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Acamprosate: A New Medication for Alcohol Use Disorders

What is acamprosate?

Acamprosate (calcium acetyl homotaurinate) is a new prescription medication to help people who are alcohol dependent. Acamprosate is the third medication, after disulfiram (Antabuse®) and naltrexone (ReVia®), to receive U.S. Food and Drug Administration (FDA) approval for postwithdrawal maintenance of alcohol abstinence. It is the first new medication approved for this purpose in a decade. FDA approved acamprosate in July 2004. It became available in the United States in January 2005, under the trade name Campral® Delayed-Release Tablets. Acamprosate has been used for nearly 20 years in Europe, where it has been found to be safe and effective for treating alcohol dependence (Mann et al. 2004; Tempesta et al. 2000).

How does acamprosate work?

Chronic, heavy use of alcohol affects several neurotransmitter systems in the brain. These neurotransmitter systems adapt to the chronic presence of alcohol. Once they have adapted, these systems are only in equilibrium with alcohol. When alcohol use ceases, the systems become disregulated and enter a pathologic hyperexcitatory state. It is thought that acamprosate helps modulate and normalize brain activity, particularly in the glutamate and gamma-aminobutyric acid (GABA) neurotransmitter systems. Although acamprosate's mechanism of action has not been clearly established, it may work by reducing symptoms of postacute (protracted) withdrawal, such as insomnia, anxiety, and restlessness.

How does acamprosate's activity compare with that of other medications used to treat alcohol dependence?

Acamprosate differs in significant ways from disulfiram and naltrexone, the other two agents approved by FDA for alcohol abstinence maintenance (table 1).

Disulfiram, used to treat alcohol dependence for decades, is an aversive medication that inhibits aldehyde dehydrogenase and leads to increased levels of acetaldehyde. When a person taking disulfiram drinks alcohol, the increased acetaldehyde causes severe physical reactions such as facial flushing, nausea, vomiting, low blood pressure, headache, and weakness. Disulfiram does not reduce craving or normalize brain functioning, as acamprosate and naltrexone are believed to do. Instead, disulfiram's effectiveness depends on the patient's reluctance to suffer the aversive effects of drinking when on disulfiram.

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Table 1: Comparison of Drugs Approved for Maintenance of Abstinence From Alcohol

Medication	Acamprosate (Campral)	Disulfiram (Antabuse)	Naltrexone (ReVia)
Mechanism of Action	Is not completely understood; appears to modulate/normalize alcohol-disrupted brain activity, particularly in the GABA and glutamate neurotransmitter systems; does not cause sickness if alcohol is ingested; reduces craving for alcohol	Inhibits aldehyde dehydrogenase causing sickness (e.g., flushing, nausea, headache, sweating, weakness, increased blood pressure) when alcohol is ingested; does not reduce craving	Blocks brain opioid receptors; eliminates euphoria associated with alcohol use; makes alcohol use less rewarding; does not cause sickness if alcohol is ingested; reduces craving
Optimal Patient Status	Abstinence at treatment initiation, immediately following acute withdrawal; commitment to recovery Patients who relapse while taking acamprosate may benefit from continuing the medication	Abstinence at treatment initiation and during ongoing administration; commitment to recovery	Abstinence at treatment initiation Patients who relapse while taking naltrexone may benefit from continuing the medication
Examples of Drugs Causing Interactions	None known	Metronidazole (Flagyl®); paraldehyde; medications containing alcohol; and phenytoin, warfarin, isoniazid, rifampin, diazepam, chlordiazepoxide, imipramine, desipramine, and oral hypoglycemics	Opioid-containing medications, thioridazine, yohimbine, and oral hypoglycemics
Side Effects	Most common: diarrhea and intestional cramps, itchiness, dizziness, muscle weakness, headache, flatulence, nausea, anxiety, and insomnia Less common, but more serious: depression and suicide risk	Most common: disulfiram-alcohol reaction (can be serious) Common but usually mild and self-limiting: drowsiness, metallic taste, headache, impotence, and acne Less common, but more serious: liver toxicity, peripheral neuropathy, psychosis, and delirium	Most common: opioid withdrawal symptoms (insomnia, nausea, vomiting, anxiety, headache, abdominal pain, muscle aches, rash, dizziness, fatigue, constipation, and chills) Less common, but more serious: potential liver toxicity (especially at high doses) and suicidal ideation
Contraindications and Cautions	Hypersensitivity to the drug; severe renal (kidney) impairment (creatinine clearance <30 mL/min) Dosage may be modified for moderate renal impairment (creatinine clearance 30–50 mL/min) Use with older adults or with patients with depression only when potential benefits justify potential risk FDA pregnancy category C*	Hypersensitivity to the drug, significant liver disease, alcohol still in system, psychosis, coronary artery disease, paraldehyde use, diabetes, and severe metronidazole use FDA pregnancy category C*	Hypersensitivity to the drug, any use of narcotic analgesics, liver disease, and acute opioid withdrawal FDA pregnancy category C*

*FDA pregnancy category C: Animal studies have indicated potential fetal risk OR have not been conducted and no or insufficient human studies have been done. The drug should be used with pregnant or lactating women only when potential benefits justify potential risk to the fetus or infant.

