BJCP British Journal of Clinical Pharmacology

DOI:10.1111/bcp.12070

# The clinical pharmacology of acamprosate

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**Keywords**
acamprosate, alcohol dependence, pharmacology

**Received**
3 August 2012

**Accepted**
20 November 2012

**Accepted Article Published Online**
25 December 2012

Acamprosate is one of the few medications licensed for prevention of relapse in alcohol dependence, and over time it has proved to be significantly, if moderately, effective, safe and tolerable. Its use is now being extended into other addictions and neurodevelopmental disorders. The mechanism of action of acamprosate has been less clear, but in the decade or more that has elapsed since its licensing, a body of translational evidence has accumulated, in which preclinical findings are replicated in clinical populations. Acamprosate modulates *N*-methyl-D-aspartic acid receptor transmission and may have indirect effects on γ-aminobutyric acid type A receptor transmission. It is known to decrease brain glutamate and increase β-endorphins in rodents and man. Acamprosate diminishes reinstatement in ethanolized rodents and promotes abstinence in humans. Although acamprosate has been called an anticraving drug, its subjective effects are subtle and relate to diminished arousal, anxiety and insomnia, which parallel preclinical findings of decreased withdrawal symptoms in animals treated with acamprosate. Further understanding of the pharmacology of acamprosate will allow appropriate targeting of therapy in individuals with alcohol dependence and extension of its use to other addictions.

## Introduction

Acamprosate can provide effective pharmacotherapy for prevention of relapse in alcohol dependence. Although this has been known for almost two decades and has been confirmed in several meta-analyses, evidence regarding its mechanism of action has accrued more slowly. In 1995, John Littleton proposed that acamprosate prevents relapse in alcohol dependence by decreasing subclinical withdrawal symptoms that may cause an individual to crave alcohol for relief, i.e. 'negative reinforcement' [1]. Its effectiveness in reducing measurable alcohol craving has been less impressive. Here, we summarize the evidence and consider to what extent it is consistent with acamprosate suppressing craving related to negative reinforcement.

## Acamprosate pharmacokinetics

Acamprosate is formulated as a dimer of acetylhomotaurine linked by a calcium salt, adjustments made to facilitate absorption. Nonetheless, oral bioavailability remains low, at around 11% [2]. In fact, the absorption of acamprosate is so slow that it acts as though it were a modified-release medication [3], with a time at the maximal concentration of 6.3 h in enteric-coated form [2]. It has a half-life of around 32 h [2], with complete elimination occurring only 4 days after cessation of therapy [4]. The steady-state plasma concentration, reached by around day 5 of treatment, varies from around 1.5 to 5 μM according to research study [2, 4–6]. Acamprosate pharmacokinetics is not affected by alcohol, benzodiazepines or disulfiram [2], but its plasma levels are increased by naltrexone [2, 5] and decreased by co-administration with food [2].

Acamprosate is not protein bound, and it is completely dissociated in plasma. It is not metabolized and is excreted unchanged in the urine. Predictably, renal impairment is related to increased plasma concentrations of acamprosate [2]; for this reason, acamprosate is contraindicated in severe renal impairment and dose reduction is advised in mild renal impairment. Plasma levels in Child's A and B liver disease are within normal limits [2]. Furthermore, there has been no increase in markers of liver dysfunction in clinical trials of acamprosate, and no increase in adverse events

was found in those participants with more severely deranged liver function tests at baseline [7]. Indeed, liver function tests usually improve with decreased drinking associated with acamprosate therapy.

## Receptor pharmacology

There have been few studies of the receptor binding properties of acamprosate. Those that exist concern the *N*-methyl-D-aspartic acid (NMDA) receptor. Acamprosate has a very low affinity for the dizocilpine and spermidine sites on the NMDA receptor, >1 mM and 600 μM, respectively [8, 9]. It has been suggested that any inhibition of binding occurs via allosteric interaction rather than direct competition [9, 10].

