# Pharmacologic Approaches to the Management of Alcoholism

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Our understanding of alcohol craving, both as a cause for chronic abuse and relapse and as a target for intervention, has been refined significantly in recent years. For example, craving experienced during alcohol withdrawal may be mediated by γ-aminobutyric acid (GABA) and glutamate receptor mechanisms, whereas the memory of the rewarding aspects of alcohol may be mediated by dopamine, opiate, and glutamate systems. Therefore, pharmacologic treatments for alcohol dependence may be targeted to numerous pathways. This article will discuss animal and clinical studies of the opioid antagonists (primarily naltrexone), acamprosate, and disulfiram. The side effects and treatment recommendations for each drug will also be reviewed. *(J Clin Psychiatry 2001;62[suppl 20]:11–17)*



The search for a substance that could reduce alcohol craving has been a long one. A century ago, well before the era of the controlled clinical study, the *Merck Manual* recommended cocaine to "remove the craving" for alcohol and spirit of ammonia as a "substitute for alcohol . . . to be taken when the craving comes on."[1] The 1899 manual further suggested that "one pint of water, drunk as hot as possible, an hour before meals will remove craving." How many people suffered scalded tongues applying the last remedy is anybody's guess.

At the turn of this new century, we are decidedly more advanced. For instance, we now know that specific areas and systems in the brain are involved in drug reinforcement and that certain neurotransmitters are associated with alcohol effects.[2,3] Animal models have been developed to test the capacity of pharmacologic agents to reduce alcohol consumption, reinforcement, and perhaps craving.[4,5]

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Our understanding of alcohol craving, both as a cause for chronic abuse and relapse and as a target for intervention, has been refined significantly in recent years.[6] In essence, craving describes a state of the brain, created by years of heavy alcohol use, that undermines "free will" and motivates alcoholics to continue to use alcohol despite irrefutable evidence of harm to themselves or the people close to them. Alcohol withdrawal appears to be an important condition for early craving, whereas the heightened and inappropriate memory of alcohol's rewarding effects is a more salient feature of craving during later periods of sobriety. In addition, people who habitually drink to reduce stress or to manage depression or anxiety syndromes may experience alcohol craving during recovery when various stressors reappear.

We now believe that the phenomena experienced as craving have their roots in neurochemistry. For example, craving experienced during alcohol withdrawal may be mediated by γ-aminobutyric acid (GABA) and glutamate receptor mechanisms, whereas the memory of the rewarding aspects of alcohol may be mediated by dopamine, opiate, and glutamate systems. Stress-induced craving may be mediated by serotonin mechanisms working in concert with any of these mechanisms. Like inflammatory mechanisms, which involve many independent, but interconnected, cytokine pathways, alcoholism may have its basis in numerous neurochemical systems interacting to initiate, maintain, and cause relapse to alcohol use. Therefore, pharmacologic treatments for alcohol dependence may be targeted to numerous pathways (Table 1).

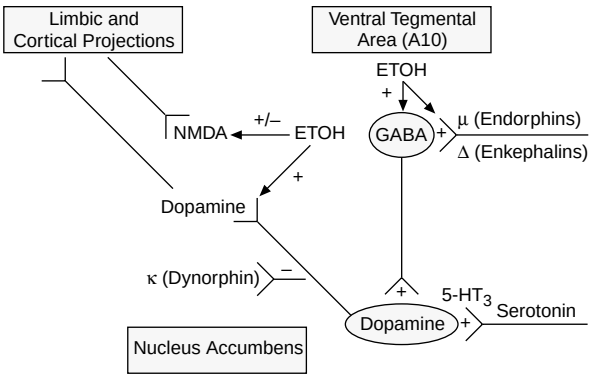
The dopamine system appears to be a particularly important target for the control of alcohol intake and craving. All drugs of abuse elevate dopamine concentrations in the nucleus accumbens; thus, it has been called the "reward center" of the brain.[7,8] Dopamine-producing cell bodies

