# Incorporating Alcohol Pharmacotherapies Into Medical Practice: A Review of the Literature*

*Treatment Improvement Protocol (TIP) Series*

# 49

## Contents



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# Contents

# Section 1—A Review of the Literature

## Overview

This literature review is part of the Substance Abuse and Mental Health Services Administration's (SAMHSA's) Treatment Improvement Protocol (TIP) 49, *Incorporating Alcohol Pharmacotherapies Into Medical Practice*. Developed by a panel of experts for SAMHSA's Center for Substance Abuse Treatment (CSAT), the TIP can assist physicians and other medical professionals in providing pharmacologic treatment, combined with psychosocial therapy, for patients who are alcohol dependent, both in primary care settings and in specialized substance abuse treatment settings.

TIP 49 focuses on the best currently recognized clinical practices for the medical maintenance of patients with alcohol use disorders (AUDs), using the four medications (disulfiram, oral naltrexone, injectable naltrexone, and acamprosate) approved by the U.S. Food and Drug Administration (FDA) for this purpose. The TIP presents best practices according to the scientific literature and the clinical experts who developed the TIP. This literature review emphasizes recent research published from 2000 to 2007 but also includes classic research studies published before 2000.

## Introduction

Recently, much new scientific knowledge has emerged concerning how pharmacotherapy can treat individuals who are alcohol dependent. Physicians can prescribe four FDA-approved medications to dampen craving, reduce heavy drinking, or promote abstinence. These medications have a mild to moderate effect and do not work for all individuals, but this first wave of effective, evidence-based medication treatments for alcoholism is at the forefront of a Government push to develop even more powerful medications. Research on pharmacotherapies for alcohol dependence is a top priority of the National Institutes of Health, which funds 68 grants totaling more than $26 million annually on medications that target the multiple neurotransmitter systems implicated in alcohol addiction (Johnson et al., 2005). Several promising drugs are in development, supported by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

For years, medications have been used primarily as an adjunct to psychosocial treatment in specialized treatment settings. With newer medications now available (naltrexone and acamprosate), interest is increasing in whether primary care physicians in routine medical practice can successfully treat with FDA-approved medications individuals who are alcohol dependent. Recent research indicates that such treatment by mainstream medical practitioners appears promising. Project COMBINE (Combining Medications and Behavioral Interventions), a recent comprehensive, well-designed NIAAA clinical trial, was carried out at 11 academic sites in the United States with nearly 1,400 patients with alcohol dependence; this project explored a variety of treatment methods—alone and in combination—in the context of low-intensity medical management (Anton et al., 2006). Alcohol consumption decreased by 80 percent over a 4-month treatment period, which suggests that medical management by primary physicians in routine practice can be a benefit in treating AUDs (Kranzler, 2006).

Emerging developments in the pharmacologic treatment of AUDs offer a significant opportunity for physicians to integrate the management of substance use disorders into primary health care. Practitioners in medical settings can add pharmacotherapies to their interventions with patients who drink heavily or are dependent on alcohol. This literature review provides resources for practitioners. Using medications to treat AUDs concerns practitioners for the following reasons:

- Up to one-half of patients with AUDs relapse shortly after detoxification and psychosocial or behavioral treatment (Johnson & Ait-Daoud, 2000). Research shows that existing approved pharmacotherapies reduce craving and help from 20 to 50 percent of patients reduce their heavy drinking and promote abstinence. When combined with primary care and psychosocial therapy, medications can effectively help many patients reduce their substance use or attain abstinence.
- Only 3 to 13 percent of patients in treatment receive naltrexone (Mark et al., 2003a). Pharmacologic treatment is grossly underused because few physicians know about these medications—or about the research showing their efficacy. The information in this literature review can assist mainstream physicians in learning about the efficacy of medications and may promote the medications' effective use in patients who could benefit from pharmacotherapy.

Practitioners should note that patients need some level of psychosocial intervention in addition to pharmacotherapy—a consistent finding across both European and U.S. research.

## Recent Pharmacological Advances

Advances in the neurobiology of addiction and improved methodology for clinical trials have recently increased the state of knowledge about pharmacotherapies for addiction. Every 3 years, the Mesa Grande project reviews clinical trials on a variety of approaches for treating AUDs. In the 2002 update, this project added 59 new controlled trials. Based on clinical trials, this review lists the most effective treatment approaches. In 2002, for the first time, two pharmacologic therapies appeared on this list. Therapies with acamprosate and naltrexone were rated third and fourth in effectiveness among 46 treatment modalities that had 3 or more studies; these pharmacotherapies were rated behind only brief intervention and motivational enhancement, which were rated first and second (Miller & Wilbourne, 2002).

The effectiveness of the new medications reflects the findings from preclinical studies, which have exploded our knowledge about the behavioral and biological underpinnings of alcoholism (Johnson & Ait-Daoud, 2000). There have been numerous advances during the past two decades in understanding the mechanisms underlying substance dependence disorders. It is now known that alcohol-seeking behavior and drinking are influenced by multiple neurotransmitter systems, as well as by neuromodulators, hormones, and various intercellular networks (Litten, Fertig, Mattson, & Egli, 2005). The multiple neurotransmitter systems implicated in addiction include dopamine, serotonin, gamma-aminobutyric acid (GABA), glutamate, and opiate systems. This means that researchers, in focusing on the biological systems underlying the disease, now have multiple potential targets for developing medications to treat substance dependence. Some promising directions of current research include the following:

- Applying pharmacogenetic techniques to the field of addiction. Some patients may possess a biological predisposition to the disease. These biologically vulnerable people may benefit from specific medications targeted toward ameliorating or correcting the underlying abnormalities.
- Learning about which subgroups of people may respond most positively to particular medications.
- Determining optimal dosage ranges and combinations of treatments—both combinations of medications and types and levels of psychosocial treatment—most likely to benefit particular groups based on their different biologies. Because medications are aimed at different neurotransmitter targets associated with addiction, combinations of pharmacological agents may have a synergistic effect.

Over the last decade, pharmaceutical companies have invested significant resources in studying and developing new formulations (Kenna, McGeary, & Swift, 2004b). In 1994, naltrexone became available for AUD treatment in the United States, and acamprosate became available in 2004. In addition, extended-release injectable naltrexone was approved by FDA on April 13, 2006, and became commercially available on June 13, 2006. Several review articles summarize the pharmacotherapy underlying these new medications and future therapies (Johnson & Ait-Daoud, 2000; Kenna, McGeary, & Swift, 2004a, 2004b; Kreek, LaForge, & Butelman, 2002; Mann, 2004; Myrick & Anton, 2004).

## Updated Findings From the Literature, October 2007

This online pharmacotherapy literature review, which covers articles published between 2000 and April 2007, is updated at 6-month intervals. This section describes findings from the latest update and primarily covers materials published from May through October 2007. This update identified 7 additional articles on alcohol pharmacotherapy published in 2006, as well as 37 new research articles published in 2007. Many of these articles make a significant contribution to existing knowledge. Three predominant themes are evident in this latest update of the literature:

1. The search found an unusually large number of comprehensive reviews on the current state of knowledge regarding pharmacotherapy for AUDs. The purpose of many of these reviews is to educate primary care physicians about current pharmacotherapies and to stimulate their interest in treating patients with AUDs. A recent editorial in *JAMA* reflects this effort to convince psychiatrists and other physicians to add medications for alcohol dependence to their continuum of care (Willenbring, 2007).
2. Several articles reflect the effort to fill in gaps in existing research knowledge—especially to cast light on which subgroups of patients will benefit most from which combinations of therapies. Some of these articles present a secondary analysis of data from large randomized controlled studies, in which the new analysis shows medication effectiveness with specific subgroups of patients in the trials.
3. The latest literature also demonstrates the ongoing surge in the number of clinical trials aimed at testing promising new pharmacotherapies for the treatment of alcohol dependence, as well as refining the use of current medications.

Much work is still needed to identify which subtypes of individuals with alcohol dependence will benefit most from a particular type of medication. Furthermore, the subtype response to a particular medication may also depend on the stage of illness at which such a person enters treatment (Ait-Daoud, Malcolm, & Johnson, 2006).