Naltrexone (an opioid antagonist) blocks opioid receptors, leading to reductions in craving and in the reinforcing effects of alcohol. Unlike naltrexone, acamprosate does not affect the action or subjective effects of alcohol (Brasser et al. 2004).

Patients with liver damage usually cannot use either naltrexone or disulfiram. However, because acamprosate is not metabolized in the liver, patients with liver damage can safely take the medication.

Preliminary evidence suggests that treatment outcomes improve when acamprosate is combined with naltrexone or with disulfiram, particularly for patients who responded poorly to therapy with any of these medications alone (Besson et al. 1998; Kiefer and Wiedemann 2003; Kiefer et al. 2003). Combination therapy also has been found to be safe. No specific protocol for combination therapy has been established as yet, but the results of a large national study, sponsored by the National Institute on Alcohol Abuse and Alcoholism, will be available soon. The study, Combining Medications and Behavioral Interventions (COMBINE), examines the effects of naltrexone and acamprosate and two psychosocial therapies, alone and in various combinations.

Are there side effects or drug interactions with acamprosate?

The most common side effects experienced by people taking acamprosate are diarrhea, insomnia, anxiety, muscle weakness, nausea, itchiness, and dizziness. Uncommon, but serious, side effects include depression and suicidal thoughts. Most side effects are usually mild and transient, lessening or disappearing within the first few weeks of treatment.

Acamprosate has not been found to be associated with any significant drug (including alcohol) interactions and does not affect the action of coadministered disulfiram, diazepam, nordiazepam, imipramine, desipramine, selective serotonin reuptake inhibitors, naltrexone, or naltrexol. No adjustment of dosage is recommended in patients taking these other medications.

Can acamprosate be used for detoxification?

Research on the effectiveness of acamprosate in treating the symptoms of acute withdrawal has been inconclusive, and FDA has not approved its use for this purpose. However, patients who are already taking acamprosate and who relapse may be medically withdrawn from alcohol without discontinuing acamprosate.

How safe is acamprosate?

Acamprosate is not addicting and appears to have no potential for abuse; patients maintained on the drug have developed no known tolerance for or dependence on it. It also carries little overdose risk. Even at overdoses up to 56 grams (a normal daily dose is 2 grams), acamprosate was generally well tolerated by patients (Thomson Healthcare, Inc. 2005).

Because acamprosate is not metabolized by the liver, it can be used by individuals with liver disease. Because acamprosate is excreted primarily from the kidneys, patients with severe renal impairment (creatinine clearance <30 mL/min) should not use acamprosate. Those with moderate renal impairment (creatinine clearance 30–50 mL/min) may be able to take the medication with dosage adjustments and careful monitoring.

Patients should be told to be cautious about driving or operating heavy machinery until they know how acamprosate will affect their ability to engage in these activities and until they have adjusted to any effects of the drug.

In clinical trials, suicidal events (suicidal ideation, attempted suicides, completed suicides), although rare, were more common in acamprosate-treated participants than in participants receiving placebo. Patients should be monitored for symptoms of depression or suicidal thinking. Families and caregivers should be informed of the need to monitor their family members for these signs and report their occurrence to the substance abuse treatment counselor or prescribing professional.

Use of acamprosate during pregnancy has not been studied with humans. Animal studies of acamprosate and pregnancy have found some potential fetal risk. The potential risk of taking acamprosate during pregnancy should be balanced with the potential benefits (considering the known adverse effects of alcohol, particularly the risk of fetal alcohol syndrome).

The use of acamprosate by older adults or by children has not been studied. Because of the higher risk of diminished renal function among older adults, acamprosate should be used with caution with this population.

Campral Dosage and Timing

- The recommended dosage of Campral is two 333 mg tablets three times a day, with or without food.
- Treatment with acamprosate should be initiated as soon as possible after alcohol withdrawal and should be maintained if the patient relapses.
- Treatment duration at this dosage ranged from 3 to 12 months in clinical trials.
- The manufacturer recommends treatment duration of 1 year.

How can treatment providers incorporate acamprosate into their programs?

Treatment program staff should be well educated about acamprosate and its effects and be able to educate clients about the medication. Acamprosate is a prescription medication, so treatment providers need to be able to provide the medication and medically monitor the patient, either on site or through relationships with medical professionals in the community.

