Traditional Pharmacotherapy of Alcohol Dependence

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Over a span of about 55 years, 4 medications have achieved U.S. Food and Drug Administration (FDA)–approved labeling in alcohol dependence: disulfiram (1951), oral naltrexone (1994), acamprosate (2004), and naltrexone for extended-release injectable suspension (2006). Although these medications have different mechanisms of action and specific FDA-approved clinical indications, the efficacy of each is increased significantly when the medication is combined with psychosocial therapy. The distinct nature of each medication allows the potential to combine them in treatment—analogous to the treatment of hypertension. While these drugs are the cornerstones of current pharmacotherapy treatment for alcohol dependence, they are still widely underutilized. This article reviews the mechanisms of action, efficacy, safety/tolerability, and clinical use of disulfiram, oral naltrexone, and acamprosate. *(J Clin Psychiatry 2006;67[suppl 14]:14–22)*

Four U.S. Food and Drug Administration (FDA)–approved medications for the treatment of alcohol dependence have been introduced in the last 55 years: disulfiram in 1951, oral naltrexone in 1994, acamprosate in 2004, and naltrexone for extended-release injectable suspension in 2006. Before the development and use of medications designed to treat alcohol dependence, psychosocial therapy was the main tool available to clinicians to deal with unhealthy alcohol use. While therapies such as motivational enhancement therapy (MET); various 12-step programs, including Alcoholics Anonymous; cognitive-behavioral therapy (CBT); and other techniques are effective, the rate of relapse can be as high as 40% to 70% within a year.[1] The availability of medications to treat alcohol dependence provides an opportunity for the combining of psychosocial treatment with pharmacotherapy in the treatment of alcohol dependence. Consequently, prescribing physicians have often joined forces with the treatment and recovery communities, coupling pharmacotherapy with various psychosocial treatments. For example, techniques for craving management and relapse prevention as part of CBT may act synergistically with the mechanisms of action of naltrexone, one of the approved drugs for alcohol dependence.[2,3] However, not all treatment centers provide CBT, because treatment is lengthy (10–12 weeks) and must be provided by skilled therapists. Thus, there is considerable interest in the issue of matching the characteristics of individual alcohol-dependent patients with specific forms of psychosocial treatment, both alone and in combination with pharmacotherapy.

Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity), for example, was a multisite psychosocial treatment study examining outcomes in subjects treated with 12-step facilitation (TSF), CBT, and MET.[4] The researchers found that CBT and TSF produced abstinence or moderate drinking without alcohol-related consequences in 41% of patients,[4] and many clinicians positively interpreted the results for all 3 treatments. However, one recent reanalysis of the data concluded that, overall, "current psychosocial treatments for alcoholism are not particularly effective."[5(p75)] These authors found that most improvement occurred in the first treatment session, and that only 3% of the drinking outcome at follow-up could be attributed to treatment. Results of treatment in alcohol-dependent patients appear to be better when psychosocial approaches are combined with pharmacotherapy.[6–9] Thus, there is clearly an impetus to develop effective medications for the treatment of alcohol dependence as part of a comprehensive biopsychosocial approach to the patient. Since the precise biological mechanisms underlying alcohol dependence are not known, there is interest in using multiple therapeutic agents—for example, naltrexone plus acamprosate—to target putative etiologic components of the biological process.[10]

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Table 1. FDA-Approved Medications for Alcohol Dependence

FDA-Approved Medication	Mechanism of Action	Dose*	Clinical Use
Disulfiram	Interferes with metabolism of acetaldehyde, a metabolite of alcohol Produces an aversive reaction if alcohol is consumed	One 250-mg dose, once daily	Used in selected patients to help them remain in enforced sobriety so that supportive and psychosocial therapy can be best used[11] Best results may occur when used under direct supervision
Naltrexone (oral and extended-release intramuscular formulations)	Opioid antagonist Blocks "reward" received from drinking alcohol and may reduce craving for alcohol	Oral: One 50-mg dose, once daily Intramuscular: one 380-mg injection, once monthly	Oral: Used in conjunction with a comprehensive counseling treatment program to treat alcohol dependence[12] Family involvement in treatment and compliance-enhancement programs may improve treatment adherence Intramuscular: Used to treat alcohol dependence as part of a comprehensive treatment plan that includes psychosocial support[13] Indicated for patients who are able to be abstinent, not actively drinking patients[13]
Acamprosate	Exact mechanism unknown, thought to modulate glutamate-mediated neurotransmission May restore balance between glutamate and GABA systems altered by chronic alcohol use and manifested during withdrawal	Two 333-mg doses, 3 times/day	Used in patients who are already abstinent to maintain abstinence[14] Patients should be detoxified and abstinent before beginning treatment with acamprosate; treatment should include psychosocial therapy[14]

*Usual maintenance dose.