**Typologies of individuals with alcohol dependence.** One approach used by researchers to improve medication efficacy is to identify alcohol-dependent subtypes who may respond preferentially to a particular medication. Although a standardized typology has not been established, two frequently used typologies are (1) early- versus late-onset alcohol dependence and (2) Type A versus Type B groupings. The Type B alcohol-dependent subgroup, as characterized by Babor and colleagues (1992), includes an early age of onset of alcohol problems, high severity of dependence, polydrug use, a high degree of concomitant psychopathology, and a poor prognosis after alcohol treatment. In contrast, Type A individuals with alcohol dependence can be characterized by a late onset of problem drinking and such features as few childhood risk factors, low severity of alcohol dependence, little drug use, few alcohol-related problems, little concomitant psychopathology, and a relatively promising prognosis with traditional alcohol treatment. The Type A group is highly heterogeneous and is therefore susceptible to further subdivisions based on other features.

**Genetic subtypes.** Another rich current area of research aims to identify genetic variants that may modify the effects of various medications in specific subgroups of people with alcohol dependence. The gene coding for the μ opiate receptor (i.e., OPRM1) gene is a current target of interest, primarily to identify a genetic marker for subgroups that are most likely to respond to naltrexone treatment.

### *New Review Articles on Pharmacotherapy for Alcohol Dependence*

The recent literature includes a number of review articles that may be helpful to practitioners. In "A Rational Approach to the Pharmacotherapy of Alcohol Dependence," Petrakis (2006) reviews the neurobiology of alcohol dependence and relates this understanding to how pharmacologic interventions can effectively address three important clinical stages in the development and maintenance of alcohol dependence. These three stages are (1) the transition between initiation of alcohol use and the start of heavy drinking, (2) the cessation of heavy drinking in individuals who want to quit, and (3) the prevention of relapse in individuals who have initiated abstinence but struggle with craving or the desire to resume alcohol use. Petrakis (2006) concludes that the best strategy in the pharmacotherapy of alcohol dependence ultimately may be based on the targeted use of medications that act on the various neurotransmitters associated with different stages of alcohol dependence.

A second overview article discusses the preclinical and clinical pharmacology of alcohol dependence, covering the most recent developments in alcohol pharmacology (Tambour & Quertemont, 2007). This article focuses on the neurobiological basis of medications for treating alcohol dependence, including promising drugs now in preliminary clinical studies.

In addition, four other reviews cover specific aspects of the pharmacotherapy of alcohol dependence. These articles include the following:

1. **A review of key studies on treating alcohol dependence published between 2005 and 2006,** particularly randomized controlled trials (Assanangkornchai & Srisurapanont, 2007). In terms of pharmacotherapies, the authors conclude that (1) recent studies show naltrexone has the most consistent effect in reducing alcohol consumption in the context of behavioral therapy and (2) topiramate is the only new medication on the horizon that has demonstrated effectiveness for treating alcohol dependence (Assanangkornchai & Srisurapanont, 2007).

2. **A summary and review of the clinical experiences reported in the literature on the four current FDA-approved medications for treating alcohol dependence**—disulfiram, naltrexone (oral and injectable forms), and acamprosate (Rosenthal, 2006). This article describes the clinical use and evidence of clinical efficacy for each medication and discusses more recent trends in combination therapies. Rosenthal (2006) also briefly discusses promising future pharmacotherapies for treating alcohol dependence, including serotonergic medications, anticonvulsants, and antipsychotics.
3. **A comprehensive review of the research on medication and psychosocial treatments for those dually diagnosed with a substance-related disorder and one of the following:** depression, anxiety disorder, schizophrenia, bipolar disorder, severe mental illness, or nonspecific mental illness (Tiet & Mausbach, 2007). The authors identified 59 studies, including 36 randomized controlled trials, and found existing treatments that effectively reduce substance use also decrease substance use in patients who are dually diagnosed. Tiet and Mausbach (2007) also concluded that research is urgently needed on the topic of alcohol dependence and co-occurring mental disorders, because the current status of the literature is so poor.
4. **A comprehensive review of research into drug pharmacotherapies, particularly single-drug therapies, for treating common dual substance abuse and dependence disorders** (Kenna, Nielsen, Mello, Schiesl, & Swift, 2007). This article covers the neurobiology and existing research on numerous approved and off-label medications for treating alcohol dependence combined with cocaine, nicotine, and opioid use disorders. The review finds strongest support for the use of disulfiram to treat co-occurring alcohol and cocaine dependence and for topiramate to treat co-occurring alcohol, nicotine, and cocaine dependence (Kenna et al., 2007).

### *New Findings on Disulfiram*

Two new studies report finding that disulfiram compares favorably in effectiveness with other pharmacotherapies for patients with alcohol dependence. Both studies involve subjects who were voluntarily seeking treatment.

#### *Medication combined with brief, manual-based intervention therapy*

Researchers in Finland have found disulfiram to be superior to both naltrexone and acamprosate in the first randomized comparison of disulfiram, naltrexone, and acamprosate with brief, manual-based intervention therapy (Laaksonen, Koski-Jännes, Salaspuro, Ahtinen, & Alho, 2007). This open-label, naturalistic trial, which took place at six different alcohol treatment and healthcare units, involved 243 Caucasian subjects who met the International Statistical Classification of Diseases and Related Health criteria for alcohol dependence; the subjects were voluntarily seeking treatment. Patients visited a physician at scheduled intervals during two phases that lasted 52 weeks; about 67 weeks after completing the study, patients were contacted for followup information—a total of 2.5 years after starting the study. This study experienced a low rate of dropout (25.1 percent after 12 weeks and 51.8 percent by the end of the 52-week study period).

During the Phase 1 continuous medication period (weeks 1–12), patients designated a contact person to be responsible for supervising and controlling their daily study medication. Patients were randomly assigned to receive (1) 50 mg of naltrexone once a day, (2) 666 mg of acamprosate 3 times a day or 1,333 mg/day for those weighing less than 60 kg, or (3) 100–200 mg of disulfiram once a day or 2 tablets (400 mg) twice a week. At

regular visits throughout the 52 weeks, patients brought in a diary of their alcohol consumption and medication intake and also used a manual with homework based on cognitive-behavioral principles. During the Phase 2 targeted medication period (weeks 13–52), patients were asked to take a daily medication dose in any "craving situation" when they perceived their propensity to drink was high. During this targeted medication phase, the study center no longer provided free medication.

The main conclusion of this study was that all three medications—disulfiram, naltrexone, and acamprosate, combined with brief manual-based intervention extended over time—significantly reduce heavy drinking, reduce craving for alcohol, and increase the quality of life. However, disulfiram was superior to the other medications, especially during the continuous medication period. The study data show that, during Phase 1, disulfiram was significantly better than naltrexone and acamprosate as follows:

- In time to first heavy drinking day—46.6±27.5 days for disulfiram versus 22.0±22.0 for naltrexone and 17.6±22.0 for acamprosate
- In time to first drink—30.4±27.8 days for disulfiram versus 16.2±20.2 for naltrexone and 11.4±17.0 for acamprosate
- In average weekly alcohol intake (g/ethanol per week)—52.0±90.7 for disulfiram versus 183.7±174.1 for naltrexone and 203.2±180.2 for acamprosate.

During Phase 2, the targeted medication period, there were no significant differences among the three medication groups on time to first heavy drinking day or in days to first drinking. Average alcohol consumption in all groups remained significantly below the baseline. However, those in the disulfiram group had significantly more abstinence days than those in the other two groups.

### *Medication for patients with co-occurring alcohol dependence and depression*

Petrakis and colleagues (2007) conducted a secondary analysis of 139 male veterans with alcohol dependence and current major depression, assessing the effectiveness of naltrexone and disulfiram in this population. As in their original large-scale study comparing naltrexone and disulfiram among 254 male veterans who had alcohol dependence and comorbid mental disorders (Petrakis et al., 2005), they found no advantage of one medication over the other. In comparison with outcomes found in the original study, a person's having a diagnosis of co-occurring depression had no significant effect on retention in treatment or on drinking outcomes, including maximum consecutive days of abstinence, percentage of heavy drinking days, or abstinence throughout the entire study period. Petrakis and colleagues (2007) concluded that both disulfiram and naltrexone are safe pharmacotherapeutic agents for treating alcohol dependence in dually diagnosed individuals with depression.

As in the original study, an unexpected finding was that patients with depression who received disulfiram reported lower craving over time than subjects with depression who received naltrexone (Petrakis et al., 2007). (For additional information on this study, see New Findings on Combined Medication Therapy below.)

