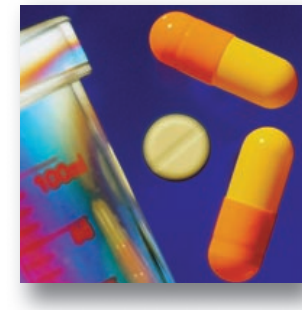

Acamprosate Calcium (Campral®): An Effective Treatment for Maintaining Abstinence in Alcohol-Dependent Patients in Combination with Psychosocial Support

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INTRODUCTION

On July 29, 2004, acamprosate calcium (Campral® Delayed-Release Tablets, Lipha/Forest), a glutamate receptor modulator, gained the U.S. Food and Drug Administration's (FDA's) approval for the maintenance of abstinence from alcohol in alcohol-dependent patients who are abstinent at the time of treatment initiation. This is the first new medication in this category for the treatment of alcohol dependence in nearly a decade. Patients taking acamprosate should also be part of a comprehensive psychosocial support program.[1,2]

Approximately nine million Americans are alcohol-dependent. Of these nine million people, 1.4 million seek treatment, but only 10,000 receive effective drug therapy. Alcohol dependence accounts for approximately 100,000 deaths per year in the U.S., with $185 billion in direct and indirect social costs per year. More than 70% of the cost is attributed to lost productivity.[3]

More than 700,000 people in the U.S. receive treatment for alcohol dependence on any given day.[4] Most patients entering treatment facilities are 36 to 40 years of age (15.6%), followed by those aged 41–45 (14.2%) and 31–35 (13.6%) (Table 1). If alcoholism is left untreated, individuals are at higher risk for heart and liver disease, infections, and cancer.[5]

Alcohol dependence is a chronic disease that is characterized by a physical craving for alcohol, impaired control over drinking, and tolerance to the substance. Alcohol-dependent individuals may recover without help, but most people need some type of assistance to stop drinking. Individuals may relapse more than once before maintaining abstinence from alcohol.[2] Patients remain at high risk of relapse during the first months after detoxification, and the major objectives during this period are maintaining abstinence and returning to a normal life with stable social and working conditions.

Other available pharmacotherapeutic agents that help promote abstinence include disulfiram (Antabuse®, Wyeth) and naltrexone HCl (ReVia®, DuPont), which are also recommended in combination with psychosocial therapies.

The mechanism of action of naltrexone in alcoholism is thought to competitively antagonize opioid receptors, resulting in elimination of the euphoric effect (Table 2).[1,2,5–9] In clinical and animal studies of naltrexone, opioid antagonists have been shown to reduce alcohol consumption. However, disulfiram produces sensitivity to alcohol, which results in an unpleasant reaction.

Patients tend to experience flushing, throbbing of the head and neck, nausea, copious vomiting, sweating, and palpitations for 30 to 60 minutes in mild cases or up to several hours in severe cases. The process of experiencing such reactions is intended to deter patients from consuming alcohol.

Acamprosate is the only medication in its drug class, and patients do not experience serious reactions as a consequence of taking both the medication and alcohol. Studies have found that individuals receiving acamprosate along with psychosocial support maintain abstinence for a longer period of time compared with patients taking placebo.[1,2,6,7]

CHEMISTRY AND PHARMACOLOGY

Acamprosate calcium is chemically designated as $C_{10}H_{20}N_2O_8S_2Ca$. Its molecular weight is 400.48. It is a white, nearly odorless powder and is freely soluble in water and insoluble in ethanol and dichloromethane. Its chemical structure is similar to that of the endogenous amino acid homotaurine (Figure 1).[1,2,10]

It is thought that acamprosate maintains the excitatory and inhibitory neurotransmitters at equilibrium. From findings in animal studies, acamprosate is

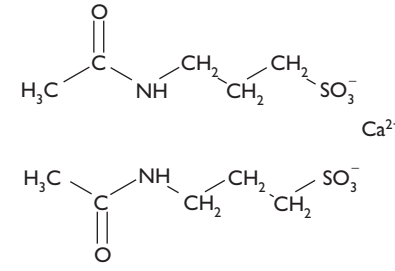

Figure 1 Chemical structure of acamprosate. (From Clinical Pharmacology 2000. Available at: www.cpip.gsm.com.[1])

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Table I **Admissions to Publicly Funded Substance Abuse Treatment Programs by Age Group, 2003**