This article briefly describes the pharmacodynamics of alcohol dependence, with particular focus on FDA-approved medications, and then reviews the mechanism of action, efficacy, safety, tolerability, and clinical use of disulfiram, naltrexone, and acamprosate (Table 1). (Naltrexone for extended-release injectable suspension is discussed in more detail in this supplement in "New Therapeutic Options for Alcohol Dependence: Long-Acting Intramuscular Formulations of Naltrexone" by James C. Garbutt, M.D.[15]) The issue of adherence to these medication regimens is also discussed, along with clinical predictors of response.

CLASSIFICATION OF PHARMACOTHERAPIES AND THEIR NEUROCHEMICAL TARGETS

The pharmacodynamic effects of disulfiram, naltrexone, and acamprosate can be classified from a number of perspectives, including mechanisms of action, application of principles of operant conditioning, and a view of the central nervous system (CNS) and behavior that considers the contrasting states of homeostasis and allostasis.[16] For example, disulfiram produces an aversion to alcohol use in a manner consistent with the operant conditioning concept of punishment (i.e., punishment weakens the behavior of alcohol use because the negative condition of the alcohol/disulfiram reaction is experienced as a consequence of the behavior). Conversely, naltrexone produces a reduction of craving for alcohol leading to decreased use and may also decrease the pleasurable effects of alcohol[17–19]; in either case, the operant conditioning principle of extinction occurs through reduction of alcohol's positive reinforcement. The following schema places current and potentially new treatments into this context:

- Aversion: Disulfiram as an agent that acts via aversion by introducing a negative state (i.e., punishment from operant conditioning) in response to the behavior of alcohol use. This is accomplished through inhibition of the enzyme aldehyde dehydrogenase, which mediates the second step in alcohol metabolism.[20] The resultant buildup of acetaldehyde leads to unpleasant autonomic reactions such as nausea, vomiting, and flushing.
- Reinforcement: Naltrexone and acamprosate as agents that extinguish alcohol use behavior via the reward-based system, including potential targeting of dopamine, β-endorphin, serotonin, glutamate, and γ-aminobutyric acid (GABA), although other neurotransmitter systems may also be affected.[21,22] Alterations in these brain chemicals appear to mediate alcohol-related pleasure, craving, and withdrawal effects.
- Allostasis: Acamprosate as an agent that may restore homeostasis or contribute to allostasis of the balance between central nervous system GABAergic and glutamatergic receptor systems.[23] Allostasis is a concept that is now gaining renewed attention. For example, if acamprosate is able to in some way restore a balance between GABAergic and glutamatergic systems that has been lost due to chronic alcohol exposure, it may do so by returning to a presumed baseline process (homeostasis) or initiating a new process that better serves the already-altered CNS (allostasis).

- Stress-based: Potential new pharmacotherapeutic agents targeting alcohol dependence through alteration of stress systems,[21,22,24] including the hypothalamic-pituitary-adrenal (HPA) axis and stress-related neuromodulators and the neuropeptides corticotropin-releasing factor (CRF) and neuropeptide Y (NPY), both of which are produced by the hypothalamus. Drugs of abuse are known to activate the CRF/HPA axis, and both CRF and NPY may modulate the stress response to alcohol abuse and/or withdrawal.[25,26] The potential therapeutic role of CRF antagonists, NPY agonists, and related agents is an active area of research in the treatment of drug and alcohol dependence.[25,27] For example, in selectively bred, alcohol-preferring rats, injection of NPY into the cerebral ventricles decreases alcohol intake.[27]

Disulfiram

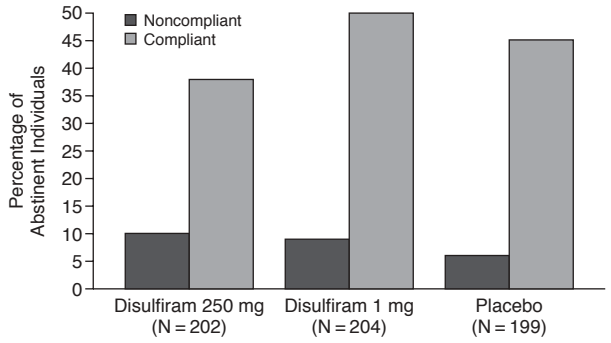
Mechanism of action. As noted, disulfiram blocks the oxidation of alcohol at the acetaldehyde stage. Patients taking disulfiram accumulate a buildup of acetaldehyde when they drink, producing hypotension, flushing, nausea, vomiting, throbbing in the head and neck, sweating, palpitations, and other aversive signs and symptoms. This reaction is proportional to the dosage of both disulfiram and alcohol, and persists as long as alcohol is being metabolized.[11]

