Treatment of Alcohol-Dependent Outpatients With Acamprosate: A Clinical Review

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Acamprosate (calcium acetyl-homotaurine) is a synthetic compound whose chemical structure resembles that of homotaurine, a naturally occurring amino acid. Acamprosate acts centrally and appears to restore the normal activity of glutaminergic neurons, which become hyperexcited as a result of chronic alcohol exposure. Although not yet approved for use in the United States, acamprosate has been available by prescription in France since 1989 and is now available in many other countries throughout the world. This article reviews data from all published double-blind, placebo-controlled clinical trials of acamprosate among alcohol-dependent outpatients. Overall, patients treated with acamprosate exhibited a significantly greater rate of treatment completion, time to first drink, abstinence rate, and/or cumulative abstinence duration than patients treated with placebo. The drug's reliable effect on prolonging abstinence, in conjunction with an excellent safety profile, suggests that acamprosate may be useful for a broad range of patients with alcohol dependence.

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Alcohol dependence can profoundly compromise the biological, psychological, and social functioning of affected individuals. Psychosocial interventions have been the mainstay of traditional efforts to moderate alcohol dependence, but often fail to prevent drinking relapse. Recent advances in our understanding of the neurobiology of alcohol dependence have led to the development of several drugs that can improve treatment outcomes. One such drug is acamprosate (calcium acetyl-homotaurine), a synthetic molecule that resembles a naturally occurring amino acid neuromediator, homotaurine.

While the precise mechanism of action of acamprosate is unknown, the compound has been shown to restore normal *N*-methyl-D-aspartate (NMDA) receptor activity in neuronal systems.[1–5] Chronic alcohol consumption increases the activity of the glutamate system[6] (as reviewed elsewhere in this supplement), which remains hyperexcitable even after alcohol intake ceases, resulting in withdrawal symptoms and a neuronal readaptation process that may require a year or more of abstinence to resolve.[7] Thus, acamprosate appears to interfere with neurobiological processes that are involved in maintaining alcohol dependence.

Acamprosate was approved for use in France in 1989, and more recently, in most European and Latin American countries, as well as Australia, Hong Kong, and South Africa. More than 1.4 million alcohol-dependent patients have been treated with the drug to date. The U.S. Food and Drug Administration has granted acamprosate Investigational New Drug status, and its efficacy recently has been evaluated in a large-scale double-blind, placebo-controlled, multicenter trial in alcohol-dependent patients in the United States (for a review of the methodology of this study, see Mason and Ownby[8]).

The goal of this article is to familiarize the U.S. clinician with available data on the safety and efficacy of acamprosate for the treatment of alcohol dependence. Reviewed below are the results of all published, double-blind, placebo-controlled clinical trials of acamprosate among alcohol-dependent outpatients.

OVERVIEW OF CLINICAL TRIALS

The efficacy of acamprosate has been evaluated in 16 controlled clinical trials conducted in 11 European countries and involving more than 4500 alcohol-dependent outpatients. Fifteen of these studies have been published and are reviewed below (Table 1 shows trial summaries). Trials are grouped according to duration, with studies involving less than 6 months of treatment designated as short-term, studies involving 6 months of treatment designated as such, and studies involving a year or more of

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treatment designated as long-term. Clinical research methodology is also discussed.

Overview of Research Methodology

Design. All of the studies discussed in this section were double-blind, placebo-controlled, parallel-group comparisons with randomized assignment of patients to treatments.

Admission criteria. Many of the trials specified a baseline γ-glutamyltransferase (GGT) level of at least twice the upper limit of normal (ULN). In addition, several studies specified an above-normal mean corpuscular volume (MCV) among inclusion criteria. Exclusion criteria included serious medical disorders, pregnancy, and use of medication likely to influence study outcomes. In all but one trial,[20] patients were required to be abstinent for a minimum of 5 days prior to random assignment and were admitted to the study immediately upon completion of alcohol detoxification, which was typically on an inpatient basis.