## *New Findings on Oral Naltrexone*

### *Effects of patient compliance on outcomes*

Research suggests that the effectiveness of naltrexone in clinical trials—and probably also in clinical treatment—can be greatly influenced by the subjects' adherence to the medication. A new study reanalyzed data, expanding the variable drinking outcomes reviewed, from an alcohol treatment trial involving 160 participants (Anton et al., 2005). This reanalysis looked specifically at how much patient compliance with naltrexone influenced the outcomes and compared two methods for measuring compliance (Baros, Latham, Moak, Voronin, & Anton, 2007). The researchers conclude that, because patient adherence to naltrexone has such a large influence on treatment outcomes, practitioners need to give utmost attention to methods for enhancing their patients' compliance. The article also summarizes evidence from the literature on strategies to use for improving compliance (Baros et al., 2007).

This study evaluated outcomes for 137 randomized patients with alcohol dependence who completed 12 weeks of naltrexone or placebo, combined with either cognitive-behavioral therapy (CBT) or motivational enhancement therapy (MET). Compliance was monitored and compared using urine riboflavin measurements during study weeks 2, 6, and 12, as well as a medication event monitoring system (MEMS) that provided a detailed computerized record of when patients opened their medication bottles. Findings included the following:

- Accounting for adherence and compliance with naltrexone changed the outcomes (not significant in the original study) to demonstrate a significant drug therapy interaction for percentage of days abstinent, number of heavy drinking days, or total standard drinks.
- MEMS and urine riboflavin measures of compliance provided similar estimates of treatment effectiveness, although combining these two measures yields the most conservative, stringent index of medication compliance.
- The size of the treatment effect approximately doubled in the most compliant individuals.
- Patients treated with naltrexone and CBT showed more days of abstinence, less relapse to heavy drinking days, and fewer total drinks than the other groups (those receiving naltrexone plus MET or placebo plus psychotherapy).
- Older age predicted pill-taking compliance.

### *Effects of naltrexone on specific subgroups or populations*

The treatment effects of naltrexone have recently been examined in several alcohol-dependent subgroups, including (1) those with a family history of alcohol problems and/or antisocial traits, (2) individuals with at least one copy of the G allele of the OPRM1 gene, and (3) women, including those with a comorbid eating disorder.

1. **Family history of alcohol problems and/or antisocial traits.** Prior research has suggested that naltrexone may be significantly more effective in moderating heavy drinking among patients with certain characteristics, including a family history of drug problems, early onset of alcohol problems, high degree of antisocial traits, and comorbid drug use. Rohsenow, Miranda, McGeary, & Monti (2007) tested the contribution of these factors to naltrexone effectiveness by reanalyzing data from 128 patients with alcohol dependence enrolled in a 12-week, double-blind clinical

trial of naltrexone. Participants in the original study had been recruited from a substance abuse day treatment program (Monti et al., 2001). Findings of the reanalysis included the following:

- Having a high percentage (at least 20 percent) of first- and second-degree family members with problem drinking significantly affected naltrexone's effects, resulting in lower drinking rates among those patients.
- Having more antisocial traits resulted in less heavy drinking on naltrexone than on placebo when the patient took at least 70 percent of the medication, whereas more socialized patients had no benefit from naltrexone regardless of compliance (degree of socialization was measured using the California Personality Inventory Socialization scale).
- Age of onset of alcohol problems and comorbid cocaine or marijuana use had no interaction effect with the medication.

This study suggests that a meaningful (and inexpensive) way to match patients to naltrexone is by identifying those who have 20 percent or more relatives with alcohol problems and/or have high antisocial scores. Patients with alcohol dependence who use marijuana or cocaine can also be benefited by naltrexone.

2. **Effects of naltrexone on alcohol sensitivity and genetic modulators of medication response.** To better understand naltrexone's mechanisms of action, particularly its effects on alcohol sensitivity and craving in persons with the A118G single nucleotide polymorphism (SNP) of the OPRM1 gene, Ray and Hutchison (2007) studied naltrexone's effects in a within-subject, double-blind, placebo-controlled laboratory trial. Naltrexone was found to blunt alcohol's effects on subjective feelings of stimulation, positive mood, craving, enjoyment, and vigor. This study suggests that, during treatment with naltrexone, carriers of the A118G SNP (the G allele) experience a more pronounced reduction in alcohol reward than others, which may explain the lower relapse rate with naltrexone treatment in these individuals. Naltrexone's dampening of the rewarding subjective effects of alcohol may thus reduce the likelihood that a slip will trigger a full-fledged relapse into heavy drinking for carriers of the G allele.

   This laboratory study tested the effects of naltrexone in 40 subjects who drank heavily (15 of whom had at least one copy of the G variant and 25 who were homozygous for the A allele) after a 5-percent ethanol solution was infused intravenously. Findings included the following:

   - Naltrexone was differentially effective based on the individual's genotype; it significantly reduced the self-reported, alcohol-induced high in participants with at least one copy of the G allele but had no effect on participants who were homozygous for the A allele.
   - After taking naltrexone, subjects with the G allele demonstrated greater blunting of the alcohol-induced high when the breath alcohol concentration (BrAC) reached 0.06 mg/L, with greatest effects at highest BrAC. This suggests that the effects of naltrexone may be alcohol-dose dependent (Ray & Hutchison, 2007).

3. **Effects of naltrexone on women who are alcohol dependent.** Relatively little is known about the efficacy of naltrexone for treating women who are alcohol dependent. The Women's Naltrexone Study investigated the safety and efficacy of naltrexone combined with cognitive-behavioral coping skills therapy (CBCST) in 103 women who are alcohol dependent, 29 of whom had comorbid eating pathology (O'Malley et al., 2007b). Participants were randomized to receive weekly group CBCST plus either naltrexone (50 mg) or placebo for 12 weeks.

   This study, which essentially measured the added effect of naltrexone over CBCST, found no significant differences between naltrexone and placebo on the primary study outcomes: time to first drinking day, time to first day of heavy drinking, or percentage of participants who continued to meet criteria for alcohol dependence. It should be noted that all groups in this study showed large improvements in drinking behavior: overall, the percentage of days abstinent during treatment more than doubled from baseline, and the number of drinks during drinking day decreased from 7.12 drinks at baseline to 1.83 drinks during treatment. However, positive outcomes specifically with naltrexone included the following:
   - Naltrexone significantly delayed the time to second and third drinking days for women who did not maintain abstinence from alcohol.
   - Symptoms of eating pathology decreased during treatment among all groups (e.g., the frequency of binge eating decreased by almost 70 percent). This suggests that treatment for alcohol dependence may be associated with improvements in eating pathology (O'Malley et al., 2007b).

   The outcomes of this study have been reexamined in a reanalysis of the data, described in the following study.

### *Reanalysis of Negative Trials of Naltrexone*

Novel approaches to data analysis may help resolve the current heterogeneity of clinical findings about naltrexone's efficacy in treating alcohol dependence. Most clinical trials show naltrexone to be effective in delaying relapse to heavy drinking, reducing the intensity of drinking, or increasing the percentage of days abstinent—usually with a small to moderate effect size. However, several randomized trials have found no significant benefit associated with naltrexone treatment. Gueorguieva and colleagues (2007) reanalyzed two such negative trials: a large Veterans Affairs (VA) clinical trial (Krystal, Cramer, Krol, Kirk, & Rosenheck, 2001) and the Women's Naltrexone Study described above (O'Malley et al., 2007b). The researchers used a trajectory-based approach—previously untried in alcohol treatment studies—to look at naltrexone efficacy by evaluating patterns of drinking rather than single events or summary measures. Findings were as follows:

- Based on the data, three distinct trajectories of daily drinking over time (both for any drinking and for heavy drinking) could be modeled using a semiparametric group-based approach. These trajectories were similar for both studies and consisted of (1) "abstainer," (2) "sporadic drinker," and (3) "consistent drinker."
- Compared with those on placebo, subjects on naltrexone were significantly more likely to be abstainers or sporadic drinkers rather than consistent drinkers.
- Naltrexone doubled the odds of following the "abstainer" trajectory instead of the "consistent drinker" trajectory.
- Medication compliance had a significant effect on the trends over time, decreasing the odds of drinking in all trajectories.

The authors suggest that trajectory-based statistical methods could play a role in the future analysis of clinical trials. This method can be used to estimate empirically the heterogeneity in the study population and to identify subgroups with similar response patterns for whom treatment is effective.