## Mechanism of action

### *Effect on receptors*

More information about the action of acamprosate at receptors has been elucidated through electrophysiological studies. Acamprosate was initially thought to modulate γ-aminobutyric acid type A ($GABA_A$) receptors [11], but *in vitro* evidence is consistent with an indirect effect. Acamprosate had no effect on $GABA_A$-mediated inhibitory postsynaptic currents in the rat nuclear accumbens (300 μM) [12], on rat cortical neurons (up to 1 mM) [13] or on recombinant human $GABA_A$ receptors (up to 100 μM) [14]. However, decreases in burst amplitude and frequency induced by acamprosate (100–400 μM) were partly reversed by bicuculline [15], and increased GABA binding in the hippocampus and thalamus has been observed after administration of acamprosate [16]. Acamprosate may influence $GABA_A$ transmission via inhibition of presynaptic γ-aminobutyric acid type B ($GABA_B$) receptors [12].

Likewise, the effect of acamprosate on NMDA receptors may be indirect. Although early electrophysiology studies showed an increase in NMDA excitation in the nucleus accumbens and hippocampus following acamprosate treatment [12, 17], this is likely to have resulted from the calcium rather than acamprosate itself [18]. Antagonism of NMDA receptors has been reported subsequently in the cortex, hippocampus and midbrain [19–21]. The effect of acamprosate on NMDA receptors may be mediated by interaction at the polyamine site. It reversed spermidine-related potentiation in a subset of striatal neurons only [19] and prevented polyamine-related neurotoxicity in hippocampal slice culture at a clinically relevant concentration (200 nM) [18]. Its effect on NMDA receptors may also be influenced by alcohol, because al Qatari and colleagues reported a biphasic influence on dizopilcine binding to the NMDA pore, with potentiation at low doses and inhibition at high doses in naïve rats but only inhibition in rats subjected to chronic inhalation of ethanol [8].

Acamprosate may also modulate the NMDA receptor response via metabotropic glutamate receptor subtype 5 (mGluR5) antagonism. Acamprosate competes with 1-aminocyclopentane-*trans*-1,3-dicarboxylic acid (*trans*-ACPD), a type I metabotropic glutamate receptor (mGluR) antagonist, and prevents *trans*-ACPD-related neurotoxicity [10]. The attenuation of the effects and withdrawal symptoms of alcohol by acamprosate was similar to that of methylphenylethynylpyridine, a known mGluR5 antagonist [22]. It does not attenuate alcohol intoxication or withdrawal in mGluR5 knock-out mice, suggesting that this receptor is essential for these actions [22]. Likewise, acamprosate may act to increase dopamine in the nucleus accumbens via an indirect pathway involving both mGluR5 and glycine receptors [23]. Preliminary results indicate that acamprosate may be of therapeutic value in fragile X syndrome, which is characterized by type 1 mGluR overactivity [24].

### *Effects on neurotransmitter concentrations*

Acamprosate (400 mg $kg^{-1}$) prevents the increase in glutamate in the nucleus accumbens of chronically alcoholized rats during alcohol withdrawal [25] and the escalation in the hyperglutamatergic state that occurs with repeated withdrawal episodes [26]. Acamprosate has been associated with an increase in β-endorphin in rats, which is more marked in alcohol-preferring rats [27].

### *Clinical studies: effect on neurotransmitters and hormones*

Preclinical effects on neurotransmitters have been replicated in man. In recently abstinent human alcohol-dependent patients, acamprosate treatment was associated with a decrease in frontal lobe glutamate as measured by magnetic resonance spectroscopy, whereas an increase was seen in a comparable placebo group [28]. Likewise, one study reported that acamprosate was associated with higher plasma β-endorphin in those with higher than median alcohol consumption prior to detoxification [29]. However, the increase in β-endorphin following acamprosate therapy has not been replicated in an independent sample, which may reflect the shorter treatment time or that the sample was not separated into different groups according to consumption [30].

The effect of acamprosate on the hypothalamo-pituitary–adrenal axis is uncertain. Although a trial of acamprosate therapy resulted in persistently raised plasma adrenocorticotrophic hormone (ACTH) and cortisol levels, whereas these normalized in the placebo group [29], other studies do not support an effect of acamprosate on the hypothalamo-pituitary–adrenal axis. A single intravenous dose had no effect on pituitary hormone secretion [31]. Treatment with acamprosate for 3 weeks resulted in no change in plasma cortisol relative to placebo [30]. There was no difference in ACTH or cortisol response to a corticotrophin-releasing hormone stimulation test in

alcohol-dependent patients after 1 week of acamprosate with respect to placebo [32]. It may be that the effect is delayed, because the single positive study measured differences in hormones at 4, 8 and 12 weeks.