Table 1. Pharmacologic Basis of Treatment of Alcoholism[a]

| Phenomenology | Neurochemistry | Pharmacology |
|---|---|---|
| Reward | Dopamine ($D_1$) | Preclinical |
| | Opiate | Naltrexone/nalmefene |
| | 5-$HT_3$ | Ondansetron |
| | Glutamate? | Acamprosate |
| Protracted withdrawal | Glutamate | Acamprosate |
| | GABA | Valproate/carbamazepine, preclinical gabapentin |
| | CRF? | CRF antagonists? |
| Affective/ impulsive | 5-$HT_2$ | SSRIs |
| | 5-$HT_{1A}$ | |
| | 5-$HT_{1B}$ | Buspirone |

[a]Abbreviations: CRF = corticotropin-releasing factor, GABA = γ-aminobutyric acid, SSRI = selective serotonin reuptake inhibitor.

Figure 1. Brain Reward System: Alcohol Effects[a]




[a]Abbreviations: ETOH = alcohol, GABA = γ-aminobutyric acid, NMDA = *N*-methyl-D-aspartate.

in the ventral tegmental area (VTA) of the brain stem connect with the nucleus accumbens in the ventral midbrain, which in turn connects to the limbic system through the amygdala and to the cortex in the dorsolateral prefrontal area as depicted in Figure 1. Animals will work to inject alcohol directly into the VTA and nucleus accumbens, where it will cause a release of dopamine. It is therefore hypothesized that pharmacologic compounds that interfere with dopamine release will reduce alcohol intake and craving in humans.

While a number of pharmaceutical agents have been found to diminish alcohol intake in animal studies, only a few have proved efficacious in the clinic. This review will focus on several of the more promising pharmacotherapies for alcoholism, including the opiate antagonists (primarily naltrexone) and acamprosate, a drug thought to work primarily on glutamate receptors. Disulfiram will also be discussed since, for many years, it was the only medication approved by the U.S. Food and Drug Administration (FDA) for use in alcoholism.

## OPIATE ANTAGONISTS (NALTREXONE AND NALMEFENE)

### Animal Studies

The efficacy of naltrexone, an opiate antagonist drug, has been supported by a number of preclinical studies. For instance, animal studies have shown that opiate antagonists block alcohol-induced dopamine release in the nucleus accumbens.[9] Furthermore, these compounds reduce both free alcohol consumption (preference) and reinforced responding (pressing a bar for alcohol) in mice, rats, and monkeys.[10–14] The latter effect is particularly important since it implies that opiate antagonists reduce the motivation (attraction) to use alcohol in animals, who are literally "voting with their feet" in pressing a bar for alcohol reward. This effect is particularly apparent in a new animal model of relapse drinking, the "alcohol deprivation effect."[5] In this model, rodents are made dependent on alcohol so that they will press a bar frequently to receive sips of alcohol. Bar-pressing becomes more frequent when alcohol is removed for a few weeks and then given back. However, naltrexone given prior to the return of alcohol diminishes this deprivation effect, suggesting that relapse could also be prevented in humans.

### Human Laboratory Studies

The effects of naltrexone have been studied only recently in humans, both in laboratory and in clinical settings. In controlled laboratory or natural observation settings (bars), naltrexone has been evaluated for its effects on alcohol-induced stimulation and craving, as well as on consumption. Naltrexone has been shown to reduce alcohol stimulation effect,[15,16] reduce the number of alcoholics who have alcohol[17] or cue-induced[18] craving, break the link between positive expectancies and stimulation to alcohol cues,[19] and increase the time to drink in a natural bar setting.[20]

### Clinical Trials

While much of the data support naltrexone's efficacy in clinics, only direct trials in alcoholics can demonstrate its utility. In 1992, studies published by the University of Pennsylvania[21] and Yale University[22] groups suggested that naltrexone could reduce relapse to heavy drinking in alcoholics. These trials, as well as other randomized controlled trials, are summarized in Table 2. To date, most of the trials have involved relatively few subjects, and none has included multiple sites. After an open-label safety study was completed, the FDA approved naltrexone in 1996 for preventing relapse in alcohol-dependent individuals.[26] Although the published controlled trials used similar outcome variables and generally excluded patients with other substance abuse or psychiatric comorbidity, they recruited alcoholics with dissimilar severity of illness. In the studies from University of Pennsylvania,[21,23] for example, most of the subjects underwent medical de-