### *New Findings on Extended-Release Injectable Naltrexone*

Researchers have conducted a secondary analysis to show the efficacy of extended-release, injectable naltrexone (XR-NTX) among a subgroup of patients enrolled in a 6-month, multicenter, randomized, double-blind, placebo-controlled trial that was previously reported in the literature (O'Malley, Garbutt, Gastfriend, Dong, & Kranzler, 2007a). The original study (Garbutt et al., 2005) found that 380 mg (the approved dose) per day of XR-NTX, combined with 12 sessions of psychosocial therapy, was significantly more effective than placebo in reducing the rate of heavy drinking among patients with alcohol dependence who had been abstinent for 7 or more days before receiving their first injection.

The question addressed in this new data analysis is, "How effective is XR-NTX among patients who had been abstinent for as few as 4 days before receiving the first injection?"—a practical issue in U.S. detoxification settings, where detoxification commonly takes 4 days (O'Malley et al., 2007a). Of 624 patients with alcohol dependence in the original study, 82 patients—the subjects of this analysis—had been voluntarily abstinent for 4 days or more before treatment started. To be eligible for the study, patients had to have had at least two episodes per week of heavy drinking (5 or more drinks per day for men and 4 or more drinks for women) in the 30 days before enrollment. O'Malley and colleagues (2007a), who analyzed the data on a wide range of drinking-related outcomes, concluded that a long period of pretreatment abstinence is not required to achieve positive outcomes among patients receiving monthly 380 mg injections of XR-NTX. The data showed that XR-NTX prolongs abstinence and reduces the number of both drinking days and heavy drinking days in patients who are abstinent for as few as 4 days before starting treatment. For these patients, the analysis showed the following:

- Their rate of abstinence throughout the entire 6-month study was nearly 3 times higher than in patients on placebo.
- Their median time to first drink was 41 days compared with 12 days for those on placebo.
- Their rate of continuous abstinence at the end of the study was 32 percent, compared with 11 percent for those on placebo.
- Their median time to first heavy drinking event was 9 times longer than median time for those on placebo (more than 180 days compared with 20 days).
- Their median number of drinking days per month decreased by 90 percent, totaling 0.7 days per month versus 2.9 days for those on placebo.
- Their median number of heavy drinking days per month decreased by 93 percent, totaling 0.2 days versus 2.9 days for those on placebo.

Responders to treatment were defined as patients who had no more than 2 heavy drinking days in any consecutive 28-day period. Among patients who abstained for as few as 4 days before receiving 380 mg of XR-NTX, 70 percent were classified as responders, more than twice as many as the 30 percent of responders on placebo. Consistent with these observed reductions in drinking, the XR-NTX treatment was associated with greater reductions in gamma glutamyltransferase (GGT) levels over time compared with placebo.

The analysis also looked at patients who received a 190 mg dose of XR-NTX. Their drinking-related outcomes generally fell in an intermediate range between those of patients receiving a 380 mg dose and those on placebo, suggesting a dose-response effect.

### *New Findings on Acamprosate*

A brief article on acamprosate reported on a previously unknown finding—three case studies of patients with long-standing alcohol dependence who had primitive reflexes that continued throughout detoxification but were completely resolved within 24 hours after initiation of acamprosate (Guzik, Bankes, & Brown, 2007). These male patients presented with the primitive snout (sucking motion) reflex and/or the grasp reflex, both of which are highly unusual in healthy adults. Primitive brain-stem reflexes are suppressed after infancy; the presence of these reflexes in adults connotes systemic, metabolic, or neurologic disease that impairs the brain's ability to suppress them. Guzik and colleagues (2007) suggest that acamprosate (at 666 mg 3 times daily) may resolve the primitive snout and grasp reflexes—a neurological finding that suggests cognitive impairment—among patients with alcohol dependence.

Primitive reflexes can be readily identified in a physical examination, and their potential value in staging various illnesses and assessing prognosis is just beginning to be studied (Guzik et al., 2007). Research is needed to determine whether monitoring primitive reflexes in patients with alcohol dependence before and after initiation of therapy with acamprosate could help identify their potential treatment responses and prognoses. This study also suggests that acamprosate may reduce the cognitive impairment that interferes with early-stage recovery for some patients who are alcohol dependent.

### *New Findings on Combined Medication Therapy*

#### *Combining naltrexone and disulfiram for patients with co-occurring alcohol dependence and depression*

Petrakis and colleagues (2007) concluded that the combined use of naltrexone and disulfiram offered no advantage over either medication alone for subjects who are alcohol dependent with co-occurring major depression. This secondary analysis of data from a large randomized controlled trial looked at 139 male veterans who were alcohol dependent with a *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994) diagnosis of current major depression. These subjects represented 54.7 percent of the 254 participants in the original study of veterans with alcohol dependence and comorbid mental disorders (Petrakis et al., 2005).

This secondary analysis showed that subjects with current co-occurring depression achieved positive outcomes comparable to all subjects in the trial—a trial in which almost 70 percent of subjects achieved complete abstinence during the 12-week study period. In addition, on the Hamilton Depression Rating Scale, these subjects with depression also showed a significant decrease in depression from baseline to posttreatment. Side effects of the combined medications, as well as naltrexone and disulfiram alone, were tolerated and consistent with those seen in patients who do not have a dual diagnosis. Because there was no advantage to the combined medication or to one pharmacotherapeutic agent over another, the choice of medication to treat AUDs in patients with depression can depend on such factors as patient preference (Petrakis et al., 2007).

### *Combining medication with psychosocial treatment*

In a review article designed for physicians, Weiss and Kueppenbender (2006) describe the significant advances made in the development, standardization, and rigorous testing of the psychotherapeutic approaches used to treat alcohol dependence. Medical management interventions are available to physicians, as are strategies for improving medication adherence. The authors discuss the evidence from the literature since 1984, particularly clinical trials, on the interactions and efficacy of disulfiram, oral naltrexone, and acamprosate with particular psychosocial treatments. Weiss and Kueppenbender (2006) recommend that physicians use these medical management techniques when prescribing pharmacologic agents to patients with alcohol dependence. They also recommend that physicians become knowledgeable about the various psychotherapies as background for referring their patients who are alcohol dependent to concurrent psychosocial treatment. Some of the conclusions made by Weiss and Kueppenbender (2006), based on their review of the literature, include the following:

- Adding medical management therapy and pills to a specialty psychosocial therapy improves outcomes for patients who are alcohol dependent.
- Psychosocial interventions, ranging from brief medical management to more intensive manual-based psychotherapies, have all been shown to produce positive outcomes in certain studies, depending on the specific medication and the study context.
- No evidence suggests that one single form of psychosocial treatment is a criterion standard for patients with alcohol dependence who receive pharmacotherapy.
- For disulfiram, a successful and promising adjunctive approach is behavioral marital therapy augmented with a disulfiram contract by the couple.
- For naltrexone, the evidence suggests (although not conclusively) that CBT may be particularly effective as adjunct therapy.
- For acamprosate, few studies have been done in combination with structured, controlled psychosocial interventions. The limited evidence suggests that acamprosate may be used equally effectively with a variety of psychosocial treatments and that little psychosocial treatment may be needed beyond medical management.

Building on the existing literature about psychosocial approaches combined with pharmacotherapy, two recent articles describe additional possible psychotherapy approaches to augment the medication. The proposed therapies, described below, include (1) the trial of a second-generation CBT combined with oral naltrexone and (2) the use of contingency management (CM) with medications for treating substance abuse.

**Broad-spectrum treatment (BST).** A 3-month, randomized controlled trial explored whether a broad-spectrum CBT would be more effective than MET for patients who are alcohol dependent treated with naltrexone (Davidson, Gulliver, Longabaugh, Wirtz, & Swift, 2007). This initial trial suggests that, at least when combined with naltrexone, a second-generation CBT may have a meaningful clinical advantage over brief interventions such as MET (Davidson et al., 2007).

This research group developed a unique CBT manual-based protocol for alcohol dependence that combined components of the three psychotherapies demonstrated to be effective in NIAAA's Project MATCH: CBT, 12-Step facilitation, and MET. This new BST approach incorporates such content material as cognitive restructuring, drink refusal, and

assertiveness training with a patient-specific selection of session modules. The treatment matching uses a decision tree, with modules tailored for the individual through a psychometric assessment of each patient's need.

In this study, 149 patients with alcohol dependence were randomly assigned to receive either BST and naltrexone or MET and naltrexone. Patients who received BST had a significantly higher percentage of days abstinent than patients receiving MET. Treatment was tailored in response to an assessment of the patients' psychosocial resources, and the differential advantage for BST was most marked for those patients with social networks that supported drinking.