Alcohol dehydrogenase (ADH) and mitochondrial aldehyde dehydrogenase (ALDH2) are responsible for metabolizing the bulk of dietary ethanol and are expressed at highest levels in the liver. Polymorphic variants of the genes for these enzymes have important implications for those who consume alcohol.[28] The *ALDH2*2* allele, which encodes a low-activity form of ALDH2, is associated with an inability to metabolize acetaldehyde and a reduced risk of alcoholism. Indeed, the *ALDH2*2* allele is the best-characterized genetic factor protecting against development of alcohol dependence. In the Asian population, this allele is found in about 50% of the population.[29] Impaired ability to metabolize acetaldehyde is found in people who are both heterozygous and homozygous for the allele, although the effect is stronger among those homozygous, with almost no alcohol-dependent persons among this group.[29,30] Pharmacogenomic research suggests that it is highly unlikely that disulfiram would be helpful in those with genetically compromised ALDH2 function, since, presumably, these individuals would already have experienced lifelong aversive effects of alcohol.[29]

Efficacy. The effectiveness of disulfiram in alcohol-dependent patients remains somewhat controversial. While there have been many studies of disulfiram, few have been controlled and well-conducted. As a controlled, blinded, multicenter study of disulfiram treatment for alcoholism, the Veterans Administration (VA) cooperative study by Fuller and colleagues[31] was one of the largest and most methodologically sound. It involved 605 men randomly assigned treatment of counseling plus disulfiram at 250 mg/day or at 1 mg/day (the lower dosage was insufficient to cause disulfiram/ethanol reaction but served as a control for the threat of this reaction) or no disulfiram. This third group, which received a vitamin instead of disulfiram, served as a control for the counseling each group received. Men in the third group were told they were receiving a vitamin; thus, there was no threat of the disulfiram/alcohol reaction. (Investigators, however, were blinded to treatments received by patients.) Bimonthly treatment assessments were done for 1 year, and self-reports of alcohol use were corroborated via blood tests, urinalysis, and interviews with family. Five outcome measures were assessed: continuous abstinence, time to first drink, number of drinking days, employment status, and social stability (i.e., living with the same friend or relative over the study duration). At the study's conclusion, the groups showed no significant differences in continuous abstinence, time to first drink, employment, or social stability. Interestingly, patients adherent to treatment, regardless of group, were better able to maintain abstinence (Figure 1). However, among subjects who drank and completed all scheduled interview assessments (almost half of all drinking patients), those given disulfiram 250 mg reported significantly fewer drinking days compared with the placebo and 1-mg disulfiram groups. The men who completed every interview were older, were more likely to live at the same address over the year, and had abused alcohol longer, compared with the men who did not attend every interview. The authors concluded that disulfiram may help reduce drinking frequency after relapse, perhaps more so in older, socially stable men, but that it does not sustain continuous abstinence or delay resumption of drinking.[31]

Safety/tolerability. Although the VA cooperative study found generally good tolerability for disulfiram (250 mg/day), about 8% of subjects experienced moderate to severe drowsiness (vs. 2% in those not given the drug).[31] Disulfiram may occasionally cause hepatic toxicity, and there have been reports of fatal hepatitis associated with disulfiram therapy.[11] Optic neuritis, peripheral neuritis or neuropathy, and psychotic reactions have been reported.[11] The disulfiram/ethanol reaction itself is sometimes associated with serious complications, including cardiovascular collapse, myocardial infarction, and even death.[11] Disulfiram is contraindicated in patients with severe myocardial disease, those with psychosis, and those who have recently received any alcohol-containing products. Owing to all these risks, the use of disulfiram is generally confined to "selected chronic alcohol patients who want to remain in a state of enforced sobriety, so that supportive and psychotherapeutic treatment may be applied to best advantage."[11(p2)]

Figure 1. Abstinence Rates for Alcohol-Dependent Men Treated With Disulfiram Plus Counseling in Veterans Administration Cooperative Study[a]



[a]Reprinted with permission from Fuller et al.[31]