## Relevance of the pharmacology of acamprosate to alcohol dependence

In summary, acamprosate has been found to modulate NMDA receptor transmission and $GABA_A$ transmission, to decrease glutamate during alcohol withdrawal, to increase β-endorphin in those with very high alcohol intake and, perhaps, to modulate the hypothalamo-pituitary–adrenal axis. The relevance of the actions of acamprosate on glutamate, NMDA and $GABA_A$ transmission to alcohol dependence is that they would compensate for the neurobiological derangement produced by alcohol withdrawal. Acute alcohol potentiates the effect of GABA on $GABA_A$ receptors and decreases NMDA, AMPA and kainate receptor function (for a review, see [33]). With chronic alcohol intake, $GABA_A$ receptors are downregulated and rendered less responsive by expression of different subtypes [34], whereas NMDA receptors are upregulated [35]. These compensatory changes produce a hyperglutamatergic, potentially excitotoxic state during alcohol withdrawal [26]. The pharmacological profile of acamprosate is therefore consistent with a medication that could target subclinical withdrawal symptoms and, indeed, even offer neuroprotection during withdrawal.

## Behavioural effects in animals

Consistent with its pharmacological actions, acamprosate decreases signs of alcohol withdrawal, such as hypermobility [36–38] and anxiety-like behaviour [39, 40], at doses from 50 mg $kg^{-1}$ $day^{-1}$ in chronically ethanolized rodents. Importantly, acamprosate reduces more severe withdrawal complications, such as handling-induced seizures in mice, with a similar reduction at a 100 mg $kg^{-1}$ dose to that seen with a diazepam dose of 0.25 mg $kg^{-1}$ [41]. Some physical consequences of withdrawal, for example, hypothermia, are not affected [37].

Several studies have found that acamprosate decreased alcohol drinking or cued responding after a period of chronic ethanolization, when alcohol was presented immediately or after up to a few days of deprivation [36, 42–44]. Interestingly, this effect was not seen when deprivation lasted 3 weeks [45]. Acamprosate also does not have as pronounced an effect in alcohol-naïve animals [42, 44, 45]. These findings support Littleton's hypothesis, in that they suggest that the effects of acamprosate may be most prominent close to withdrawal.

Acamprosate does not have abuse potential. Animal experiments suggest that there is little liability for causing self-administration in birds, rodents or primates and there is no generalizability from alcohol [46, 47]. In rodents, the direct NMDA antagonist dizopilcine completely substituted for alcohol in a cue-related protocol, but acamprosate did not [47].

## Clinical effectiveness of acamprosate

Acamprosate has been demonstrated to be effective in preventing relapse in studies conducted worldwide. Several good-quality systematic reviews and meta-analyses have summarized existing clinical trials, including those by Rosner *et al*. (Cochrane) [48], National Institute for Clinical Excellence (NICE) CG115 [49], Slattery *et al*. (Health Technology Board of Scotland) [50], Berglund *et al*. (Swedish Board) [51] and Bouza *et al*. (Spanish Agency for Health Technology Assessment) [52], in addition to those by Mann *et al*. [53], Kranzler and Van Kirk [54], Mason and Ownby [55], Rosner *et al*. [56] and Mason and Heyser [57]. Acamprosate increased the chance of abstinence after detoxification by about 15%; Rosner *et al*. [48] report a relative risk (RR) of 0.86 [95% confidence interval (CI) 0.81–0.91] and NICE CG115 [49] reports RR = 0.83 (95% CI 0.77–0.88), a moderate effect. The 'number needed to treat' to result in one more patient becoming abstinent as a result was calculated as 9–11 (e.g. [48, 50]). The smaller effect size in later reviews is a consequence of recent studies done in America and Australia where acamprosate was not superior to placebo [58–60]. This may reflect the severity of dependence seen in clinical populations in Europe and elsewhere relative to American samples, and some authors have suggested that patients with more severe dependence may benefit more from acamprosate [61]. However, recent meta-analyses [49, 62] found no relationship between severity of dependence and response to acamprosate.