**Contingency management.** Clinical trials have demonstrated the effectiveness of CM procedures—an approach in which patients receive concrete rewards or reinforcers for discrete targeted behaviors. However, few trials have assessed the value of CM procedures when combined with pharmacotherapy for alcohol dependence. Carroll and Rounsaville (2007) review the existing evidence and suggest that CM would be an ideal platform for addressing the weaknesses of many pharmacotherapies used to treat drug abuse. CM can directly reinforce medication adherence, which may substantially improve compliance in treatment where unpleasant side effects must be overcome or where compliance is not strongly reinforced by rapid benefits from the treatment itself. The authors describe a variety of CM strategies used to improve compliance with disulfiram among patients with alcohol dependence.

A recent pilot double-blind trial of memantine—a selective noncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist—among 34 individuals with alcohol dependence did not support the use of memantine for treating patients who are actively drinking. However, this study did support the use of voucher incentives to facilitate retention. With voucher incentives for clinic attendance, 80 percent of subjects completed the 16-week trial (Evans, Levin, Brooks, & Garawi, 2007).

### *New Findings on Promising Drugs*

In a review of the evidence supporting use of medications for alcohol withdrawal and dependence, Ait-Daoud, Malcolm, and Johnson (2006) discuss clinical trial findings on naltrexone and acamprosate but focus particularly on anticonvulsants. The article presents the neurochemical rationale and research evidence supporting use of anticonvulsants, particularly carbamazepine, valproate, and topiramate, for treating alcohol dependence. On the basis of controlled trials to date, the authors conclude:

- Valproate may be a promising medication for treating patients who are alcohol dependent with a comorbid bipolar disorder.
- Topiramate, a potent novel anticonvulsant, offers promising evidence of being a safe and effective option for the pharmacological treatment of alcohol dependence, warranting further study.
- Anticonvulsants such as valproate and topiramate may offer the advantage of being single medications that can be used from detoxification through the treatment process—being used first to treat the acute withdrawal symptoms and then, once abstinence has been achieved, to prevent relapse by modulating postcessation craving and affective disturbance (Ait-Daoud, Malcolm, & Johnson, 2006).

### *Topiramate*

Recent research shows that topiramate, a drug with complex actions that include activity at the GABA and glutamate receptors, is a promising treatment for alcohol dependence. Although only two major studies have been conducted, the consistency and size of topiramate's clinical efficacy suggest the need for further research, particularly on the most efficacious ceiling dose, the impact of longer periods of treatment, and the subtypes of alcoholism most benefited by treatment with topiramate (Johnson et al., 2007).

A 17-site, double-blind, placebo-controlled trial with 371 men and women who were alcohol dependent found that up to 300 mg per day of topiramate reduced the percentage of heavy drinking days from baseline to week 14 and produced significant and meaningful improvement in a wide variety of self-reported drinking outcomes (Johnson et al., 2007). Topiramate compared with placebo treatment was associated with a significantly higher rate of achieving 28 or more days of continuous nonheavy drinking and 28 or more days of continuous abstinence. Furthermore, using two different analytic approaches, the topiramate group reached 28 or more days of continuous abstinence significantly faster than the placebo group (Johnson et al., 2007). Topiramate also decreased plasma GGT in the heterogeneous and graphically diverse population. These positive findings replicated the results of a smaller, randomized controlled trial (Johnson et al., 2003b). Topiramate's therapeutic effect was evident no later than week 4. At the end of the 14-week trial, differences between topiramate and placebo were still increasing, suggesting that even more improvement may occur with longer administration (Willenbring, 2007).

Two additional factors make topiramate seem particularly promising for treating alcohol dependence in primary care settings. First, topiramate proved effective with patients who were actively drinking rather than abstinent at the time medication was started. Patients in the multisite study were drinking heavily at the time of enrollment and study randomization (men were drinking 35 or more and women 28 or more standard drinks per week). These patients were not required to stop drinking before entering the study, although they had to express a desire to stop or reduce their consumption of alcohol with the possible long-term goal of abstinence. Second, the study provided only minimal behavioral support that focused on enhancing medication compliance and encouraging abstinence—a brief intervention that could be provided by nonspecialist health practitioners (Johnson et al., 2007).

At least 10 percent of participants reported adverse events; the events reported most by those on topiramate, as compared with placebo, included paresthesia, taste perversion, anorexia, difficulty with concentration and attention, and pruritus (Johnson et al., 2007). In the multisite study, where topiramate was titrated over a 6-week period, the attrition that was due to adverse events was 18.6 percent for the topiramate group and 4.3 percent for controls. In the earlier study (Johnson et al., 2003a), where adverse events were similar but titration occurred over a longer, 8-week period, retention rates for the topiramate and control groups were similar. However, in the multisite study, the researchers found that completion rates approached 90 percent among practitioners experienced in administering topiramate, whereas less experienced practitioners had more difficulty with retention. To enhance adherence, the authors advise clinicians to use a slow titration schedule over 8 weeks and to provide focused education for patients on how to manage emergent adverse events (Johnson et al., 2007).

The efficacy of topiramate was also supported in the following two small studies:

- **Topiramate as add-on therapy for patients with alcohol dependence who do not respond to standard treatment.** In an observational open-label, multisite study in Spain, 64 patients who were alcohol dependent with poor outcomes in standard treatment were provided with a mean dose of almost 200 mg per day of topiramate and monitored over a 12-month period (Fernández Miranda et al., 2007). The addition of topiramate resulted in a significant decrease in all outcomes measured—number of drinking days per month and standard drinking units consumed per day, craving, priming, dependence intensity scales, and serum transaminase levels.
- **Ability of topiramate to increase periods of continuous "safe" drinking** (defined by NIAAA as 1 or fewer standard drinks per day for women and 2 or fewer standard drinks per day for men). Some patients with alcohol dependence do not achieve abstinence during treatment. Researchers carried out a secondary analysis of data from a double-blind, randomized, controlled 12-week trial (Johnson et al., 2003b) to determine whether topiramate recipients were able to achieve longer continuous periods of "safe" drinking than those on placebo (Ma, Ait-Daoud, & Johnson, 2006). The analysis found that soon after topiramate was administered, recipients began to achieve increasing lengths of "safe" drinking relative to placebo. Furthermore, these early treatment gains appear to be predictive of continuing improvement as the length of time in treatment increases (Ma et al., 2006).

### *Other medications under development*

In addition to topiramate, the 2007 literature search identified positive reports on controlled clinical trials of two potential medications for treating alcohol dependence: (1) nalmefene, an opioid antagonist, and (2) quetiapine, an atypical antipsychotic that targets both dopamine and serotonin receptors. Findings were as follows:

- **Targeted nalmefene.** A multisite, randomized double-blind study in Finland found that 10 to 40 mg doses of nalmefene were safe and reduced heavy drinking among 242 subjects with self-identified drinking problems (Karhuvaara et al., 2007). Subjects received minimal psychosocial intervention and took nalmefene only when drinking seemed imminent. After 28 weeks, 57 subjects on nalmefene continued into a 24-week extension period with randomization to continued nalmefene or placebo. Decrease in drinking was significantly greater for subjects on nalmefene than on placebo, which was corroborated by significant decreases in alanine aminotransferase and GGT. During this randomized withdrawal period, subjects remaining on nalmefene maintained the drinking level achieved in the initial 28 weeks, whereas those switched to placebo seemed to return to more frequent heavy drinking.
- **Quetiapine.** According to a double-blind, placebo-controlled 12-week trial among 61 subjects who were alcohol dependent, quetiapine (400 mg per day) may be more effective in treating people with the more severely affected Type B alcoholism compared with those with Type A alcoholism. This small study found a significant interaction between quetiapine and alcoholic subtype (Kampman et al., 2007). As predicted, Type B subjects treated with quetiapine had significantly fewer days of drinking and fewer days of heavy drinking than Type B subjects on placebo. Compared with those on placebo, people with Type B alcoholism who were treated with quetiapine had alcohol craving significantly reduced. Among the patients with Type A alcoholism, quetiapine offered no advantage over placebo in improving

drinking outcomes. Nine patients treated with quetiapine (31 percent) maintained complete abstinence compared with two patients on placebo (6 percent).

