, multi-center (18), 3 month post-treatment	1998 mg/day (n = 164) Placebo (n = 166)	110 ± 77* 89 ± 77	76.9%–84.5% (no group specific values provided)
Gual and Leher ⁶⁰	6 month randomized, double-blind, placebo-controlled, multi-center (11)	1998 mg/day (n = 141) Placebo (n = 147)	93 ± 75* 74 ± 75	91.5% 91.4%
Namkoong et al ⁶¹	2 month randomized, double-blind, placebo-controlled, multi-center (12)	ABW (n = 72) Placebo (n = 70)	81.2 ± 23.7 (n.s.) 78.5 ± 27.8	80.5% 74.3%
Baltieri and De Andrade ⁶²	3 month randomized, double-blind, placebo-controlled, 3 month post-treatment; patients were encouraged to participate in Alcoholics Anonymous (AA)	1998 mg/day (n = 40) Placebo (n = 35)	19.45 ± 6.20* (no AA) 9.7 ± 10.19 (no AA)	NR
Kiritzé-Topor et al ⁶³	12 month randomized, open-label design; two groups: standard care alone or standard care with acamprosate	ABW (n = 211) Standard care (n = 211)	81%* 67%	NR
Anton et al ⁶⁴	4 month randomized, double-blind, placebo-controlled; 12 month follow-up	3000 mg/day (n = 605) Placebo (n = 616)	87.8 ± 28.3 (n.s.) 86.9 ± 28.4	84.2%
Mason et al ⁶⁵	6 month randomized, double-blind, placebo-controlled, multi-center (21), 8 week post-treatment	2000 mg/day (n = 253) 3000 mg/day (n = 82) Placebo (n = 257)	56.1% (unadjusted: n.s.) 60.7% (unadjusted: n.s.) 54.3%	88.9% 92.6%



Morley et al ⁶⁶	3 month randomized, double-blind, placebo-controlled, multi-center (3)	1998 mg/day (n = 55) Placebo (n = 61)	66.3 ± 25.2 (n.s.) 56.7 ± 31.4	Approx. 80% of those that completed the study were 80% compliant
Berger et al ⁶⁷	3 month randomized, double-blind, placebo-controlled, multi-center (2)	1998 mg/day (n = 51) Placebo (n = 49)	Approx. 55% (n.s.) Approx. 54%	NR
Tolliver et al ⁶⁸	2 month randomized, double-blind, placebo-controlled	1998 mg/day (n = 16) Placebo (n = 17)	79.6 ± 29.1 (n.s.) 73.3 ± 29.1	NR

Notes: Cumulative abstinence duration = cumulative number of abstinent days during the study period; * $P < 0.05$ vs. placebo; n.s.: $P > 0.05$ vs. placebo.

Abbreviations: A, Acamprostate; ABW, Adjusted for body weight; NR, Not reported; P, Placebo.

Table 2. Summary of findings from recent meta-analyses.

Study (citation)	Number of trials comparing acamprostate to placebo	Total number of participants	Increase in CAD in acamprostate treated patients	Increase in continuous AR in acamprostate treated patients
Kranzler and Gage ⁷¹	Reanalysis of 3 European double-blind RCTs used by FDA	998	Yes	Yes
Dranitsaris et al ⁷²	10 RCTs for CAD 16 RCTs for AR	NR	Yes*	Yes*
Koeter et al ⁷³	11 double-blind RCTs	2305	No	No
Rosner et al ⁷⁴	24 double-blind RCTs	6915	Yes	Yes (3–12 months post-treatment)
Mason and Leher ⁷⁴	22 double-blind RCTs	6111	Yes (did not differ between men and women)	Yes (did not differ between men and women)

Notes: Cumulative abstinence duration = cumulative number of abstinent days during the study period. *COMBINE trial results contributed a weight of less than 15% to the final pooled statistical outcomes.