Dosing. In earlier studies, dosing of acamprosate was usually adjusted by body weight in a standard manner: patients weighing 132 lb or more (≥ 60 kg) received 1998 mg/day or identical placebo, and those weighing less than 132 lb received 1332 mg/day (Table 1).[11–18,23] More recent studies used a fixed dose of 1998 mg/day.[19,20]

Research assessments. Assessments were minimally performed at days 0, 30, 90, 180, 270, and 360, depending on study duration (see Table 1), as well as at 3-month intervals during posttreatment follow-up, during which no study medication was administered. The duration of posttreatment follow-up ranged from 0 to 12 months (see Table 1).

Outcomes. For most of the clinical studies, outcome parameters included rate of study completion, rate of abstinence for the interval preceding each study visit, rate of patients' completing the trial without having a single drink (rate of total abstinence), time to any relapse of drinking, and the cumulative abstinence duration (CAD). In earlier studies, the CAD was defined as the total number of days of complete abstinence; in later studies, it was defined as the percentage of abstinent days during the total possible duration of exposure to double-blind treatment. Drinking outcomes were typically determined by a combination of self-report; clinical interview; measures of alcohol in blood, urine, or breath; and biological marker data. Some studies also employed a collateral informant to corroborate outcomes.

Definition of nonabstinence. Patients who took a single drink, missed visits, or had a self-report that was discrepant with biological marker data or collateral report were categorized as nonabstinent for the entire corresponding rating interval.

Statistical analyses. Primary endpoint analyses were conducted under an intention-to-treat statistical plan that included any randomly assigned patient who had taken at least one dose of study medication and who supplied data on at least one key efficacy variable.

Compliance. Treatment compliance was determined by counting returned pills at each study visit.

Adverse drug events. Treatment-related adverse events were determined by physical examination, laboratory evaluation, spontaneous complaints, and complaints elicited by a standardized questionnaire.

Psychosocial treatments. All patients were offered the type and frequency of psychosocial treatment for alcoholism usually administered at the study site. All forms of behavioral therapy were generally permitted; there was no standardized program of behavioral intervention across the studies.

Short-Term Efficacy Studies

The efficacy of acamprosate in patients with alcohol dependence was first assessed in France in a single-center trial involving 85 patients with severe alcoholism.[9] Treatment success was defined as complete abstinence over the 3-month study, as determined by clinical interview, a GGT level within the normal range, and decreased MCV. The success rate was significantly higher among acamprosate-treated patients compared with placebo-treated patients (61% vs. 32%).

In the first multicenter trial, Lhuintre et al.[10] evaluated the effect of acamprosate on biological markers of alcohol intake in 569 alcohol-dependent patients, with GGT level as the primary endpoint. All patients received a fixed dose of acamprosate (1332 mg/day) or matched placebo. Patients treated with acamprosate exhibited significantly lower GGT levels than placebo patients (1.4 ± 1.56 vs. $2.0 \pm 3.19 \times$ ULN, $p = .016$) after 3 months of treatment. Acamprosate appeared to exhibit dose-related effects; patients with a normal GGT level at 3 months had a lower initial body weight than those with an abnormal GGT level at 3 months. No weight-specific differences in GGT level were seen among placebo-treated patients.

In a single-center study conducted by Rousseaux et al.,[13] 127 patients with a DSM-III-R[24] diagnosis of either alcohol abuse or alcohol dependence were randomly assigned to 3 months of double-blind treatment with acamprosate or placebo. Medication dosing was determined by body weight (Table 1). The authors suggested that the failure of acamprosate to separate from placebo in this study may have been due to several factors. First, the single success criterion of 3 months of complete abstinence may have been unreasonably stringent for a patient population whose degree of alcohol dependence required a 2-week inpatient detoxification. Second, the dosing schedule in the low-dose/low body weight condition may have been subtherapeutic, given the poor absorption of acamprosate.[21,22]

Pelc et al.[22] compared 2 doses of acamprosate (1332 mg/day and 1998 mg/day) among 188 patients in a

Table 1. Acamprosate's Efficacy in Alcohol-Dependent Outpatients: A Summary of Randomized, Double-Blind, Placebo-Controlled Clinical Trials[a]