### *New Findings on Pharmacotherapy Use by Medical Care Providers*

Relatively few specialized addiction treatment programs use pharmacotherapies for alcohol dependence, according to recent data collected from large samples of specialty programs in the public and private sectors (Ducharme, Knudsen, & Roman, 2006). Even as evidence for the efficacy of these medications has increased, the longitudinal data in this study suggest that the proportion of treatment programs using pharmacotherapies has actually been declining over time and the number of patients who receive medications remains low. Ducharme and colleagues (2006) discuss historical patterns among addiction treatment programs, as well as the numerous structural and philosophical barriers that impede the adoption of pharmacotherapies by the specialty treatment system. This article suggests a wide range of specific environmental, funding, regulatory, and linking structures and strategies that could help reduce resistance and promote the adoption of medications in addiction treatment (Ducharme et al., 2006).

#### *Attitudes of professional alcohol counselors*

Community-based addiction treatment centers rarely use pharmacotherapies for treating their patients who are alcohol dependent (Thomas, Wallack, Lee, McCarty, & Swift, 2003). Before initiating pharmacotherapy education at six community-based addiction treatment centers, Thomas and Miller (2007) collected baseline data on the knowledge and attitudes of 84 counselors and administrators attending a staff education project. Respondents came only from centers that had no on-staff medical provider. The data showed the following:

- These counselors and administrators, with just one exception, had very little or no knowledge about naltrexone.
- Most believed that adjunctive pharmacotherapy is ineffectual in treating alcohol dependence.

The authors concluded that lack of knowledge and confidence about pharmacotherapy by counselors is a barrier to more widespread referral and use of pharmacotherapies in alcohol treatment centers. Focused education will be needed for both counselors and administrators.

The study suggests that educational efforts do not need to overcome negative opinions about adjunctive pharmacotherapies. Instead, the intent should be to convey accurate and empirically supported information about the value of current medications. The respondents' personal recovery status from addiction did not appear related to their valuation of pharmacotherapies. The most senior addiction professionals—those with more than 10 years of experience in the addiction field—were generally more positive in their valuation of adjunctive pharmacotherapy (Thomas & Miller, 2007).

#### *Attitudes of patients toward pharmacotherapy*

A second study looked at whether medically hospitalized patients with alcohol dependence are interested in pharmacotherapy and primary care to treat their alcoholism (Stewart & Connors, 2007). This survey covered 50 inpatients identified as alcohol dependent; all were receiving internal medicine services in a university-affiliated public hospital. Most survey participants were socioeconomically disadvantaged males admitted with disorders that heavy alcohol use would typically cause or exacerbate. In the month before being admitted

to the hospital, these patients on average had been drinking on 86 percent of days and had averaged 8.4 drinks per drinking day. Their responses suggest that many such patients will be interested in receiving medication for alcoholism:

- 84 percent agreed they needed to stop drinking.
- 50 percent agreed that medication helps prevent drinking.
- 66 percent agreed they would like to receive an effective medication to help prevent drinking.

Interest in receiving effective pharmacotherapy was positively associated with addiction severity, adverse consequences, recognition of the problem, and drinking frequency. The reaction to primary care was mixed; only 32 percent of these patients were interested in primary care treatment for their alcoholism. The authors conclude that primary care followup alone may not adequately address patients' perceived needs; many patients may also require prompt referral to specialty care after hospitalization (Stewart & Connors, 2007).

## Approved Drugs for Treating Patients Dependent on Alcohol

The following review of the literature covers major research articles published between 2000 and April 2007. The focus is on drugs currently approved by FDA for treating alcohol dependence (disulfiram, oral naltrexone, long-term injectable naltrexone, and acamprosate).

### *Disulfiram*

The first medication for alcohol dependence, approved by FDA almost 60 years ago, is an aversive therapy still used today. Disulfiram (Antabuse®) irreversibly inhibits acetaldehyde dehydrogenase, an enzyme involved in alcohol metabolism, which leads to an accumulation of acetaldehyde. This accumulation leads to a severe reaction when alcohol is consumed. Disulfiram also inhibits dopamine ß-hydroxylase in the brain and may have a direct effect on brain catecholamines. Disulfiram causes a variety of unpleasant symptoms when a person drinks alcohol, such as nausea, vomiting, hypotension, and facial flushing. Despite these reactions, approximately 15 percent of patients continue to drink alcohol while taking disulfiram (Myrick, 2002). When daily dosages of 1,000–3,000 mg were used, deaths were reported from disulfiram–alcohol reactions (Fuller & Gordis, 2004). The reasonable startup dose today is 250 mg, and, if the patient drinks and does not experience a disulfiram–alcohol reaction, the dose can be increased to 500 mg (Fuller & Gordis, 2004).

Fuller and Gordis (2004), asking "Does disulfiram have a role in alcoholism treatment today?" respond with a qualified "yes." They conclude that the field needs to move beyond disulfiram and develop better pharmacotherapies that act on the neurobiological processes underlying alcohol dependence. Fuller and Gordis suggest that physicians do not need to prescribe disulfiram when patients first enter treatment. But if a patient is struggling to maintain sobriety, the supervised use of disulfiram is warranted (Fuller & Gordis, 2004). Side effects are usually minor; serious adverse reactions are uncommon, although the physician needs to monitor for hepatotoxicity.

#### *Research on disulfiram*

Research studies and clinical experience over 55 years offer valuable information about the efficacy and safety of disulfiram. Almost 40 years elapsed from the time disulfiram became available before the first multisite, randomized clinical trial covering 605 participants was

published (Fuller et al., 1986). Many large double-blind studies of disulfiram show no therapeutic effect compared with placebo (reviewed by Myrick, 2002). There is still no unequivocal evidence from randomized, controlled trials to show that disulfiram improves abstinence rates over the long term (Mann, 2004).

Brewer, Meyers, and Johnsen (2000) reviewed all published clinical studies in which there had been attempts to directly supervise the administration of disulfiram at least weekly. Adequate supervision included appropriate training of supervisors and review of their ability to supervise. These researchers found 13 controlled and 5 uncontrolled studies with supervised disulfiram administration and reported positive findings in all but 1 study. In general, the better the supervision, the better the outcomes. Under supervised situations, disulfiram reduced drinking, prolonged remissions, improved treatment retention, and facilitated compliance with psychosocial interventions.

Anton (2001), in a review of the literature, concluded that the evidence for disulfiram is mixed. According to Anton (2001), the most reliable study suggests that disulfiram is not better than placebo. In the reviewed studies, Anton (2001) reported that the factors that seem to improve treatment effectiveness with disulfiram include patient motivation, patient monitoring, being an older man, and concomitant treatment with acamprosate.

The most recent comprehensive review of the literature, done by Suh, Pettinati, Kampman, & O'Brien (2006) and covering the literature from 1937 to 2005, concluded that supervised disulfiram can be an effective treatment for alcohol dependence. The reviewers recommended that more research be done on disulfiram combined with other—and especially newer—psychotherapies.

### *Disulfiram use in primary care*

**Adverse events.** Disulfiram is well tolerated in most patients, with the most common adverse effects being tiredness, headache, and sleepiness (Chick, 1999). Toxicities such as psychotic reactions, confusional states, and neuropathy are rare and appear to be dose related (Bevilacqua, Diaz, Diaz, Silva, & Fruns, 2002; Chick, 1999).

Disulfiram hepatitis is a very rare, sometimes fatal complication that particularly affects women (Brewer & Hardt, 1999). A Danish study of adverse reactions to disulfiram over a 22-year period estimated the rate of fatal disulfiram-induced hepatitis to be 1 per 25,000 patients treated per year, with the peak of hepatotoxicity occurring 60 days after the beginning of treatment. Because hepatotoxicity can usually be reversed if disulfiram is stopped before liver disease is clinically evident, Wright, Valfier, and Lake (1988) recommend liver function testing before treatment, at 2-week intervals for 2 months, and at 3- to 6-month intervals thereafter. Chick (1999) recommends informing the patient and the patient's family and physician of the risk and immediately stopping the drug if adverse effects, such as fever preceding jaundice, are noted. Fuller and Gordis (2004) recommend supervised administration of disulfiram, along with careful monitoring for hepatotoxicity.

**Conditions excluding treatment with disulfiram.** Patients with cardiovascular or cerebrovascular disease are excluded from treatment because hypotension can occur during a disulfiram–alcohol interaction (Fuller & Gordis, 2004). Disulfiram has been reported to cause fetal abnormalities, so pregnant women should not use it. Disulfiram is also contraindicated in patients who have an idiopathic seizure disorder or cannot understand

the risks associated with use of the drug. Disulfiram may influence adversely the pharmacokinetics and, therefore, the effects of medications metabolized by the cytochrome p450 system, such as warfarin, phenytoin, amitriptyline, and benzodiazepines (including chlordiazepoxide and diazepam but not lorazepam and oxazepam). Disulfiram also interferes with the pharmacokinetics of the tricyclic antidepressants. Fuller and Gordis (2004) report that the literature indicates disulfiram is unsafe to use concomitantly with monoamine oxidase inhibitors.