**Table 2. Published Placebo-Controlled Naltrexone Studies[a]**

| Study | N | Degree of Illness | Therapy | Relapse | % of Days Abstinent | Drinks Per Day of Drinking | Craving |
|---|---|---|---|---|---|---|---|
| Volpicelli et al[21] | 70 | Severe; most underwent detoxification | Intensive multimodal | + | + | ? | + |
| O'Malley et al[22] | 97 | Moderate | Coping skills or supportive | + | + | + | +/– |
| Volpicelli et al[23] | 97[b] | Moderate–severe; most underwent detoxification | Relapse prevention | + | + | ? | – |
| Anton et al[24] | 131 | Moderate | CBT | + | + | + | +/– |
| Kranzler et al[25c] | 124 | Moderate | Coping skills | – | – | ? | – |

[a]Abbreviation: CBT = cognitive-behavioral therapy. Symbols: + = statistically significant effect favoring naltrexone, – = naltrexone did not show efficacy compared with placebo, ? = not measured or not reported.
[b]Results given for compliant patients only.
[c]Study was a 3-group design comparing naltrexone with nefazodone and placebo. The N given is for naltrexone and placebo groups only.

**Table 3. Other Placebo-Controlled Naltrexone Studies[a]**

| Study | N | Degree of Illness | Therapy | Relapse | % of Days Abstinent | Drinks Per Day of Drinking | Craving |
|---|---|---|---|---|---|---|---|
| United Kingdom multisite[27b] | 175 | Severe | Not specified | +/– | + | +/– | + |
| Sweden multisite[28b] | 118 | Moderate | Supportive | – | – | – | – |
| | | | CBT | +/– | – | + | + |
| Australia multisite[29] | 111 | Moderate–severe, with comorbidity | Group relapse prevention | + | – | + | ? |
| Finland[30b] | 121 | Mild–moderate | Supportive | – | ? | ? | ? |
| | | | CBT | + | ? | ? | ? |

[a]Abbreviation: CBT = cognitive-behavioral therapy. Symbols: + = effect favoring naltrexone, – = naltrexone did not show efficacy compared with placebo, ? = not measured or not reported.
[b]Indicates 6-month studies.



toxification prior to starting treatment, whereas the studies conducted at Yale University[22] and at our site (The Medical University of South Carolina)[24] recruited less severely affected outpatients who generally did not require medical detoxification. All published studies except one[25] found positive effects of naltrexone over placebo. The positive studies[21–24] found that naltrexone prolonged the time to first relapse day (5 or more drinks for men and 4 or more for women), particularly when combined with relapse prevention or cognitive-behavioral therapy (CBT). O'Malley and colleagues[22] also reported that naltrexone combined with an abstinence-based therapy increased the time to first drink (total abstinence). All of the positive studies, including the one conducted by my colleagues and me,[24] found that naltrexone increased the percentage of days during the trial in which full abstinence was present. Therefore, the weight of the evidence suggests that naltrexone not only reduces risk for relapse but also promotes abstinence. The only published negative trial[25] compared naltrexone with both nefazodone and placebo, and as such it was a more complicated study design with more doses taken per day. In contrast to findings in the other studies, the negative study found that side effects in the naltrexone group were quite high, leading to noncompliance. The reason for this discrepancy with other published studies is unclear.