Percentage of Admissions (%)	Age Group (Years)
15.6	36–40
14.2	41–45
13.6	31–35
13.3	21–25
11.3	26–30
9.0	46–50
8.5	12–17
6.5	18–20
4.5	51–55
1.8	56–60
0.7	61–65
0.5	66 or older
0.2	11 or younger
0.2	Unknown age

Adapted from 2003 Treatment Episode Data Set (TEDS). Office of Applied Studies, Substance Abuse and Mental Health Services Administration, U.S. Department of Health and Human Services. Revised March 2005.

believed to interact with glutamate and gamma-aminobutyric acid (GABA) neurotransmitter systems centrally. Acamprosate maintains a balance between both neurotransmitters, thereby blocking the response to environmental and learned cues.[1,2,10] It is an analogue of homotaurine, a GABA-ergic agonist.

The neurotransmitter GABA appears to affect the action of alcohol on the central nervous system and the control of ethanol-induced behavior.[10] Acamprosate's proposed mechanism of action is the stimulation of inhibitory GABA-ergic neurotransmission in the brain and the antagonizing of the effects of certain excitatory amino acids (e.g., glutamate) (Figure 2).

PHARMACOKINETICS

Absorption of acamprosate takes place via the gastrointestinal tract. The agent's bioavailability is 11% after oral administration. Absorption is decreased when acamprosate is given with food. The steady state is reached within five days of therapy. The steady-state peak plasma concentration averages 350 ng/ml when two 333-mg tablets are administered three times a day. Peak plasma concentrations are reached within three to eight hours after the acamprosate dose is taken.

The drug's volume of distribution (V_d) is estimated to be 72 to 109 liters (approximately1 L/kg) with intravenous administration. Its plasma binding is insignificant. Acamprosate does not undergo metabolism, and it is excreted unchanged via the renal route. The half-life is approximately 20 to 33 hours.[1,2,10]

CLINICAL TRIALS

Maintaining Abstinence

The Paille Study[11]

Paille et al. conducted a 12-month double-blind, randomized, multicenter study. A total of 538 patients from 18 to 65 years of age who were dependent on alcohol, according to *the Diagnostic and Statistical Manual of Mental Disorders,* 3rd edition revised *(DSM III-R)* criteria, were enrolled in the study. Three patient groups were studied: a placebo group (n = 177), a group receiving acamprosate 1,998 mg/day (n = 173), and a group receiving acamprosate 1,332 mg/day (n = 188). The patients began treatment with the medication seven to 28 days after their last alcoholic drink and were provided with supportive psychotherapy throughout the study.

The primary efficacy endpoint was the assessment of abstinence from alcohol for 12 months. An additional efficacy endpoint evaluated changes in outcome on withdrawal of acamprosate over a six-month follow-up period. Efficacy assessments were made every month for the first six months and every two months for the following 12 months.

The acamprosate 1,998-mg/day group, in addition to receiving psychosocial therapy, had the highest rate of individuals maintaining abstinence. Acamprosate therapy was also more efficacious than placebo in maintaining abstinence in the six months following the treatment period. Overall, acamprosate was superior to placebo in maintaining abstinence (Figure 3).[11]