Clinical use. Notwithstanding the equivocal results of placebo-controlled studies, some experts in the treatment of alcoholism maintain that "for some patients, disulfiram use is worthwhile, especially early in treatment."[32(p139)] Ciraulo and colleagues suggest that the best results are seen when patients "take their daily doses under the supervision of a monitor, preferably a person who has a strong investment in the patient's abstinence and who is willing to attend some therapy sessions."[32(p139)] A study performed in India by De Sousa and De Sousa[18] supports this approach. In this study, in which family members were used as monitors and attended clinical appointments, results showed that patients taking disulfiram remained abstinent at a mean of 119 days, with 86% of them remaining abstinent throughout the 1-year study. (This study is also discussed below in the section entitled "Naltrexone," since study patients were randomly assigned to receive either disulfiram or naltrexone.) Improved adherence to disulfiram treatment was also found among 17 court-ordered patients who had adherence rates 3 times higher than adherence rates in 19 voluntary patients over 15 months.[33] While improved treatment efficacy might be presumed with improved adherence in these court-ordered patients, that question was not specifically answered in this study.[33]

Prior to starting treatment with disulfiram, the clinician and patient must participate in a careful discussion of risks versus benefits. Patients must be warned, for example, to avoid alcohol in all forms, including cough syrups, vinegar, mouthwash, and the like. Ciraulo and colleagues[32] have observed that disulfiram/ethanol reactions may be less likely in patients who are well motivated, socially stable, extremely careful, and not depressed or suicidal. These features, unfortunately, probably characterize only a small subgroup of alcohol-dependent patients.

Disulfiram may help in the treatment of cocaine dependence.[34] This finding is potentially important because a significant number of individuals who are dependent on cocaine are also alcohol-dependent. Interestingly, cocaine-dependent patients who were not alcohol-dependent at baseline or who abstained from drinking during treatment with disulfiram had the best treatment outcomes.[34] Disulfiram inhibits the enzyme dopamine β-hydroxylase, leading to increases in brain dopamine[35]; increased dopamine may reduce the incentive for cocaine use.

Naltrexone

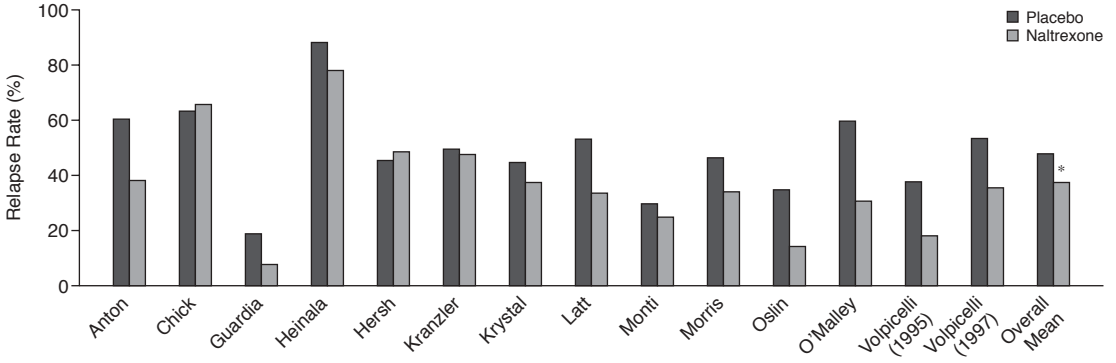
Mechanism of action. Naltrexone is a nonspecific opioid antagonist that blocks mu, delta, and kappa opioid receptors, with greatest affinity for the mu receptor.[36] Both animal studies and clinical data support the role of endogenous opioids, such as β-endorphin, in the rewarding effects of alcohol. It is hypothesized that alcohol consumption releases endogenous opioids, which, in turn, activate neurotransmitters linked with rewarding effects, such as dopamine. Naltrexone consistently reduces alcohol consumption in animal studies, apparently by blocking opiate receptors in the brain's reward system.[21]

In so doing, naltrexone may interfere with alcohol-induced release of dopamine in the nucleus accumbens, a major reward center of the brain. Peak concentrations of naltrexone and its major metabolite, 6-B-naltrexol, occur within 1 hour of oral administration.

Efficacy. The efficacy of naltrexone in alcohol dependence has been a matter of some uncertainty; some clinical trials have yielded positive results, and some have been negative. This is probably due to variability in study populations, the type of adjunctive psychosocial treatment, biologically heterogeneous subtypes of alcohol-dependent persons, and varying degrees of adherence to naltrexone treatment.[21] These factors need to be taken into account when evaluating studies of naltrexone. For example, a study by Volpicelli et al.[37] and one by Pettinati et al.[38] found substantial differences in the effect of naltrexone on drinking outcomes between patients who adhered to treatment and those who didn't. Naltrexone significantly reduced relapse rates compared with placebo in treatment-adherent patients, but differences between treatments were not significant in nonadherent patients[38] or when looking at the treatment groups as a whole, which included nonadherent patients.[38] (See "Improving Medication Adherence in Alcohol Dependence" by Helen M. Pettinati, Ph.D., in this supplement for more on adherence with naltrexone.[39]) Although such factors can confound the true effect of naltrexone, a meta-analysis of 14 short-term studies involving almost 2100 patients found that naltrexone significantly improved relapse rates compared with placebo[40] (Figure 2).