Country (Reference)	N	% of Patients Abstinent at Day 1	Months of Study/ Follow-Up	Dose	Days to First Drink	Rate of Total Abstinence, %[b]	Cumulative Abstinence Duration[c]	Treatment Completion, %
Clinical efficacy studies								
France (Lhuintre et al, 1985)[9]	85 (Acamprosate: 42, Placebo: 43)	100	3/0	25 g/kg/d	NR	Acamprosate: 61,[d] Placebo: 32	NR	Acamprosate: 47, Placebo: 37
France (Lhuintre et al, 1990)[10]	569 (Acamprosate: 279, Placebo: 290)	100	3/3	1332 mg/d	NR[e]	NR[e]	NR[e]	Acamprosate: 61, Placebo: 62
Belgium (Pelc et al, 1992)[11]	102 (Acamprosate: 55, Placebo: 47)	100	6/6	ABW	NR	Acamprosate: 24,[d] Placebo: 4	Acamprosate: 60 d,[d] Placebo: 49 d	Acamprosate: 66,[d] Placebo: 21
Switzerland (Ladewig et al, 1993)[12]	61 (Acamprosate: 29, Placebo: 32)	100	6/6	ABW	NR	Acamprosate: 38,[f] Placebo: 17	Acamprosate: 43%,[d] Placebo: 24%	NR
Belgium (Rousseaux et al, 1996)[13]	127 (Acamprosate: 63, Placebo: 64)	100	3/0	ABW	NR	Acamprosate: 29, Placebo: 33	NR	Acamprosate: 31, Placebo: 29
Germany (Sass et al, 1996)[14]	272 (Acamprosate: 136, Placebo: 136)	100	12/12	ABW	Acamprosate: 165,[d] Placebo: 112	Acamprosate: 43,[d] Placebo: 21	Acamprosate: 62%,[d] Placebo: 45%	Acamprosate: 58,[d] Placebo: 40
Austria (Whitworth et al, 1996)[15]	448 (Acamprosate: 224, Placebo: 224)	100	12/12	ABW	Acamprosate: 55,[d] Placebo: 43	Acamprosate: 18,[d] Placebo: 7	Acamprosate: 139 d, Placebo: 104 d	Acamprosate: 42, Placebo: 37
Belgium, the Netherlands, and Luxembourg (Geerlings et al, 1997)[16]	262 (Acamprosate: 128, Placebo: 134)	100	6/6	ABW	Acamprosate: 45,[d] Placebo: 15	Acamprosate: 20,[d] Placebo: 10	Acamprosate: 34%,[d] Placebo: 24%	Acamprosate: 41,[d] Placebo: 31
Portugal (Barrias et al, 1997)[17]	302 (Acamprosate: 150, Placebo: 152)	100	6/12	ABW	Acamprosate: 111,[d] Placebo: 55	Acamprosate: 39,[d] Placebo: 26	Acamprosate: 49%,[d] Placebo: 36%	Acamprosate: 57,[d] Placebo: 55
Italy (Poldrugo, 1997)[18]	246 (Acamprosate: 122, Placebo: 124)	100	6/6	ABW	Acamprosate: 151,[d] Placebo: 61	Acamprosate: 43,[d] Placebo: 30	Acamprosate: 72%,[d] Placebo: 59%	Acamprosate: 53,[d] Placebo: 38
Italy (Tempesta et al, 2000)[19]	330 (Acamprosate: 164, Placebo: 166)	100	6/3	1998 mg/d	Acamprosate: 158,[d] Placebo: 58	Acamprosate: 58,[d] Placebo: 45	Acamprosate: 66%,[d] Placebo: 54%	Acamprosate: 76,[d] Placebo: 74
United Kingdom (Chick et al, 2000)[20]	581 (Acamprosate: 289, Placebo: 292)	68	6/1.5	1998 mg/d	Acamprosate: 37, Placebo: 40	Acamprosate: 34, Placebo: 39	Acamprosate: 77 d, Placebo: 81 d	Acamprosate: 35, Placebo: 35
Dose-ranging studies								
France (Paille et al, 1995)[21]	538 (Acamprosate: 361, Placebo: 177)	100	12/6	1998 mg/d (N = 173) 1332 mg/d (N = 185)	Acamprosate, 1998 mg: 153,[d] Acamprosate, 1332 mg: 136,[d] Placebo: 102	Acamprosate, 1998 mg: 19.1 Acamprosate, 1332 mg: 18.1, Placebo: 11.3	Acamprosate, 1998 mg: 223 d[d] Acamprosate, 1332 mg: 198 d,[d] Placebo: 173 d	Acamprosate, 1998 mg: 55[d] Acamprosate, 1332 mg: 47,[d] Placebo: 36
Belgium/France (Pelc et al, 1997)[22]	188 (Acamprosate: 126, Placebo: 62)	100	3/0	1332 mg/d (N = 63) 1998 mg/d (N = 63)	Acamprosate, 1998 mg: 56[d] Acamprosate, 1332 mg: 56,[d] Placebo: 15	Acamprosate, 1998 mg: 51[d] Acamprosate, 1332 mg: 44,[d] Placebo: 26	Acamprosate, 1998 mg: 63%[d] Acamprosate, 1332 mg: 59%,[d] Placebo: 38.1%	Acamprosate, 1998 mg: 68[d] Acamprosate, 1332 mg: 70,[d] Placebo: 52
Combined efficacy of acamprosate and disulfiram								
Switzerland (Besson et al, 1998)[23]	110 (Acamprosate: 31, Placebo: 33, Acamprosate + disulfiram: 24, Placebo + disulfiram: 22)	100	12/12	ABW	NR	Acamprosate: 25,[d] Placebo: 5 Acamprosate + disulfiram: NR Placebo + disulfiram: NR	Acamprosate: 40%,[d] Placebo: 21% Acamprosate + disulfiram: 55%[g] Placebo + disulfiram: 31%	Acamprosate: 35,[d] Placebo: 35 Acamprosate + disulfiram: NR Placebo + disulfiram: NR