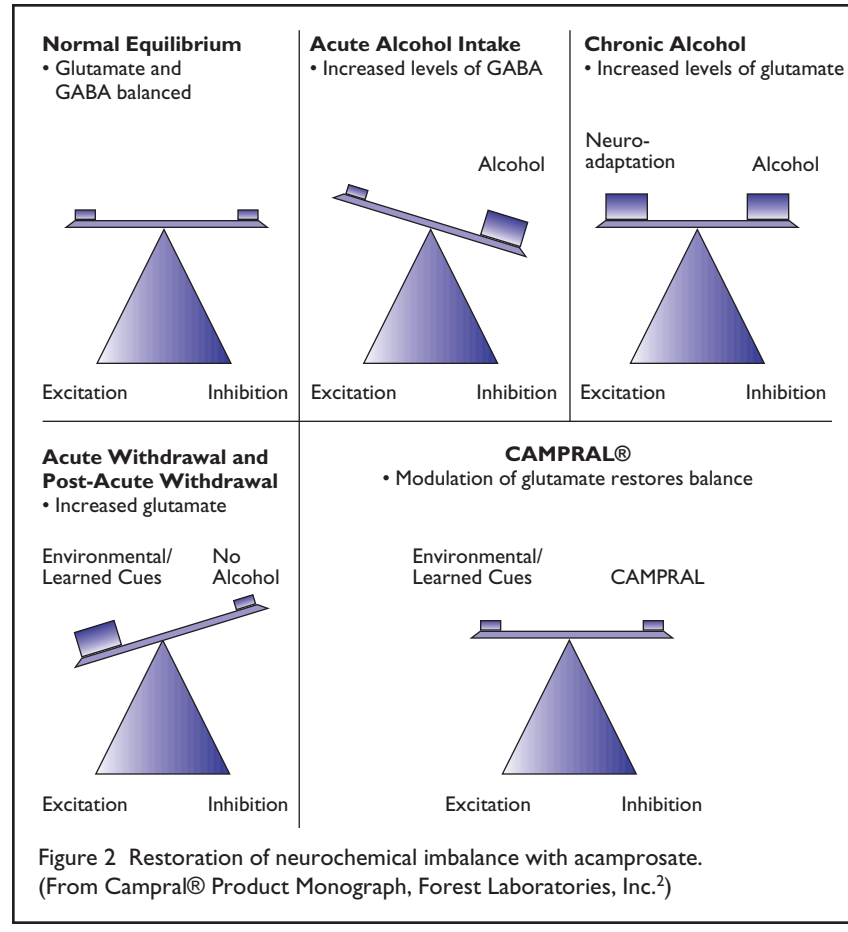

Figure 2 Restoration of neurochemical imbalance with acamprosate. (From Campral® Product Monograph, Forest Laboratories, Inc.[2])

Table 2 **Comparison of Therapies for Alcohol Abstinence**

	Acamprosate Calcium (Campral®)	Naltrexone (ReVia®)	Disulfiram (Antabuse®)
		Clinical Pharmacology	
Mechanism of action	Exact mechanism of action is unknown. It is theorized that acamprosate maintains the excitatory and inhibitory neurotransmitters at equilibrium.	Not fully understood; an opioid antagonist	Blocks oxidation of alcohol, causing an increase in acetaldehyde
Available formulations and indicated strengths	Tablet contains 333 mg of Campral®	Tablet contains 50 or 100 mg of ReVia®	Tablet contains 250 or 500 mg of Antabuse®
Dosage	Two tablets (333 mg each) three times daily	50 mg once daily with food for 12 weeks	500 mg every morning for 1–2 weeks, then reduced to 250 mg daily; duration of treatment ranges from months to years
		Pharmacokinetics	
Absorption	GI tract; bioavailability 11% after oral absorption	GI tract; peak plasma level occurs within 1 hour of dosing	GI tract
Distribution	Protein binding negligible; V_d = 72–109 L	21% bound to plasma protein; V_d = 1,350 L	3–12 hours before effects of drug are evident
Metabolism	Does not undergo metabolism; half-life = 20–33 hours	Extensive first-pass metabolism in the liver; mean elimination half-life of 4 hours	Undergoes slow hepatic metabolism; one-fifth of dose remains in body for a week or longer
Excretion	Excreted unchanged renally	Naltrexone and metabolites excreted renally (53%–79% of the dose)	5%–20% of oral dose excreted unchanged in feces; the rest is excreted primarily in the urine as metabolites
		Special Populations	
Liver impairment	No guidelines available for dosage adjustment in hepatic impairment	Dosage should be adjusted in patients with hepatic impairment; no specific dosage guidelines available for these patients	No guidelines available
Renal impairment	CrCl > 50 ml/minute: no dose adjustment CrCl = 30–50 ml/minute: starting dose of 333 mg three times daily CrCl < 30 ml/minute: drug contraindicated	Dosage should be adjusted in renally impaired patients; no specific guidelines available for dosage	Specific guidelines for dosage adjustment in renal impairment not available
		Other	
Drug interactions	Naltrexone	Clonidine, disulfiram, mixed opiate agonist/antagonist, opiate agonists, phenothiazines	Inhibitor of CYP450 2C9; alprazolam, chlordiazepoxide, clorazepate, cocaine, diazepam, ethanol isoniazid, metronidazole, midazolam, omeprazole, phenytoin, sertraline, tricyclic antidepressants
Cost	Average wholesale price, $130.50 for a 30-day supply	50-mg 30-count bottle, $152.45; 100-mg 30-count bottle, $508.16	250-mg 100-count bottle, $140.40

CrCl = creatinine clearance; CYP = cytochrome; GI = gastrointestinal; L = liters; V_d = volume of distribution.
Data from Forest Laboratories, Clinical Pharmacology 2000, *Drug Topics*, Rite Aid, and various monographs.[1,2,5–9]