Biological variability may also affect response to naltrexone. For example, individuals who have a positive family history for alcoholism are more likely to respond to alcohol with an increase in plasma β-endorphin and probably with a corresponding increase in CNS opioids.[21]

Figure 2. Relapse Rates for Alcohol-Dependent Patients Treated With Oral Naltrexone or Placebo in 14 Studies[a]



[a]Data from Bouza et al.[40]
*p < .00001.

One might expect a more robust response to naltrexone in this subgroup than in a group that does not manifest an alcohol-induced surge in endogenous opioids. Since it is not possible to directly measure such biological differences in human subjects, the use of proxy measures is sometimes required. For example, special markers of biological vulnerability may include positive family history of alcoholism, early age at onset of drinking problems, and comorbid use of other drugs of abuse.[41] A recent study by Rubio et al.[41] looked at these variables in relation to naltrexone response. It was found that naltrexone was most beneficial in those patients with onset of alcohol abuse before age 25, family history of alcoholism, and history of abuse of other substances. One limitation of the study, however, was the lack of a double-blind design.

Naltrexone also appears to reduce craving for alcohol. One early study by Volpicelli et al.[17] treated 70 male alcoholics with naltrexone at 50 mg/day or placebo for 12 weeks. Subjects also received a relatively intensive psychosocial intervention during the early at-risk-for-relapse period. Naltrexone-treated subjects showed a reduced relapse rate, lower overall number of drinking days, and reduced craving, in comparison with the placebo group. However, the intensity of the psychosocial intervention may have aided in medication compliance.[2] In an attempt to clarify this issue, Anton et al.[2] conducted a randomized, double-blind, 12-week trial of naltrexone or placebo, added to CBT, in alcoholic outpatients. Consistent with earlier data, naltrexone-treated subjects had fewer drinking days and fewer drinks per drinking day, and took longer to relapse than did those not treated with the drug. The authors hypothesized that "naltrexone increases control over alcohol urges and improves cognitive resistance to thoughts about drinking."[2(p1758)]

The comparative efficacy of disulfiram versus naltrexone was investigated by De Sousa and De Sousa[18] in 100 alcoholic men undergoing detoxification in an Indian psychiatric hospital. Subjects were randomly allocated to a year of treatment with either naltrexone or disulfiram and were accompanied to appointments by a family member. Disulfiram was found superior to naltrexone in preventing relapse; specifically, relapse occurred at a mean of 119 days with disulfiram, versus 63 days with naltrexone (p = .020). Moreover, 86% of patients remained abstinent throughout the study with disulfiram, compared with 44% with naltrexone (p = .0009). However, naltrexone-treated patients had significantly lower craving than those treated with disulfiram, as might be predicted from naltrexone's mechanism of action. This study is limited by the fact that it was open and the investigators were not blinded, which may have introduced bias.

Safety/tolerability. In general, naltrexone produces a relatively mild side effect profile, usually characterized by nausea (14%), headache (15%), dizziness (12%), or asthenia (10%), according to a recent meta-analysis by Bouza et al.[40] Hepatotoxicity may occur in doses higher than those recommended for alcohol dependence.[32,42] Reversible, transient elevations in liver enzymes have been observed,[43] but liver enzymes may actually decline with time in alcoholics treated with naltrexone.[32] Nevertheless, routine monitoring of liver functions is recommended, and signs of hepatotoxicity warrant discontinuation of the drug.[32] Precipitation of opioid withdrawal is a risk if naltrexone is administered to alcoholic patients who are covertly using opioids; however, the likelihood of this risk may be reduced by means of a pretreatment urine screen.[32]

Clinical use. Orally administered naltrexone may be more useful in programs aimed at reducing alcohol consumption than in achieving outright abstinence.[40,44] Before treatment with naltrexone, a urine drug screen is recommended for the detection of covert opioid use. Patients are generally started on a dose of 25 mg naltrexone per day, in order to minimize early complaints of nausea and

headache. Although the usual therapeutic dose is 50 mg/day, some clinicians prescribe doses as high as 150 to 200 mg/day in treatment-resistant cases.[32]