**Patients appropriate for disulfiram.** Data suggest that disulfiram is most effective in older, motivated individuals and in those who are supervised during daily ingestion. Predictors of efficacy with disulfiram include patients highly motivated for abstinence, people who are married or have a good support system, people with behavioral contracts to take the medication, and people legally compelled to take disulfiram (Myrick & Anton, 2004; O'Farrell, Allen, & Litten, 1995). Disulfiram can also support abstinence when people who are alcohol dependent attend events that involve alcohol, such as family celebrations.

In general, disulfiram seems to have limited acceptance in the treatment of alcohol dependence (Anton & Swift, 2003). Several recent, small pilot studies suggest that disulfiram might be safe and useful for the following types of patients:

- **Patients who are positive for the hepatitis C virus (HCV).** A recent review of the literature recommends monitored disulfiram treatment for patients positive for HCV (Kulig & Beresford, 2005).
- **Patients who are court ordered.** Martin, Clapp, Alfers, and Beresford (2004) found that compliance with treatment was 61 percent after 18 months for those with court-ordered, supervised disulfiram treatment. This compared with 18-percent compliance among those in a voluntary, supervised disulfiram group.
- **Adolescent patients.** In a small, preliminary study, Niederhofer and Staffen (2003) compared 13 adolescents ages 16–19 on disulfiram with 13 controls. After 90 days, the mean abstinence duration was significantly greater for the disulfiram group than for the placebo-treated controls (68.5 days [SD 37.5] vs. 29.7 days [SD 19.0]). Disulfiram was well tolerated in adolescents, except for occasional diarrhea.
- **Patients with severe mental illness.** A preliminary study of 33 patients with severe mental illness and alcohol dependence found that supervised disulfiram treatment was associated with decreases in the number of days hospitalized. Controlled research is needed to evaluate the effects of disulfiram in this population (Mueser, Noordsy, Fox, & Wolfe, 2003).
- **Patients codependent on alcohol and cocaine.** Disulfiram's main effects in initiating abstinence in cocaine and alcohol use were still maintained a year after patients with codependence received short-term (12-week) treatment with disulfiram combined with psychotherapy (Carroll et al., 2000). Ninety-six patients who were codependent randomly received CBT either with or without disulfiram, 12-Step facilitation with or without disulfiram, or clinical management with disulfiram. Carroll and associates (2000) concluded that this randomized controlled trial supports the efficacy of disulfiram with this challenging codependent population. The findings suggest long-term benefits can result from comparatively brief treatments that facilitate the initiation of abstinence.

### *Research needs*

The effects of disulfiram on craving have not been widely studied, but disulfiram is unlikely to be very powerful in reducing craving, especially if a patient has not achieved sustained abstinence (Anton & Swift, 2003). For better information about the use of disulfiram today, randomized clinical trials need to determine whether supervised ingestion of disulfiram:

- Would be useful to ensure sobriety for such high-risk groups as criminal offenders and those who have failed previous attempts at treatment
- Is better if supervision is performed by a clinic staff member or by a relative
- Would improve treatment outcomes when combined with newer pharmacotherapies (Fuller & Gordis, 2004).

## ***Oral Naltrexone***

In 1994, FDA approved naltrexone, an OPRM1 antagonist, as a 50 mg oral tablet for the prevention of relapse to alcohol use. Before its approval for alcohol dependence, naltrexone had been approved by FDA for use in opioid dependence. Adding alcohol treatment as an indicator for use of naltrexone was based on the results of two single-site studies that evaluated the medication as an adjunct to relapse prevention psychotherapy. These studies found that naltrexone reduced drinking frequency and the likelihood of relapses to heavy drinking (O'Malley et al., 1992; Volpicelli, Alterman, Hayashida, & O'Brien, 1992).

Naltrexone represented a new era of medications studied specifically to treat AUDs. Disulfiram's mechanism of action centers on its use as an aversive agent, whereas naltrexone is thought to act directly on the brain as an anticraving compound (Myrick & Anton, 2004). As an opioid antagonist, naltrexone is thought to reduce the reinforcing subjective or behavioral response to alcohol (Davidson, Palfai, Bird, & Swift, 1999; Garbutt et al., 2005; McCaul, Wand, Stauffer, Lee, & Rohde, 2001). Naltrexone must be prescribed with caution because individuals abusing opioids may experience withdrawal and those receiving opioids for analgesia will find them ineffective during naltrexone treatment. Patients receiving naltrexone should carry an explanatory card to show to healthcare personnel in an emergency.

### *Research on naltrexone*

In the last decade, the efficacy of naltrexone for alcohol dependence has been extensively studied, particularly in the United States. At least 19 published controlled studies of about 3,200 patients have compared the effects of oral naltrexone with placebo; nearly all showed efficacy in the treatment of alcohol dependence (Garbutt et al., 2005). The majority of clinical trials support the hypothesis that naltrexone can reduce the urge to drink, increase the number of days abstinent, and minimize the risk of relapse to heavy drinking in some patients (O'Malley & Froehlich, 2003). However, two recent studies, including a large, multisite VA study, have reported no or minimal effectiveness in reducing drinking behavior as compared with placebo (reviewed by Krystal et al., 2001). One reason for this ineffectiveness may be the high rate of noncompliance among patients in the VA study. Lack of compliance with oral naltrexone is a problem that varied greatly across studies, with 40 to 90 percent of subjects completing treatment in the studies.

The lack of consistent findings on the effects of oral naltrexone may be the result, at least in part, of variations in how compliant patients are with the medication. A number of studies indicate that poor compliance with therapy can limit the effectiveness of oral naltrexone (Johnson & Ait-Daoud, 2000; Kranzler, Wesson, & Billot, 2004). For example, in a 3-month

followup study, Volpicelli and colleagues (1997) found that only patients who took their oral daily dose on at least 90 percent of study days improved their drinking outcomes. No differences were found between the placebo group and those who took naltrexone on fewer than 90 percent of study days on any drinking measure; 50 percent of these subjects relapsed, changing from abstinence to clinically significant drinking during the study. In a large, 1-year collaborative study in the United Kingdom, only patients who took at least 80 percent of their naltrexone tablets experienced better drinking outcomes than those on placebo (Chick et al., 2000). The outcomes in 17 clinical trials of naltrexone at a dose of 50 mg per day are shown in Exhibit 1 (Mann, 2004).

**Exhibit 1**
**Published Placebo-Controlled Clinical Trials of Naltrexone 50 mg/day in Alcohol Dependence[a]**

| Study | Country | No. of Patients | Duration (mo) | Outcome Measure | Result[b] |
|---|---|---|---|---|---|
| **Oral Naltrexone** | | | | | |
| Krystal et al., 2001 | US | 627 | 3 or 12 | TFR | No effect |
| Gastpar et al., 2002 | Germany | 342 | 3 | TFR | No effect |
| Guardia et al., 2002 | Spain | 202 | 3 | TFR | Increased |
| Kranzler et al., 2000 | US | 183 | 3 | TFR | No effect |
| Kranzler et al., 2000 | US | 183 | 3 | TFD | No effect |
| Chick et al., 2000 | UK | 169 | 3 | TFR | No effect |
| Anton et al., 1999 | US | 131 | 3 | TFR | Increased |
| Anton et al., 1999 | US | 131 | 3 | %DA | Increased |
| Anton et al., 1999 | US | 131 | 3 | DDD | Decreased |
| Heinälä et al., 2001 | Finland | 121 | 3 | %RHD | Reduced (CS group) |
| Heinälä et al., 2001 | Finland | 121 | 3 | None | No effect (ST group) |
| Balldin et al., 2003 | Sweden | 118 | 6 | %HDD | Reduced (CS group) |
| Monti et al., 1999 | US | 116 | 3 | HDD | (Decreased)[c] |
| Monti et al., 1999 | US | 116 | 3 | DDD | (Decreased)[c] |
| Monti et al., 1999 | US | 116 | 3 | None | No effect (ST group) |
| Morris et al., 2001 | Australia | 111 | 3 | TFD | No effect |
| Morris et al., 2001 | Australia | 111 | 3 | TFR | Increased |
| Latt et al., 2002 | Australia | 107 | 3 | %RHD | Decreased |
| Latt et al., 2002 | Australia | 107 | 3 | TFR | Longer |
| O'Malley et al., 1992 | US | 97 | 3 | TFR | Increased (CS group) |
| O'Malley et al., 1992 | US | 97 | 3 | None | Increased (ST group) |
| Volpicelli et al., 1997 | US | 97 | 3 | TFR | Increased in compliant patients |
| Volpicelli et al., 1992 | US | 70 | 3 | TFR | Increased |
| Hersh et al., 1998 | US | 64[d] | 2 | TFD | No effect |
| Oslin et al., 1997b | US | 44 | 3 | %RHD | No change |
| **Injectable Naltrexone** | | | | | |
| Kranzler et al., 1998 | US | 20 | 2 | %HDD | Reduced |

a Studies are ranked by size.
b The results of the studies are identified as "increased" or "decreased" only when the intergroup difference was statistically significant at the level of 0.05.
c Positive results were obtained in this study only once the 40 noncompliant patients were excluded from the analysis.
d This study was performed in patients with concomitant alcohol and substance abuse.