Table 3 **Common Adverse Drug Events after Acamprosate Therapy in Placebo-Controlled Trials**

Event	Patients Taking Acamprosate (n = 2,019)	Patients Taking Placebo (n = 1,706)
Diarrhea	16%	10%
Asthenia	6%	5%
Nausea	4%	3%
Pruritus	4%	3%
Flatulence	3%	2%

Data from Campral® Product Monograph, Forest Laboratories, Inc.[2]

The Pelc Study[12]

Pelc et al. conducted a 13-week multicenter, randomized, 90-day double-blind, parallel-group, placebo-controlled study to assess the efficacy and safety of acamprosate in detoxified alcohol-dependent patients. Patients between 18 and 65 years of age who were alcohol-dependent, according to *DSM III-R* criteria; who had a drinking history of at least 12 months; and who had undergone a 14-day inpatient detoxification process were enrolled in the study. The patients were later assigned to receive placebo (n = 62), acamprosate 1,332 mg/day (n = 63), or acamprosate 1,998 mg/day (n = 63). The primary outcome of the study was the cumulative abstinence duration (CAD).

The most common adverse event (ADE) reported by the acamprosate and placebo groups was diarrhea.

The patients who received 1,332 mg and 1,998 mg remained abstinent for a significantly longer duration (51.9 ± 4.69 and 56.6 ± 4.25 days, respectively) than the placebo group (34.3 ± 4.29 days). Again, diarrhea was the most commonly reported ADE.

In summary, the study confirmed that acamprosate could be used with psychosocial therapy for maintaining abstinence in detoxified alcoholic patients (Figure 4).[12]

Prevention of Relapse

The Sass Study[13]

Sass et al. conducted a multicenter, randomized, double-blind comparison of acamprosate and placebo in alcohol-dependent patients over a 48-week period. Patients were randomly assigned to receive placebo (n = 136) or acamprosate (n = 136). Patients had to be between 21 and 65 years of age and alcohol-dependent, according to at least five *DSM III-R* criteria and the Munich Alcoholism Test. Patients were not permitted to have consumed alcohol for 14 to 28 days, and they had to be free of withdrawal symptoms.

After the patients were assigned to a treatment group, they received the study drug for 48 weeks, followed by a 48-week observation period. Patients receiving acamprosate and who weighed 60 kg or more received 1,998 mg/day; patients weighing below 60 kg received 1,332 mg/day.

The primary endpoint was the assessment of the effectiveness of acamprosate as a therapy for maintaining abstinence. More patients taking acamprosate maintained complete abstinence throughout the 48 weeks of active treatment (P = .002). Twice as many acamprosate patients as placebo patients maintained complete abstinence at the endpoint.

ADEs were more common throughout the first four weeks of treatment. Diarrhea and headache were the most frequently reported ADEs.

Overall, acamprosate proved safe and efficacious (Figure 5).[13]

DRUG INTERACTIONS

Acamprosate does not induce or inhibit the cytochrome P450 isoenzymes. No effect on the pharmacokinetic profile of acamprosate was observed when it was taken with ethanol, disulfiram, or diazepam. On the other hand, the pharmacokinetic properties of ethanol, diazepam, nordiazepam, imipramine, and desipramine were not affected by the coadministration of acamprosate.

The use of naltrexone with acamprosate tends to increase the area-under-the-curve (AUC) and maximum concentration (C_{max}) of acamprosate. No dosage adjustment of acamprosate is needed when it is used concomitantly with naltrexone.[1,2,10]

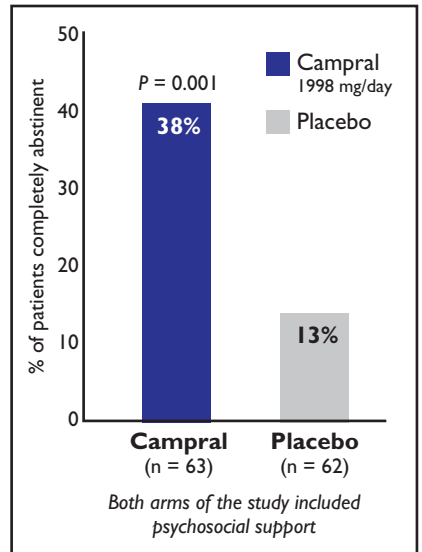

Figure 3 Percentage of patients who maintained complete abstinence over 13 weeks of acamprosate treatment in combination with psychosocial support. (From Campral® Product Monograph, Forest Laboratories, Inc.[2])