Multisite randomized controlled trials with naltrexone conducted in other countries have been presented at international meetings in the past few years.[27–30] For the sake of completeness, these are summarized in Table 3. However, it must be noted that most of these studies have not been published at this time. Since these are multisite studies, their sample sizes are noticeably larger. Two of the trials[28,30] used manual-guided psychotherapy approaches. The United Kingdom trial[27] did not specify any psychosocial intervention, and the Australian trial[29] utilized group relapse prevention. It is evident that the results generally favor naltrexone efficacy; however, the Swedish[28] and Finnish[30] trials also utilized CBT. The Australian trial is of interest because it included alcoholics with comorbid psychiatric disorders and reported that naltrexone, in combination with group relapse-prevention therapy, was more effective than placebo in this difficult patient group.[29]

Nalmefene, another opiate antagonist medication with similar properties to naltrexone, also has been reported to reduce relapse and improve outcome in combination with CBT.[31] A multisite trial is currently underway to confirm and extend these initial promising results.

## Craving

Although naltrexone has been called an "anticraving" compound, the data supporting the distinction between this

type of compound and compounds that target other factors in alcohol abuse, such as withdrawal or impulsive behavior, are not consistent (see Tables 2 and 3). Using a single-item analog scale, Volpicelli and colleagues[21] initially reported that naltrexone reduced craving, but this was not confirmed in their subsequent study.[23] O'Malley and colleagues[22] also measured craving by a single-item analog scale and reported that it was reduced in the group receiving CBT and that higher craving was a predictor of naltrexone response.

Using the multi-item Obsessive Compulsive Drinking Scale (OCDS) questionnaire, Anton and colleagues[24] found that naltrexone reduced thoughts of drinking as well as the compulsive urge to consume alcohol. A subscale of the OCDS, the "resistance-control impairment factor," was more favorably affected by naltrexone than placebo when these treatments were combined with CBT.[32] The studies in the United Kingdom[27] and Sweden[28] also observed a positive effect in this OCDS aspect of craving. However, the Swedish study found this effect only in the group also receiving CBT. Since craving and alcohol consumption are intertwined, it is usually difficult to determine which appeared first. Analyses by my colleagues and me[32] as well as clinical laboratory studies[18] indicate that increases in craving precede alcohol consumption and that naltrexone reduces craving independent of alcohol drinking. Thus, while some data, as well as anecdotal reports, suggest that naltrexone reduces alcohol craving, further investigation is needed.

## Side Effects

Single-site studies indicate that nausea, abdominal pain, and headaches are the main side effects to emerge with naltrexone treatment in comparison to placebo.[22,24] Information from these trials suggests that women are more sensitive than men to the gastrointestinal effects of naltrexone. In a large multisite usage study,[26] nausea (9.8% of individuals) and headache (6.6% of individuals) were the most common side effects reported by subjects taking naltrexone; 15% of all patients discontinued, most frequently due to nausea. Of interest, naltrexone was well tolerated when taken with a variety of other medications. Although liver function tended initially to decrease slightly, enzyme levels generally normalized during treatment, most likely reflecting decreased alcohol consumption. To reduce the incidence of side effects, it has been recommended that naltrexone be started at a lower dose of 25 mg/day for several days before increasing to 50 mg/day, the maintenance dose. In addition, a few days of alcohol abstinence should be achieved prior to taking naltrexone in order to minimize the interaction between gastrointestinal side effects and alcohol withdrawal symptoms.

One caution should be noted in the use of naltrexone: since it is an opiate antagonist, individuals abusing opiates or taking them for medical indications will either go into opiate withdrawal or find the opiates ineffective during naltrexone treatment. Therefore, a complete history of opiate ingestion and a urine drug screen are indicated. In addition, if acute opiate analgesia is required during the course of treatment, caution should be taken. Higher doses of opiates may be required, and signs of respiratory distress should be monitored. Patients taking naltrexone should carry a card explaining these issues and provide it to health care personnel in an emergency situation.

## Indications

Researchers and practicing clinicians, in conjunction with the United States Substance Abuse and Mental Health Administration, have established guidelines for naltrexone usage.[33] This panel of experts recommended the following naltrexone treatment eligibility guidelines:

- Individuals who have been diagnosed as alcohol dependent, are medically stable, and are not currently (or recently) using opioids
- Individuals who are willing to be in a supportive relationship with a health care provider or support group to enhance treatment compliance and work toward a common goal of sobriety
- Individuals with an interest and willingness to take naltrexone

The following individuals are not suitable for inclusion: individuals with acute hepatitis or liver failure, patients requiring narcotic analgesia, pregnant or nursing women, and, possibly, the very obese.