Rates of adherence with naltrexone range from 40% to 87%, and high degrees of nonadherence are said to limit naltrexone's effectiveness in clinical practice.[37,40] However, in the Anton et al.[2] study, only 1 of 68 naltrexone-treated patients dropped out because of a stated adverse effect of naltrexone. Another study found that poor adherence with naltrexone was associated with high scores on the Obsessive Compulsive Drinking Scale.[45] However, the participation of a concerned family member and compliance-enhancing programs aimed at ensuring daily use of the drug may improve adherence to naltrexone treatment.[45]

Despite the apparent benefits of naltrexone treatment of persons with alcohol dependence, a number of problems contribute to its suboptimal use, including physicians' reluctance to prescribe it,[47,48] poor patient adherence to treatment,[37,45,48] and financial burden,[47,49] especially if there is a lack of coverage by third-party payors and other providers. According to the 2001 MarketScan database, which contained standardized claims from 37 providers covering 3.7 million covered lives, including Blue Cross and Blue Shield, preferred provider organizations, health maintenance organizations, and point-of-service plans (both capitated and noncapitated plans), the rate of disulfiram use was 22 per 100,000 persons, and the rate of naltrexone use was 19 per 100,000.[50] Similarly, according to a Medicaid database (representing about 5 million covered lives at any given time), the rate of disulfiram use was 21 per 100,000 persons, and the rate of naltrexone use was 7 per 100,000.[50] In both cases, the rate of naltrexone use is considered very low.[46,50] Long-acting formulations of naltrexone have been studied and may improve adherence to treatment. This topic is covered in more detail in this supplement in "Improving Medication Adherence in Alcohol Dependence" by Helen M. Pettinati, Ph.D.,[39] and "New Therapeutic Options for Alcohol Dependence: Long-Acting Intramuscular Formulations of Naltrexone" by James C. Garbutt, M.D.[15]

Acamprosate

Mechanism of action. Acamprosate is a synthetic drug (calcium acetylhomotaurinate) approved for treating alcohol dependence. Acamprosate is a derivative of the amino acid taurine and shows structural similarity to GABA.[40] Its precise mechanism of action in alcoholism, however, is not known.[51] In animal models, acamprosate appears to be devoid of hypnotic, anxiolytic, or muscle-relaxant properties that characterize barbiturates or benzodiazepines.[51] It has been hypothesized that acamprosate modulates glutamate activity by acting at *N*-methyl-D-aspartate (NMDA) and mGluR5 receptors and thus affects the balance of glutamate and GABA in the brain.[23] Specifically, acamprosate may normalize the dysregulation of NMDA- and mGluR5-mediated glutamatergic neurotransmission thought to occur during chronic alcohol consumption and withdrawal. By modulating the ratio of glutamatergic to GABAergic transmission, acamprosate may attenuate one mechanism underlying alcoholic relapse and cue-induced craving[23,32] and may also offer a mechanism of action that complements that of naltrexone.[10]

Efficacy. Mason[10,52] has comprehensively reviewed efficacy studies of acamprosate that comprise about 4500 outpatients from 14 countries. In most of the 18 studies reviewed, patients received the psychosocial intervention typical of their treatment setting. Most patients had been recently detoxified with at least 5 days of abstinence at entry into treatment, which ranged from 2 to 12 months in duration. Total abstinence was the principal efficacy measure in most studies. The results of these studies generally show a significant advantage for acamprosate (vs. placebo), with respect to the rate of total abstinence and cumulative abstinence duration.[10,52] Figure 3 summarizes the rates of complete abstinence derived from selected European studies.[52] Importantly, a number of these studies also found that acamprosate efficacy was maintained for up to 12 months posttreatment, relative to placebo.[10,52]

Sass et al.[51] provided one of the best-designed analyses of acamprosate in a 1-year, randomized, double-blind, placebo-controlled study of 272 alcohol-dependent patients who had been through short-term detoxification. Patients received routine counseling and either acamprosate or placebo for 48 weeks and then were followed for another 48 weeks, without acamprosate. Acamprosate-treated patients showed a significantly higher continuous abstinence rate during the first 60 days of treatment compared with placebo-treated patients (67% vs. 50%). After 1 year of treatment, 44.8% of acamprosate-treated patients never had a relapse, compared with 25.3% of placebo-treated patients ($p = .005$, in the intention-to-treat analysis). Dropout rates after 1 year were 41% in the active drug group versus 60% in the placebo group, and acamprosate was generally found to be safe and well tolerated. Among remaining patients, the difference in abstinence rates between the groups remained significant during the 48-week follow-up period.