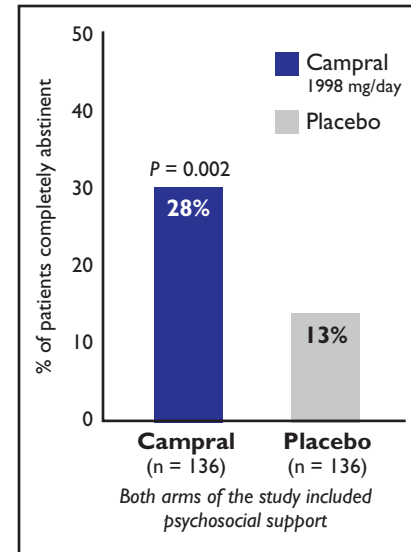

Figure 4 Percentage of patients who maintained complete abstinence over 48 weeks of acamprosate treatment in combination with psychosocial support. (From Campral® Product Monograph, Forest Laboratories, Inc.[2])

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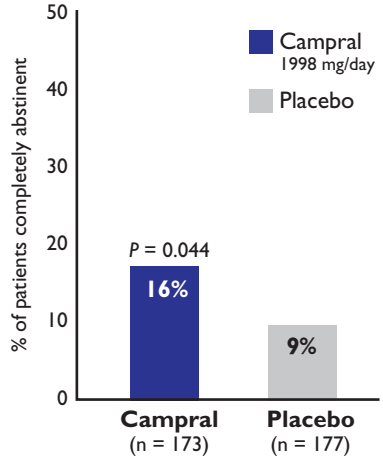

Figure 5 Percentage of patients who maintained complete abstinence over 52 weeks of acamprosate treatment in combination with psychosocial support. (From Campral® Product Monograph, Forest Laboratories, Inc.[2])

DOSAGE AND ADMINISTRATION

The recommended dose of acamprosate is two tablets (333 mg each) three times daily with or without food. Acamprosate should be initiated after alcohol withdrawal when the patient has achieved abstinence, and it should be maintained if relapse occurs.

The initial dose in patients with a creatinine clearance of 30 to 50 ml/minute is 333 mg three times daily. Patients with a creatinine clearance of less than 30 ml/minute should not receive acamprosate. Dosage adjustments may be required in elderly patients because of the decreased renal function in this population.[1,2,10]

OVERDOSAGE

The only symptom that might be logically associated with acamprosate overdose, based on total reported doses of up to 56 grams of the drug, was diarrhea. Treatment of overdoses should be symptomatic and supportive. Hypercalcemia has not been reported after acute overdoses but should be considered in chronic overdoses only.

ADVERSE DRUG REACTIONS

The most common adverse drug reactions (ADRs) reported with the use of acamprosate, compared with placebo, were diarrhea, nausea, asthenia, pruritus, and flatulence (Table 3). Other ADRs reported were depression, insomnia, anxiety, dizziness, and pain.[1,2,10,14]

CONTRAINDICATIONS AND PRECAUTIONS

The use of acamprosate is contraindicated in patients who are hypersensitive to it or any of its components. Patients with severe renal failure (a creatinine clearance or 30 ml/minute or less) should not use acamprosate. The product should be used with caution in patients with depression or suicidality or moderate renal failure (creatinine clearance of 30–50 ml/minute). [1,2,10,14]

Acamprosate does not eliminate or diminish withdrawal symptoms.[2]

DISCONTINUATION OF THERAPY

Currently, no guidelines have been implemented for discontinuing acamprosate.

COST

Acamprosate is available in a 30-day Dose Pak (which contains a structured morning, afternoon, and evening routine) and in a 180-count bottle. The average wholesale price is $104.40.[8]

Acamprosate 333-mg tablets are enteric-coated, white, round, and biconvex, and they are identified with "333" debossed on one side.

CONCLUSION

Acamprosate is the first agent in its class developed to maintain abstinence in alcohol-dependent patients. It is thought to interact with glutamate and GABA neurotransmitter systems centrally. Acamprosate maintains a balance between both neurotransmitters, thereby blocking the response to environmental and learned cues.[1,2,6]

Acamprosate should be part of a comprehensive treatment plan that includes psychosocial support. Studies have confirmed that acamprosate, along with psychosocial therapy, is superior in maintaining abstinence in detoxified alcoholic patients when compared with placebo.[11] As a recent therapy for maintaining abstinence in alcohol-dependent patients after withdrawal, acamprosate offers a new prospect for the future.[1,2,10]

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