The last item was included because an earlier report indicated that morbidly obese individuals treated with very high doses (300 mg/day) of naltrexone developed liver toxicity. However, an improvement of liver function has been generally observed in the published clinical trials and in the multisite usage study.[26]

## Length of Treatment

Clinicians and patients all pose the following question: "How long should treatment with naltrexone be continued?" The answer lies in empirical data from well-designed studies. Follow-up data from several of the trials indicate that, for some individuals, naltrexone treatment should be continued after the initial 12 weeks of treatment.[34,35] For instance, O'Malley and colleagues[34] reported that subjects who were improved at the end of the active treatment relapsed at the same rate as placebo-treated subjects, 6 months after treatment. Anton and colleagues[35] found that 4 months after the end of active treatment, the rate of heavy drinking days increased, resulting in similar relapse rates between the naltrexone and placebo groups. Observational data by these investigators suggest that lack of complete abstinence predicts which individuals need continuous naltrexone treatment, yet further studies are necessary to guide clinicians in this regard. Several ongoing and soon-to-be

completed trials are specifically designed to address the issue of length of treatment.

## ACAMPROSATE

### Pharmacology and Animal Studies

Acamprosate (calcium homotaurinate) is a derivative of the naturally occurring amino acid taurine. The compound was found to block alcohol consumption in animals,[36] and its subsequent development proceeded without much knowledge of its basic neuropharmacology. However, data collected more recently suggest that its main effect is on glutamate receptors in the brain, with lesser effects on GABA receptors.[37–39] Of interest, acamprosate seems to modulate transmission of glutamate,[40,41] which has been implicated in chronic alcohol effects[42] and in substance abuse sensitization.[43] Theoretically, chronic alcohol use and dependence may be mediated in part by adaptations in both glutamate receptors and glutaminergic transmission. During chronic ingestion of alcohol, there appears to be a down-regulation of these receptors. After alcohol withdrawal, a glutaminergic deficiency state could underlie some aspects of craving for alcohol. Acamprosate has been reported to reduce alcohol consumption in rats with unlimited free access to alcohol[36] and also to decrease excessive alcohol consumption in the rat alcohol-deprivation relapse model.[44,45] There is also some suggestion that acamprosate may moderate acute alcohol withdrawal effects; however, the data are not robust.[46,47]

### Human Laboratory Studies

To date, there have been no clinical laboratory studies evaluating acamprosate and alcohol craving and consumption reported.

### Clinical Trials

Reviews of alcoholism pharmacotherapies have systematically evaluated the published acamprosate trials,[48,49] most of which were conducted in Europe, as summarized in Table 4.[49] In general, the European double-blind randomized controlled multisite trials used very conservative drinking outcome measures such as "time to first drink" and "total abstinent days." These published studies provide evidence that acamprosate increases the time to first drink and the number of abstinent days when compared with placebo treatments. Although craving was not uniformly assessed in many of the trials, one trial reported a decrease in craving attributable to acamprosate.[50] This is of interest since acamprosate, like naltrexone, is often termed an "anticraving drug." However, there is limited evidence of acamprosate's effects on craving at this time.

In contrast to the psychosocial therapies in the American trials with naltrexone, psychosocial therapies used in the European acamprosate trials were not standardized or thoroughly described. Generally, they appeared to be eclectic, supportive, medically based, and not manual guided, leading to several possible conclusions. First, if the studies had included structured and manual-driven therapy, the effects of acamprosate might have been magnified due to enhanced medication compliance. Next, since many different approaches were utilized, the effectiveness of acamprosate is likely to be generalizable to many different populations and treatment settings. For these reasons, it is not clear whether acamprosate would have improved efficacy over a well-delivered structured psychosocial intervention such as CBT or other relapse prevention/coping skills/motivation-enhancing therapies. A large National Institute on Alcohol Abuse and Alcoholism (NIAAA)–funded multisite trial, Combining Medications and Behavioral Interventions (COMBINE), is currently evaluating this issue.