[a]Adapted from Mason and Ownby.[8] All studies required detoxification. Abbreviations: ABW = adjusted for body weight (1998 mg/day ≥ 60 kg; 1332 mg/day < 60 kg), NR = not reported.
[b]Defined as the proportion of randomly assigned patients completing double-blind treatment without having a single drink.
[c]Defined as the total number of days of complete abstinence or the percentage of abstinent days during the total possible duration of exposure to double-blind treatment.
[d]Difference between acamprosate and placebo groups: $p < .05$.
[e]γ-Glutamyltransferase level was the primary outcome measure in this study and was significantly lower in acamprosate patients than in placebo patients after 3 months of treatment (1.4 ± 1.56 vs. $2.0 \pm 3.19 \times$ upper limit of normal, $p = .016$).
[f]Difference between acamprosate and placebo groups, $p < .10$ and $p > .05$.
[g]Difference between acamprosate plus disulfiram subgroups vs. other subgroups, $p < .05$.

3-month, multicenter, placebo-controlled trial. All participants in the study weighed > 60 kg and were randomly assigned to 1 of 3 treatment groups (Table 1). Drinking diaries were reviewed, and urine alcohol levels were assessed at each study visit. The estimated rate of compliance was 95%, based on returned pill counts. Study completion rate, CAD, relapse rate, time to first relapse, and rate of complete abstinence were higher in the acamprosate treatment groups than in the placebo group. The higher dose of acamprosate exhibited a trend toward better outcome compared with the lower dose, a difference that was likewise reflected in GGT values.

Six-Month Efficacy Studies

Pelc et al.[11] conducted a 6-month multicenter trial among 102 patients to evaluate the efficacy of acamprosate under conditions typical of clinical practice. Significantly more acamprosate patients than placebo patients completed the trial and were continuously abstinent; acamprosate patients also had longer CADs than placebo patients. Mean GGT values confirmed drinking data and showed significantly greater improvement from baseline in acamprosate patients compared with placebo patients. Thus, this more naturalistic trial corroborated earlier reports suggesting that acamprosate improved abstinence rates and treatment retention. In the 6-month posttreatment follow-up phase, 13 of 55 acamprosate patients and 2 of 47 placebo patients remained completely abstinent.