In addition to its effect on abstinence, some studies and reviews have found that acamprosate reduces heavy drinking in those patients who do relapse [49, 63]. Effects on symptoms associated with alcohol withdrawal have also been reported. Acamprosate has been shown to be effective in decreasing sleep disturbance in withdrawal [64] and during abstinence up to 6 months [65]. It reduced arousal during withdrawal as measured by magnetoencephalography [66]. A slight anxiolytic effect in abstinent alcohol-dependent patients has been reported [67], and it has been found that acamprosate treatment may offset the poorer prognosis conferred by higher anxiety at baseline [68]. Preliminary results of acamprosate adjuvant therapy for treatment of anxiety disorders are promising [69]. Although acamprosate treatment is associated with an

increased recovery from depression, this is mediated via the abstinence effect [70].

In observations that replicated preclinical data, acamprosate was less effective when the start of treatment was delayed long after detoxification. A secondary analysis of the COMBINE trial showed that a longer period of pretreatment abstinence predicted a poorer response [71]. The failure of another study to demonstrate efficacy was also attributed to the greater mean duration of abstinence [67]. Although preliminary data have suggested that some drinking outcomes may worsen if acamprosate is started during detoxification, this is still recommended based on the other trial evidence, as well as preclinical evidence of its neuroprotective effect [72]. Certainly, less severe withdrawal symptoms have been reported with acamprosate therapy [60].

The benefits of acamprosate in maintaining abstinence have been shown to persist for 3–12 months after stopping treatment, with a 9% lower risk to return to any drinking in patients who received acamprosate (RR 0.91; 95% CI 0.87–0.96) and a 9% higher continuous abstinence duration (mean difference 8.92; 95% CI 5.08–12.77) [48], compared with those who received placebo. The number needed to treat for prevention of drinking beyond cessation of therapy to post-treatment evaluation was 12.5 (95% CI 9.09–25.00).

There are few predictors of treatment efficacy that might enable us to target acamprosate treatment to patients who might benefit most from it, apart from a goal of abstinence [59] and recent detoxification. A secondary analysis of seven European trials reported that negative family history, late age of onset, anxiety symptoms, severe craving and female gender did not predict response to acamprosate [62]. Psychiatric comorbidity should not limit its use, because it does not worsen symptoms in schizophrenia [73], bipolar affective disorder [74] and depression [70]. However, effectiveness has not been demonstrated in schizophrenia and bipolar affective disorder [70, 74].

The usual dose of acamprosate prescribed is 1998 g daily for those over 60 kg and 1332 g for those under 60 kg. A higher dose (3 g $day^{-1}$) has been reported to be more efficacious [75]. However, a small study compared the tolerability of a 3 g daily dose with a 2 g dose and found that participants reported more nervousness at the higher dose [6]. In general, acamprosate is a well-tolerated drug, with self-limiting diarrhoea being the main side-effect [7].

Acamprosate is frequently described as an 'anticraving' drug. Craving is complex and variously conceptualized [76]. Its use clinically may denote a variety of processes, including withdrawal symptoms themselves [77], but also 'liking, wanting, urges, desires, need, intention or compulsion' ([76], p. 35). In fact, so problematic was the definition and operationalization of craving that the World Health Organization suggested it should not be used in clinical research into alcohol dependence [78]. It is therefore perhaps not surprising that studies of the effect of acamprosate on craving have not been consistent.

Three clinical trials of acamprosate found a decrease in craving in the acamprosate group relative to placebo at time points within 1 month of withdrawal [30, 67] and at 3 months [79]. However, the majority of trials in which craving was measured have found no difference relative to placebo [58–60, 80–85].

Experimental protocols that induce craving have yielded mixed results. treatment with acamprosate for 3 weeks decreased craving after a priming dose of alcohol but not at baseline [4]. Pharmacologically induced craving with yohimbine and meta-chlorophenylpiperazine challenge robustly induced craving, but craving did not diminish in response to acamprosate [86]. Interestingly, head-to-head comparison of naltrexone and acamprosate in reducing cue-induced craving found that naltrexone reduced subjective craving more than acamprosate [87]. In clinical trials where acamprosate and naltrexone were compared with each other and with placebo, naltrexone was reported to reduce craving [58, 82] and to reduce drinking when craving was self-rated as high [85], but acamprosate was not. It may be that the questionnaires or visual analog scales do not detect or differentiate that part of craving relating to subclinical withdrawal/negative reinforcement. This is supported by the finding that acamprosate reduced tachycardia associated with craving rather than a subjective measure of craving itself [87].