Interestingly, the published acamprosate studies were generally longer than the American naltrexone trials, lasting 6 to 12 months. However, the effect on the time to first drink measure was seen in the first 3 months, similar to that observed in the naltrexone trials. Finally, it is unclear whether acamprosate should be given for prolonged periods of time.

**Table 4. Controlled Acamprosate Trials[a]**

| Study | Year | N | Duration (wk) | Abstinent Days | Time to First Drink | Craving |
|---|---|---|---|---|---|---|
| Ladewig et al | 1993 | 61 | 24 | + | ? | ? |
| Paille et al | 1995 | 538 | 52 | + | + | – |
| Sass et al | 1996 | 272 | 48 | + | + | – |
| Whitworth et al | 1996 | 448 | 52 | + | + | ? |
| Geerlings et al | 1997 | 262 | 24 | + | – | ? |
| Pelc et al | 1997 | 188 | 12 | + | + | + |
| Poldrugo et al | 1997 | 246 | 26 | + | + | – |

[a]Adapted from Garbutt et al.[49] Symbols: + = effect favoring acamprosate, – = acamprosate did not show efficacy compared with placebo, ? = not measured or not reported.

## DISULFIRAM

A review of the pharmacotherapy for alcoholism would be incomplete without a discussion of disulfiram. Although this medication has been available for clinical use for approximately 40 years, it has found varied clinical acceptance. It is common knowledge that disulfiram blocks the metabolism of acetaldehyde, itself a breakdown product of alcohol. After alcohol consumption, the accumulation of acetaldehyde leads to flushing of the skin, nausea, vomiting, and autonomic changes best described as unpleasant and dysphoric. This has led to disulfiram being classified as an "aversive agent." The drug is hepatically active and does not affect the underlying neurochemical basis of alcohol dependence or craving. Since it has little effect on craving, patients must have a strong level of self-motivation or external pressure to begin and maintain disulfiram treatment.

The large Veterans Administration Cooperative Study is the most definitive trial of disulfiram.[51] This trial concluded that disulfiram was not better than placebo, indicating that its overall use is limited. However, post hoc analysis suggested that older, more severely affected men, with good motivation, may benefit from disulfiram treatment. Other controlled studies have indicated that disulfiram is useful when patients are carefully monitored.[52] One study suggested that concomitant disulfiram and acamprosate treatment increases the number of abstinent days in comparison to when the drugs are used alone.[53] It is intriguing that a neuroactive drug that potentially reduces craving may motivate individuals to ingest an aversive agent to bolster cognitive restraint during high-risk drinking periods, yet this possibility requires further study.

## COMMENTARY

It is clear that the discovery of medications for the treatment of alcoholism is accelerating. More targeted therapies will be developed as we increase our knowledge of the basic neurochemistry of alcohol addiction. It is likely that combinations of medications may be more beneficial than single medications, at least for some alcoholics. In addition, it is still not clear whether more frequent and complex psychosocial interventions are interactive or additive to pharmacotherapy. Some of these issues are being addressed in the COMBINE study. Furthermore, the most appropriate pharmacotherapy for individuals with alcoholism comorbid with other psychiatric conditions (such as depression and/or various anxiety disorders) still needs to be clarified. Other ongoing or recently finished clinical trials (including a large multisite trial of depressed alcoholics) will also provide additional guidance in this regard (also see the articles in this supplement by Pettinati[54] and Thase et al.[55]).

The matching of alcoholic subtypes to various pharmacotherapies and/or psychosocial approaches is still in its infancy.[56] Data on matching, including possible genetic predictors of response (pharmacogenomics), will lead to improved therapeutics. This information, combined with advances in pharmacotherapeutics, will most likely improve the treatment of alcohol dependence.

*Drug names:* carbamazepine (Tegretol and others), disulfiram (Antabuse), gabapentin (Neurontin), nalmefene (Revex), naltrexone (ReVia), ondansetron (Zofran).

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