Abbreviations: AR, abstinence rate; CAD, cumulative abstinence duration; NR, not reported; RCT, randomized controlled trial.



placebo was not found when acamprosate was administered alone or in combination with naltrexone and/or behavioral therapies. The reason the COMBINE study failed to support the significant effects of acamprosate found in the European studies may be attributed to a difference in study design. The COMBINE trial only required 4 days of abstinence prior to randomization which was conducted on an outpatient basis, while positive European studies required complete detoxification which was typically completed on an inpatient basis.⁶⁴ The United States study conducted by Kampman and colleagues compared the efficacy of acamprosate treatment started during detoxification with acamprosate started after complete detoxification. They did not find significant differences between acamprosate and placebo when acamprosate treatment was started prior to complete detoxification.⁷⁶ A recent meta-analysis by Maisel and colleagues confirmed that the efficacy of acamprosate is increased when detoxification is required before medication administration.⁶⁶ The “placebo effect” observed in the COMBINE study may have made it difficult to detect any additional effects of acamprosate, thus also explaining the difference in findings from the European trials.¹¹ Finally, Dranitsaris and colleagues included the results from the COMBINE trial in a meta-analysis to evaluate the impact of the negative findings of the study.⁷² The results revealed that acamprosate was superior to placebo in both cumulative abstinence days and in rates of abstinence (in contrast to the COMBINE study), and the authors concluded that acamprosate is an effective agent in the treatment of alcohol dependence. Given that the literature has revealed mixed results regarding acamprosate efficacy, recent research has begun to assess the possibility that acamprosate effectiveness is linked to individual or genetic differences. Several investigators have suggested that there are different types of alcohol craving based on different neurotransmitter systems, and acamprosate or naltrexone may specifically target a certain type.^{31,78,79} The dopaminergic/opioidergic positive reinforcement system is associated with reward drinking (ie, drinking to induce a feeling of euphoria), while the glutamatergic/GABAergic negative reinforcement system is associated with relief drinking (ie, drinking to relieve stress or anxiety). Therefore, naltrexone (an opioid receptor antagonist) is hypothesized to benefit patients characterized as

“reward drinkers,” whereas acamprosate is thought to be more effective in treating “relief drinkers.”^{31,80} A recent pharmacogenomic study by Ooteman and colleagues investigated whether genetic indicators for relief and reward drinking could predict the efficacy of acamprosate or naltrexone using cue-induced craving and physiological cue reactivity as outcome measures.⁸⁰ The study found medication benefits to be dependent upon polymorphisms in four out of the seven genes tested. Significant effects were found for the DRD2 (dopamine receptor), GABRA6 (GABA_A receptor subunit α 6), and GABRB2 (GABA_A receptor subunit β 2) genotypes, and a trend was found for the OPRM1 (μ opioid receptor) genotype. While these studies reveal potential new insights into acamprosate efficacy, the notion that the effectiveness of acamprosate is mediated by genetic and individual factors is still in its infancy, and more research is required before definitive conclusions can be made.

Patient preference

A patient’s preference for a therapeutic strategy is an important aspect of successful treatment, as compliance greatly affects medication efficacy. A meta-analysis by Koeter and colleagues evaluated the influence of patient compliance on abstinence duration in 11 randomized controlled trials of acamprosate versus placebo.⁷³ They found that early compliance, defined as compliance between baseline and the first visit after baseline, was associated with abstinence at the start of treatment as well as motivation to become fully abstinent. Late compliance, defined as compliance between the first post-baseline visit and the end of treatment, in combination with treatment condition (acamprosate or placebo) and motivation for complete abstinence, was shown to predict abstinence duration. Therefore, successful treatment with acamprosate appears to rely on medication compliance and motivation for complete abstinence.⁷³ A meta-analysis of 33 randomized controlled trials that compared naltrexone or acamprosate with placebo showed that overall compliance was low for both medications with only half of patients completing treatment.⁷⁰ Motivation to start treatment as well as compliance to treatment has been found to be significantly lower in depressed as compared with non-depressed patients.⁸¹ Therapeutic decisions should be based, at least in part, on the ultimate goal of the



patient given that either acamprosate or naltrexone is more appropriate for achieving complete abstinence or moderate/nonproblem drinking, respectively.^{65,82}