Treatment providers should assess patients' clinical appropriateness for acamprosate. Patients who have been in treatment multiple times but have been unable to sustain abstinence or those for whom disulfiram or naltrexone or both have not been effective may be particularly appropriate candidates for acamprosate. However, given the medication's good safety profile, patients new to treatment also may be considered good candidates for acamprosate therapy. A good candidate also is interested in trying the medication and willing and able to take it regularly as prescribed.

Motivation is an important factor. Clinical trials found that participants receiving acamprosate who were motivated and committed to total abstinence at the start of treatment had lower relapse risk than less motivated participants (FDA Psychopharmacologic Drugs Advisory Committee 2002). Less motivated patients are those whose personal goals, for instance, allow for slips, controlled drinking, other modified alcohol consumption, or other substance abuse. Research has not documented the effectiveness of acamprosate with patients who use multiple substances in addition to alcohol.

Researchers also have looked at whether certain clinical characteristics (e.g., age of onset of alcohol use disorder, level of craving, gender, family history of alcohol use)

might predict which individuals are more likely than others to abstain from alcohol successfully on acamprosate. This research did not find a relationship between patient characteristics and successful acamprosate therapy (Verheul et al. 2005). Any patient who is found to be both medically and motivationally appropriate for acamprosate therapy and wants to try the medication should be given the opportunity.

Once the treatment provider and patient decide that acamprosate may help, the client should be referred to a person who can prescribe it. The prescribing professional should assess the patient's medical appropriateness for therapy with acamprosate by conducting a medical examination, including laboratory tests to obtain baseline readings of kidney function.

Medications for alcohol use disorders do not replace counseling. Individuals taking acamprosate should be expected to participate fully in a treatment program's activities, including attending 12-Step or mutual-help group meetings. In addition, they may need ongoing motivational counseling specifically geared to helping them comply with a drug regimen.

Regular communication between treatment providers and the prescribing medical professional is essential. In particular, treatment providers need to communicate information concerning the patient to the prescribing professional such as

- Reported or detected drinking or drug use episodes
- Patient concerns about side effects
- Issues affecting the patient's safety (suicidal ideation, reported or observed increase in levels of depression or anxiety, or significant physical complaints)
- Medication compliance issues
- Expressed desire to stop taking the medication

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What To Tell the Patient

Treatment program staff can support patients taking acamprosate by educating them about the drug, including

- Informing them about the benefits and limitations of the medication
- Informing them that it can take 5 to 8 days before acamprosate is fully effective
- Stressing the importance of taking the medication as prescribed
- Encouraging them to talk to their prescribing professional about the duration of acamprosate therapy
- Encouraging them to talk to their prescribing professional about other medications they are taking
- Encouraging them to report side effects of the drug and explaining that most of these resolve fairly quickly
- Encouraging women to inform all treatment providers immediately if they become pregnant during therapy, if they are trying to become pregnant, or if they are breast-feeding
- Stressing the importance of continuing counseling and 12-Step or mutual-help group participation
- Stressing the need for caution in driving or operating heavy machinery until they are certain that acamprosate has no adverse effects on their participation in these activities and they have adjusted to the drug
- Advising them to continue taking the medication if a slip or relapse occurs and to inform their counselor and prescribing professional immediately

Treatment providers should encourage patients to talk directly to their prescribing professionals about these and other issues or questions they may have.

How long should an individual take acamprosate?

The manufacturer of acamprosate recommends that acamprosate therapy be continued for 1 year (the effectiveness and safety of the medication have not been evaluated for periods of use longer than a year). Given that guideline, the length of time a particular patient takes acamprosate will be determined, ideally, with input from the prescribing professional, the treatment provider, and the patient. Discontinuation of acamprosate may be considered once a patient has achieved stable abstinence from alcohol, reports diminished craving, and has established a sound plan and support for ongoing recovery. Acamprosate therapy also may be discontinued if a patient is not compliant with the medication regimen. Acamprosate should not be discontinued just because a patient slips or relapses.

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Resources for Additional Information

Substance Abuse and Mental Health Services Administration (SAMHSA)
1 Choke Cherry Road
Room 8-1054
Rockville, MD 20857
Phone: 240-276-2130 (Office of Communications)
Web: www.samhsa.gov

National Clearinghouse for Alcohol and Drug Information (NCADI)
Phone: 800-729-6686
Español: 877-767-8432
TDD: 800-487-4889
Web: www.ncadi.samhsa.gov

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
5635 Fishers Lane, MSC 9304
Bethesda, MD 20892-9304
Web: www.niaaa.nih.gov

U.S. Food and Drug Administration (FDA)
5600 Fishers Lane
Rockville, MD 20857-0001
Phone: 888-INFO-FDA (888-463-6332)
Web: www.fda.gov

Selected Publications

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