Ladewig et al.[12] evaluated acamprosate efficacy in 61 psychiatric patients with severe alcohol dependence in a 6-month study with a 6-month period of posttreatment follow-up. Patients treated with acamprosate exhibited a significantly greater CAD and rate of abstinence at day 30, and these differences were maintained throughout the trial; however, patient attrition reduced statistical significance. Likewise, survival analyses suggested that there was a higher proportion of abstinent patients in the acamprosate group at the end of treatment and throughout the follow-up phase, although differences did not reach statistical significance in this reduced sample.

Geerlings et al.[16] studied the efficacy of acamprosate among 262 patients recruited from 22 detoxification clinics in Belgium, the Netherlands, and Luxembourg. In the 6-month treatment phase of the study, the acamprosate group displayed a significantly longer mean time to first drink, a greater CAD, a higher percentage of abstinent patients at each study visit, and a greater likelihood of remaining abstinent. More patients in the acamprosate group completed treatment, and on average these patients also remained in treatment longer than placebo-treated patients (mean ± SD = 102 ± 71 vs. 88 ± 73 days). Rate of medication compliance was ≥ 86%. Only 56 of 262 patients (21%) completed the 6-month posttreatment follow-up. The high rate of attrition was probably due to the limited amount of counseling received by the patients; on average, study subjects had only 20 minutes of contact with their clinician per month. The authors recommended that future follow-up studies focus more on motivation and prevention of dropout.

In a study by Poldrugo,[18] 246 participants in community-based outpatient alcoholism rehabilitation programs were randomly assigned to either acamprosate or placebo for 6 months. A subset of patients in each treatment group (acamprosate, 19.7%; placebo, 21.8%) elected to receive concomitant disulfiram. Compared with placebo, acamprosate was associated with a significantly higher rate of study completion, a higher rate of abstinence, a longer time to relapse, and a greater CAD. These effects were reflected in a lower rate of abnormal GGT levels over the treatment period in acamprosate patients. Outcomes did not differ between patients who took disulfiram and those who did not. Measures of craving showed no treatment effects. Higher rates of treatment participation (49.1% vs. 33.8%) and longer mean CAD (167.70 ± 151.05 vs. 120.48 ± 146.82 days, p = .01) were associated with acamprosate compared with placebo over the entire 12-month study and follow-up.

Chick et al.[20] conducted a 6-month efficacy study (N = 581) at 20 treatment centers in the United Kingdom in which patients received a fixed dose of acamprosate (1998 mg/day) or identical placebo. Although acamprosate appeared to decrease craving at 2 and 4 weeks, treatment effects were not observed for rate or duration of abstinence. Furthermore, subset analyses did not reveal any differences in treatment response among subpopulations of patients. It should be noted, however, that there was a long interval (up to 56 days) between the beginning of detoxification and the beginning of the study, and many patients (32%) were not abstinent at day 1 of treatment. Compliance was poor, and the treatment completion rate was very low (35%).

Tempesta et al.[19] studied the efficacy of acamprosate in 246 outpatients recruited from 18 centers in southern Italy (330 patients began the study, and 25% discontinued). Patients participated in a comprehensive outpatient alcoholism treatment program and received a fixed dose of acamprosate or identical placebo (Table 1). Mean rate of medication compliance was > 77% by returned pill count. Patients treated with acamprosate had significantly lower relapse rates, a longer time to relapse, a higher rate of total abstinence, and a longer CAD than patients treated with placebo. Acamprosate modestly reduced alcohol consumption in nonabstinent patients, suggesting enhanced control over consumption. Acamprosate did not appear to affect craving.

Long-Term Efficacy Studies

In a 12-month study with a 6-month follow-up phase, Barrias et al.[17] evaluated the efficacy of acamprosate among 302 patients from 9 centers. In the treatment phase, overall medication compliance was 87%, and the rate of

total abstinence and the proportion of patients abstinent at each study visit were consistently higher in the acamprosate group than in the placebo group. Acamprosate-treated patients also had a significantly longer CAD and latency to relapse than patients treated with placebo. During the 6-month follow-up, the proportion of abstinent patients on acamprosate gradually decreased relative to placebo; however, during the entire period of 540 days, mean CAD was significantly longer among acamprosate patients than placebo patients (225.1 ± 210.6 vs. 172.7 ± 198.7 days, p = .025). Mean GGT level decreased in both groups, with a numerically lower mean value in acamprosate patients, which corresponded with alcohol-drinking data. Acamprosate did not appear to affect measures of psychological dependence, physiologic dependence, or craving.