As reviewed above, both acamprosate and naltrexone are associated with various side effects that may serve as barriers to medication compliance. The Cochrane review found that acamprosate was associated with a greater risk of diarrhea as a side effect than naltrexone; however, naltrexone caused more nausea, vomiting, and somnolence.⁴⁷ In addition, patients receiving acamprosate had a 24% lower risk of dropping out of a study early due to adverse events compared with patients receiving naltrexone.⁴⁷ Mason and Leher found that acamprosate was associated with significantly higher rates of treatment completion and medication compliance than placebo, and they did not find significant differences between acamprosate and placebo in premature withdrawals from treatment due to adverse events.⁷⁴ Therefore, the side effects of acamprosate do not seem to be a significant factor leading to the high rate of noncompliance. Instead, noncompliance observed in acamprosate groups may be due to the requirement of three doses per day or the presence of comorbid psychiatric diseases.⁷⁰

Place in therapy

The general consensus among the trials and reviews conducted to date is that acamprosate is a safe and effective treatment, at least in subsets of individuals, for alcohol dependence. Certain subpopulations of alcohol dependent patients may benefit from treatment more than others, and this differential effect may be partially explained by genetics.^{31,75} Depending on patient genotype, acamprosate and naltrexone have been shown to outperform one another, suggesting that it may be useful to genetically match certain patients to specific treatments in clinical practice in order to increase treatment outcomes.⁸⁰ In addition, side effect profiles are important contributors to medication effectiveness. Acamprosate side effects are relatively mild and result in fewer withdrawals from treatment compared with naltrexone.⁷⁵ Despite these positive findings, the results from clinical trials do not fully predict the efficacy of acamprosate in clinical practice. Medication compliance varies greatly in different care settings and is not likely to be as high as compliance observed in controlled clinical trials. As noted in the previous section,

compliance is an important factor of treatment success. To observe therapeutic benefits in clinical practice that are similar to those seen in clinical trials, adjunctive psychosocial and cognitive-behavioral interventions should be considered. Finally, the cost-effectiveness of using acamprosate for the treatment for alcohol dependence has been demonstrated in several European studies which claim the superiority of using acamprosate over rehabilitation strategies that do not involve pharmacotherapy.^{83–85} The COMBINE trial found that the combination of naltrexone with acamprosate as well as naltrexone monotherapy were cost-effective strategies in general and from the patient's perspective (including total costs, effectiveness, and patient time costs).⁶⁴

Conclusions

The data reviewed here on the safety, tolerability, efficacy, side effect profile, cost-effectiveness, and patient preference of acamprosate suggest that this medication has numerous favorable properties as a pharmacological adjunct to standard approaches to treating alcoholism. However, data on the efficacy of acamprosate in reducing alcohol craving and relapse and in promoting abstinence is mixed. This may be attributable to intertrial differences in outcome measures, medication compliance issues, and suboptimal pharmacokinetic properties including low oral bioavailability and multiple within-day dosings. Nonetheless, research should continue to identify indicators and characteristics of specific patient populations who are likely to exhibit positive clinical outcomes with the use of acamprosate.

One such area of research that would potentially improve the therapeutic efficacy of acamprosate is the identification of its precise mechanism of action. While the general consensus to date is that acamprosate is an NMDA receptor modulator and restores alcohol dependence-induced imbalances between excitatory and inhibitory neurotransmission, its precise molecular target(s) remain elusive. In general, receptor binding and cell-based receptor screening assays have not provided substantial insight into the substrate(s) at which acamprosate acts and have often been hampered by the presence of high concentrations of calcium salts. An alternative approach would be to assess the effects of therapeutic doses of acamprosate on gene expression using microarray or next-generation sequences



methodologies in laboratory animals with a history of alcohol dependence. Additional molecular studies could also assess epigenetic modifications that occur in response to acamprosate. To our knowledge, such molecular genetic studies have not yet been conducted. The identification of specific acamprosate-induced genetic or epigenetic changes might not only identify one or more molecular targets of acamprosate, which would allow for the development of homotaurine analogues with improved pharmacokinetic properties, but may also lead to the identification of genetic polymorphisms that predict individual clinical responsiveness to acamprosate.

Author Contributions

Wrote the first draft of the manuscript: SLY, LRW. Contributed to the writing of the manuscript: SLY, LRW, MFO. Agree with manuscript results and conclusions: SLY, LRW, MFO. Jointly developed the structure and arguments for the paper: SLY, LRW, MFO. Made critical revisions and approved final version: SLY, LRW, MFO. All authors reviewed and approved of the final manuscript.

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Competing Interests

Authors disclose no potential conflicts of interest.

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