An alternative conceptualization of the effectiveness of acamprosate in alcohol dependence is that it is substitution therapy, defined as 'a medication which has one or more of the pharmacological effects of the drug of interest' [88]. The receptor pharmacology of acamprosate raises this possibility, as does the evidence described above that it ameliorates some symptoms of withdrawal. However, implicit in the concept of substitution is that the subjective effects of the medication are similar to the drug replaced and that the patient experiences dependence on the medication. Acamprosate does not fit this profile; it does not produce alcohol-like intoxication [89], and there are no cases reported of dose escalation and dependence [88].

## Acamprosate in other addictions

Following the success of acamprosate in preventing relapse in alcohol dependence, there have been investigations into its utility in treatment of other drug dependencies. Although it reduced the aversive effects of opiate withdrawal in rodents [90], it has not been shown to block opiate reinstatement [91] or sensitization [92]. A single study has reported that acamprosate blocked cue-induced reinstatement of responding to acquire nicotine in rats [93]. Despite early promise that high (>100 mg $kg^{-1}$), but not lower (30 mg $kg^{-1}$) doses, of acamprosate

diminished cue- and cocaine-induced reinstatement of conditioned place preference [91, 94, 95], a single randomized controlled trial in cocaine-dependent patients found no significant effect on cocaine use, craving or withdrawal symptoms [96].

Clinical studies of acamprosate have been carried out in pathological gambling and binge-eating disorder. The rationale for the use of acamprosate in pathological gambling was based on early theories that acamprosate acts via $GABA_A$ receptors, inhibiting dopaminergic release in response to gambling and thus the experience of reward [97]. A small open-label trial ($n = 26$) found that the number of gambling episodes and obsessional thinking about gambling decreased [98]. However, a randomized, single-blind trial of acamprosate *vs*. baclofen ($n = 17$) found that all participants relapsed within 6 months, and there were no changes from baseline in any subjective measures [97].

Antagonism of the NMDA receptor by acamprosate was suggested to be of value in binge eating, because NMDA receptors in the hypothalamus regulate appetite [99], and other NMDA antagonists, such as memantine, have proved effective in two open-label trials [100, 101]. Furthermore, acamprosate treatment is associated with decreased food craving in alcohol-dependent patients [102]. Treatment of binge-eating disorder with acamprosate has been attempted in one, small ($n = 20$ per group) placebo-controlled study [103]. Although the primary outcome of reduction in bingeing episodes was not different between groups, there was significant decrease in craving as measured by the Yale Brown Obsessive Compulsive Score – Binge Eating and slight weight loss in the active group *vs*. slight weight gain in the placebo group.

## Conclusions

Although acamprosate was initially thought to act at $GABA_A$ receptors, the bulk of the literature has subsequently focused on glutamate and NMDA receptors. More is now known about the mechanism by which acamprosate modulates NMDA transmission. Further investigation of other mechanisms of action, for example via glycine and $GABA_B$ receptors, is warranted.

The effect of acamprosate on reinstatement of drinking after a period of abstinence in dependent animals has been demonstrated in clinical trials, which have shown increased abstinence and decreased level of drinking after relapse. In rodent studies, this effect is maximal close to withdrawal, and in human studies initiation close to withdrawal provides greater benefit. Acamprosate may also be of benefit as neuroprotection in withdrawal; preclinical and clinical evidence has demonstrated that it decreased the hyperglutamatergic state associated with withdrawal. It has been shown to decrease the behavioural manifestations of withdrawal in rodents and man. Clinical trials suggest that symptoms that are associated with prolonged or subclinical withdrawal, such as anxiety and insomnia, are improved by acamprosate. Taken together, the evidence is consistent with John Littleton's hypothesis that acamprosate targets negative reinforcement craving produced by withdrawal. Unfortunately, most measures of craving in clinical samples do not assess this directly, which may explain why acamprosate has been associated with decreased craving in only a minority of studies in clinical populations. Use of camprosate in other addictive disorders has shown mixed outcomes. Understanding its mechanism of action more fully will allow a more targeted approach to its extension to other uses.

## Competing Interests

The authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

*N.J.K. is supported by a Wellcome Trust GSK Translational Medicine Training Fellowship.*

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