In a trial involving 272 patients recruited from 12 outpatient psychiatry clinics, Sass et al.[14] assessed the efficacy of acamprosate over 48 weeks of treatment and 48 weeks of posttreatment follow-up. Throughout the treatment phase, overall medication compliance was ≥ 94%, and acamprosate was associated with a significantly higher continuous rate of abstinence (43% vs. 21%, log rank p = .005) and a higher duration of abstinence compared with placebo (224 vs. 163 days, or 62% vs. 45% days abstinent; p < .001). In the follow-up phase, significantly more acamprosate patients than placebo patients remained abstinent (39.9% vs. 17.3%, p = .003). Across the entire 2-year study, CAD was significantly longer in the acamprosate group than in the placebo group (54% vs. 35% abstinent days, p = .001).

Whitworth et al.[15] also studied the efficacy of acamprosate in a 1-year study with an additional year of posttreatment follow-up. Of the 448 patients who took at least one dose of study medication, 179 (40%) completed the treatment phase, and 148 (33%) completed the follow-up phase. Survival analyses showed that the proportion of patients who remained abstinent was higher in the acamprosate group than in the placebo group throughout 1 year of treatment (p = .007). Acamprosate continued to show an advantage over placebo through the follow-up period, with 27 acamprosate-treated patients (11.9%) and 11 placebo-treated patients (4.9%) remaining continuously abstinent for 2 years. Mean CAD was significantly greater with acamprosate than placebo across the entire study (230.8 ± 259.1 vs. 183.0 ± 235.2 days, p = .039).

Paille et al.[21] assessed the dose-dependent effects of acamprosate in 538 patients from 31 centers in France. Patients were randomly assigned to receive acamprosate, 1998 mg/day (N = 173), 1332 mg/day (N = 185), or placebo (N = 177), regardless of body weight. Following a 1-year double-blind treatment phase, patients entered a 6-month single-blind placebo phase (i.e., they were unaware that placebo had been substituted for acamprosate) to assess the effect of drug withdrawal on outcome. At all assessment points, the percentage of patients continuously abstinent was highest in the 1998-mg/day group and lowest in the placebo group. Dose-dependent effects also were observed for time to first relapse, treatment retention, CAD, and rate of abstinence at the 18-month follow-up visit. Mean GGT values were not sensitive to dose effects, but the rate of normal GGT levels was significantly higher in acamprosate groups than in placebo groups at 6 and 12 months. Craving did not show a dose effect and was not substantially changed by acamprosate. There was no evidence of increased risk of relapse following drug withdrawal under single-blind conditions.

In a 12-month multicenter, double-blind, placebo-controlled study among 110 detoxified outpatients, Besson et al.[23] evaluated the safety and efficacy of acamprosate administered alone or in combination with disulfiram. Disulfiram was administered open-label by request of the patients, with 22 of 55 placebo patients and 24 of 55 acamprosate patients receiving the drug. Patients requesting disulfiram had significantly greater baseline severity of dependence, craving, and drinking-related functional impairment, as well as longer duration of alcohol dependence compared with patients not choosing disulfiram. Because medical personnel dispensed disulfiram tablets on a daily basis, disulfiram patients received additional interpersonal support and cognitive reinforcement of abstinence relative to other patients in the study. Acamprosate was dosed according to body weight (Table 1).

Patients receiving acamprosate exhibited significantly higher abstinence rates than did placebo patients after 30 days of treatment (73% vs. 43%, p = .019), as well as at the end of treatment (Table 1). The mean CAD also was significantly greater in acamprosate patients than in placebo patients (136.9 ± 147.5 vs. 74.7 ± 107.9 days, or 40% vs. 21%, p = .013). Placebo-treated patients had significantly higher GGT values than acamprosate-treated patients at days 30, 90, and 180. Analysis of results stratified for the concomitant use of disulfiram (Table 1) showed a significantly longer CAD in the subgroup receiving both medications, whereas patients receiving neither medication had the briefest CAD. Patients who received acamprosate alone exhibited a cumulative abstinence comparable to that of patients receiving disulfiram alone. Craving was not affected by treatment. No adverse interactions between acamprosate and disulfiram occurred, and neither medication dependence nor rebound drinking were reported during a 1-year follow-up period.