Most recently, Mason and colleagues[53] published the first U.S. study evaluating acamprosate's efficacy. While most previous studies of acamprosate measured complete abstinence rates, this U.S. study of 601 patients used percentage of alcohol-free days as its primary outcome. This trial differed from most earlier studies because results showed there were no significant differences in the primary outcome between patients treated with placebo or with acamprosate. In a post hoc subgroup analysis of patients who had a goal of abstinence prior to treatment, those treated with acamprosate had a significantly higher percentage of alcohol-free days compared with patients

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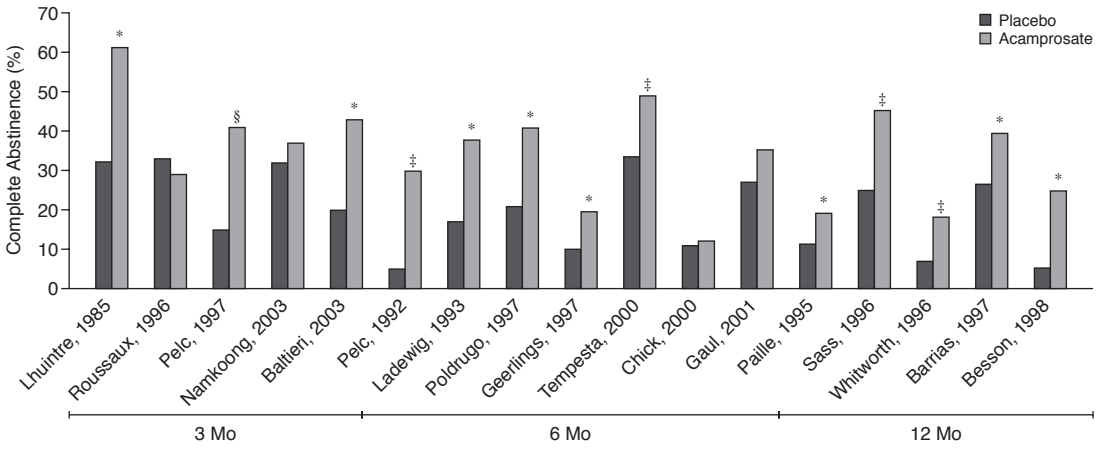
Figure 3. Abstinence Rates for Alcohol-Dependent Patients Treated With Acamprosate or Placebo in European Studies[a]



[a]Reprinted with permission from Mason.[52]
*p < .05.
‡p < .01.
§p < .001.

receiving placebo. The authors concluded that this finding suggests that motivated patients may be more likely to have a good outcome with acamprosate.

Safety/tolerability. The most common side effects seen with acamprosate are diarrhea and headache, although some patients report pruritus and rash.[32] Although statistical analysis of side effects was not provided in the Sass et al. study,[51] the number of reported side effects was similar in the acamprosate and placebo groups; diarrhea and headache were most commonly reported. No serious adverse drug reactions were reported by Kiefer et al.,[54] although combination treatment with naltrexone did seem to produce higher rates of diarrhea and nausea than did either agent alone (see below). Current prescribing information[14] also lists asthenia, pain, anorexia, anxiety, depression, dizziness, insomnia, and paresthesias as "adverse reactions" from acamprosate, but there are no adverse pharmacokinetic drug interactions when the drug is combined with disulfiram. Combining acamprosate with naltrexone appears to increase acamprosate plasma levels without a decrease in tolerability.[10] Since acamprosate is cleared by the kidneys, the drug is contraindicated in patients with significant renal impairment.[32]

Clinical use. Clinical experience with acamprosate in the United States is limited, but based on experience to date, the recommended dose is two 333-mg tablets 3 times a day (1998 mg/day).[14] For patients with renal impairment (creatinine clearance < 30–50 mL/min), the dose is cut in half. In contrast, reduced hepatic function—often seen in alcoholic patients—should not substantially affect bioavailability or dosing of acamprosate, except in cases of frank hepatic failure.[32] In general, titrating the dosage is not necessary.[32] Acamprosate is recommended for use in patients who are already abstinent in order to maintain abstinence.[14] Since most studies have evaluated the drug in the context of cotreatment with psychosocial therapy, it is recommended that the latter be included in the patient's treatment program. It has also been suggested that patients who are not genetically predisposed to drinking or who slowly develop alcoholism[55] may demonstrate more benefit from acamprosate therapy.[56]