SAFETY

In randomized, double-blind clinical trials, mild diarrhea or a loose stool was the only adverse event that consistently occurred more frequently with acamprosate than with placebo, affecting approximately 10% of patients. In a study by Paille et al.,[21] the proportion of patients experiencing diarrhea appeared to be dose-dependent: 7.5% of

patients receiving 1332 mg/day of acamprosate reported diarrhea versus 12% of patients receiving 1998 mg/day (the rate of diarrhea among placebo patients was 3.4%). However, no dose effect on adverse events was noted in a second dose-response study by Pelc et al.[22]

Across the clinical trials, the rate of early terminations due to drug-related adverse events did not differ between acamprosate- and placebo-treated patients. Adverse events associated with acamprosate tended to be mild and transient in nature.

In conjunction with the safety profile observed in clinical trials, several pharmacokinetic and pharmacodynamic characteristics make acamprosate well suited for the treatment of a broad population of alcohol-dependent patients. First, it has no abuse potential and appears to have minimal pharmacologic effects apart from those involved in reducing alcohol consumption.[25] Second, it does not appear to interact with ethanol or compounds commonly prescribed for treatment of alcoholism (e.g., disulfiram, antidepressants, anxiolytics, neuroleptics, or hypnotics),[26] nor does it appear to interact with naltrexone.[27] Third, it can be administered to patients with liver dysfunction, since it does not undergo significant hepatic metabolism (it should not be used in patients with renal insufficiency, however).[28] Finally, acamprosate does not cause acute opioid withdrawal symptoms in patients using opioids; thus, it may be useful for methadone-maintained patients dependent on both alcohol and narcotics.

COMMENTARY

Overall, double-blind, placebo-controlled trials published to date have suggested that acamprosate is a safe and well-accepted therapy that prolongs abstinence and reduces the rate of relapse among alcohol-dependent patients. Although effect sizes varied from study to study, both primary and secondary efficacy outcomes (e.g., GGT levels) typically favored acamprosate over placebo. Differences in abstinence rates between acamprosate patients and placebo patients generally emerged within the first 30 to 90 days of treatment, were sustained for up to 1 year of treatment, and were maintained for as long as 12 months after treatment.[11,12,14–19] The compound did not appear to reduce craving relative to placebo. Thus, although acamprosate is commonly referred to as an anticraving agent, it is more accurately described as a relapse-prevention drug.

Acamprosate failed to demonstrate a significant effect on primary outcome measurements relative to placebo in 2 of the 15 published studies. However, both of these investigations had unusual and potentially confounding design characteristics. For example, the study conducted by Rousseaux et al.[13] assessed treatment success using a single, narrowly defined outcome criterion and utilized possibly insufficient dosing for some patients. The second inconclusive investigation[20] postponed therapy until up to 2 months after detoxification, such that a third of the subjects had relapsed by day 1 of double-blind treatment.

In contrast to the recent U.S. trial, which mandated a standardized behavioral treatment program in all participating sites,[29] the European multicenter studies allowed each site to provide the behavioral therapy routinely offered in its setting. The results of these highly variable studies suggest that acamprosate can be used to good effect with a diverse range of concomitant psychosocial interventions.

Acamprosate appears to be useful for a broad range of alcohol-dependent patients. In addition to being generally safe and well tolerated, acamprosate is suitable for use in patients with liver dysfunction[28] or concomitant opioid dependence. It is also safe for patients receiving other medications used in the treatment of alcohol dependence, including disulfiram and naltrexone.[23,27] The efficacy of combination pharmacotherapy with acamprosate and naltrexone is under evaluation in a number of studies and may expand the options for treatment-refractory patients.

In summary, acamprosate modestly but consistently promotes abstinence and prevents drinking relapse among alcohol-dependent patients. Its safety, tolerability, and compatibility with a wide spectrum of concomitant pharmacologic and behavioral treatments make it well suited for the treatment of alcohol dependence.

Drug names: disulfiram (Antabuse), naltrexone (ReVia).

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