COMBINING MEDICATIONS: NALTREXONE AND ACAMPROSATE

The combining of medications with different mechanisms of action is now a common practice in many fields of medicine. The introduction of acamprosate, with a mechanism of action clearly different from that of naltrexone, raised the issue of whether combining acamprosate pharmacotherapy with naltrexone might produce an overall effect that would surpass the efficacy of either medication alone. In an initial pharmacotherapy trial that addressed this issue, Kiefer et al.[54] performed a randomized, double-blind, placebo-controlled study combining acamprosate and naltrexone in 160 patients with alcoholism, following detoxification. Patients received naltrexone (50 mg/day), acamprosate (1998 mg/day), naltrexone plus acamprosate (50 mg/day and 1998 mg/day, respectively), or placebo for 12 weeks. In addition, all patients received CBT group sessions for 12 weeks. Time to first drink, time to relapse, and cumulative abstinence time were the primary outcome measures. Regarding duration of abstinence, Mason[10] has noted that, in the Kiefer et al.[54] trial, patients who relapsed were removed from the study, which contributed to a high dropout rate (53.1%) and precluded

the traditional assessment of cumulative abstinence over the complete study duration. Naltrexone, acamprosate, and the combination regimen were all significantly more effective than placebo in the 3 measures, with naltrexone showing a tendency for a better outcome regarding time to first drink and time to relapse. Yet, whereas the combination regimen was effective, producing significantly lower relapse rates than placebo and acamprosate alone, the combination was not significantly superior to naltrexone alone. As discussed below, the recently published National Institute on Alcoholism and Alcohol Abuse COMBINE study (Combined pharmacotherapies and behavioral interventions for alcohol dependence)[43] also found that combining acamprosate with naltrexone did not produce any added benefit above that for naltrexone alone. The only side effects of the combination therapy that occurred more frequently than with either drug alone were diarrhea and nausea, but study withdrawals due to adverse effects were similar among the combination and single-drug treatment groups.

The COMBINE study[43] examined optimal combinations of pharmacotherapy (naltrexone, acamprosate, and the combination of the 2) and manualized psychosocial treatments (medical management alone vs. medical management plus moderate-intensity specialty alcohol dependence therapy) over 16 weeks. Eight treatment groups received medical management (MM), and 4 of these received naltrexone (100 mg/day), acamprosate (3 g/day), both naltrexone and acamprosate, or placebo pills. The other 4 groups mirrored those just described, but in addition received specialized alcohol counseling, termed *combined behavioral intervention* (CBI). CBI therapy integrates CBT, MET, and techniques to enhance mutual-help group participation. A ninth group received CBI alone, without MM or pills.

Overall, the results show that patients did well regardless of group assignment, increasing abstinent days from 25.2% to 73.1%; however, there were differences among groups. Patients who received naltrexone (along with MM), specialized alcohol counseling, or both demonstrated the best drinking outcomes after 16 weeks of outpatient treatment. The group that received CBI only and without pills demonstrated the worst outcomes, suggesting that adding MM and medication (even placebo) to CBI improved the outcomes. Acamprosate did not show effectiveness, alone or in combination with naltrexone (combining acamprosate with naltrexone did not enhance outcome beyond that achieved for naltrexone alone).[43] The finding of a lack of efficacy for acamprosate was unexpected. In an accompanying editorial, Kranzler[57] suggested that lack of effect for acamprosate may be due to the overall level of improvement regardless of treatment group and the differences in experimental design from European studies in which acamprosate has been found to be effective. As in the study by Kiefer et al.,[54] combining medications was generally well tolerated; 4% of patients taking the combined regimen withdrew from the study due to adverse events, but this rate was comparable to withdrawal rates for acamprosate (3%) and naltrexone (4%) alone.[43]

CONCLUSION

The pharmacotherapy of alcohol dependence may be entering a new age, as clinicians become increasingly sophisticated at combining optimal pharmacologic and psychosocial treatments. Nevertheless, the precise role each component of treatment plays in enhancing abstinence is still being clarified, and we have, as yet, no reliable way of matching a particular patient with the optimal treatment regimen. Disulfiram, naltrexone, and acamprosate have advantages and disadvantages. The introduction of newer medications, such as acamprosate, has not displaced use of either disulfiram or oral naltrexone. Rather, all 3 are being used by clinicians to treat alcohol dependence, and newer medications and formulations will add to the treatment options available. Thus far, however, combining acamprosate with naltrexone has not proven effective. Use of pharmacotherapy for treatment of alcohol dependence by physicians in contact with persons with alcohol use disorders is suboptimal. Once pharmacotherapy is instituted, an important challenge facing clinicians is to improve adherence to pharmacotherapy. In addition to encouraging family involvement in treatment, we need to explore the use of specific interventions aimed at improving adherence. Psychiatrists have the opportunity to play a leading role in the development of models for pharmacotherapeutic treatment matching, as well as the development of interventions that target treatment adherence.

Drug names: acamprosate (Campral), disulfiram (Antabuse), naltrexone (ReVia, Vivitrol, and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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