CS = coping skills training.
DDD = drinks per drinking day.
HDD = heavy drinking days.
ST = supportive therapy.
TFD = time to first drink.
TFR = time to first relapse.
%DA = percentage of days abstinent.
%HDD = percentage of heavy drinking days.
%RHD = percentage of patients relapsing to heavy drinking.

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The extensive research on oral naltrexone has produced numerous review articles and several meta-analyses of the literature. Three meta-analyses concluded that the effect of naltrexone is significantly greater, on average, than that of placebo (Kranzler & Van Kirk, 2001; Srisurapanont & Jarusuraisin, 2005; Streeton & Whelan, 2001). The meta-analysis by Streeton and Whelan (2001) found that, after 12 weeks of naltrexone treatment, patients experience significantly fewer episodes of relapse and significantly more remain abstinent compared with subjects on placebo. The meta-analysis by Srisurapanont and Jarusuraisin (2005), which covered 3,048 subjects in 27 randomized controlled trials from 34 published and unpublished papers, concluded the following:

- **Short-term treatment.** Naltrexone should be accepted as a short-term treatment for alcoholism. In comparison with placebo, short-term treatment significantly reduces the chance of alcohol relapse for 36 percent of patients, is likely to reduce the chance of returning to drinking for 13 percent, and can lower the risk of withdrawing from treatment for 28 percent of patients.
- **Medium-term treatment.** Medium-term naltrexone treatment gives no benefit over placebo in terms of relapse prevention, but it does increase the time to first drink and diminishes craving. In this regard, naltrexone plus intensive psychosocial treatment is superior to naltrexone plus a simple psychosocial treatment. Naltrexone is also superior to acamprosate in reducing relapses, number of drinks, and craving.
- **Concomitant treatment strategies.** To improve treatment adherence and to ensure that real-world treatment is as effective as research findings, some form of psychosocial intervention and management of adverse effects needs to accompany naltrexone therapy.
- **Unanswered questions.** The existing research is limited because many trials are of short duration and have small sample sizes. Important areas of concern include the lack of data on different psychosocial benefits and on how long patients who respond to naltrexone should continue their treatment. The evidence for longer term (more than 8 months) efficacy of naltrexone remains to be demonstrated (Mason, 2003).

Recently, Pettinati and colleagues (2006) reviewed all published, randomized placebo-controlled trials of naltrexone to resolve inconsistencies in naltrexone's reported efficacy across trials. Drinking outcomes measured in these studies related to four outcomes: two pertaining to "any drinking" and two pertaining to "heavy or excessive drinking." This review found an advantage for naltrexone over placebo in 70 percent of clinical trials that measured reductions in "heavy or excessive drinking" but in only 36 percent of trials that measured abstinence or "any drinking." Pettinati and colleagues (2006) concluded that naltrexone's therapeutic effects are most related to outcomes pertaining to heavy or excessive drinking.

### *Naltrexone use in primary care*

Of particular interest to physicians in primary healthcare settings is one recent study that looked at whether general internists and primary care physicians, using naltrexone, could treat patients who are alcohol dependent as effectively as addiction specialists can (O'Malley et al., 2003). Results indicated that primary care counseling with naltrexone pharmacotherapy can be effective in select patients. Study subjects were recruited from newspaper ads and required to be abstinent from alcohol for 5 to 30 days before initiating

treatment. In this nested sequence of randomized, placebo-controlled trials, patients received the following:

- Phase I—197 patients received 10 weeks of naltrexone and either (1) brief counseling from a primary care physician (an initial 45-minute visit followed by 15- to 20-minute sessions in weeks 1 through 4, 6, 8, and 10) ***or*** (2) CBT from an addiction specialist (an initial 1.25-hour session followed by weekly 50-minute sessions for 10 weeks).
- Phase II—Responders from both groups received 24 weeks of continuing maintenance with naltrexone.

In Phase I, the results were comparable in the two groups, with 84.1 percent of primary care patients and 86.5 percent of CBT patients avoiding persistent heavy drinking. Persistent heavy drinking was defined as more than 2 days of heavy drinking (5 or more drinks per day for men and 4 or more drinks per day for women) during the last 28 days of Phase I. In Phase II, the response to naltrexone maintenance was better maintained among those who received primary care than in those with counseling appointments (O'Malley et al., 2003). Monterosso and colleagues (2001) also found a significant advantage of naltrexone use over placebo in patients who received 12 weeks of concurrent primary counseling.

The results are available from NIAAA's COMBINE study, a multisite, randomized, controlled trial that evaluated medical management with naltrexone, acamprosate, or both, with or without additional specialist treatment (combined behavioral intervention). Participants received interventions over a 4-month period and were evaluated for up to 1 year after treatment. Findings from this study suggest that naltrexone with medical management can be delivered successfully in healthcare settings, which would greatly expand the number of people receiving treatment (Anton et al., 2006). In fact, the COMBINE data suggest that naltrexone can be effective in the context of medical management without specialized behavioral treatment.

In the COMBINE study, participants taking naltrexone received 25 mg on days 1 through 4, 50 mg on days 5 through 7, and 100 mg on days 8 through 112. Doses were chosen based on preliminary evidence that doses higher than those commonly prescribed could be more efficacious and provide better coverage for missed doses; two pilot studies confirmed the tolerability of these doses (Anton et al., 2006). Ongoing or recurrent dose reductions could be made for individual participants and were made in 12.1 percent of patients for naltrexone, compared with 11.9 percent for acamprosate, 20.9 percent for acamprosate plus naltrexone, and 7.8 percent for placebo. On average, 88 mg of naltrexone was taken daily, and the mean medication adherence rate for naltrexone was 85.4 percent—similar to the adherence rates for those receiving acamprosate or combined behavioral interventions. The COMBINE study confirmed the efficacy of naltrexone in reducing drinking among volunteers who were newly abstinent from alcohol. Key findings included the following:

- Participants receiving naltrexone plus medical management had a higher percentage of days abstinent (80.6 percent) than those receiving placebos and medical management only (75.1 percent).
- Naltrexone reduced the risk of a first heavy drinking day over time; the reduction in risk was 0.28, consistent with meta-analyses of other naltrexone trials that used 50 mg per day and included specialist care (Anton et al., 2006).

Other findings from the COMBINE study are detailed in the sections on acamprosate and on combined medication therapy.

**Adverse events.** Some researchers have attributed the low degree of compliance with naltrexone to poor tolerability and hepatic toxicity (Volpicelli et al., 1997). However, a recent meta-analysis of naltrexone studies concluded that only 10 percent of patients fail to complete treatment because of one or more adverse drug effects and that hepatic toxicity is very unlikely at the current dose of 50 mg of oral naltrexone daily (Bouza, Magro, Muñoz, & Amate, 2004; Yen, Ko, Tang, Lu, & Hong, 2006). Yen and colleagues (2006) concluded that naltrexone is not hepatotoxic at the recommended daily dose and may be beneficial for patients with elevated liver enzymes. In the COMBINE study, with its higher naltrexone dosage, only 1 of 70 serious adverse events could have been related to the medication. Of the 601 participants, 12 (primarily those in the naltrexone groups) had treatment-emergent levels of liver enzymes (aspartate aminotransferase or alanine aminotransferase) greater than five times the upper limit of normal; these cases resolved once the medication was discontinued except for two cases (one participant did not return for retesting and the other continued heavy drinking) (Anton et al., 2006).

**Conditions excluding treatment with naltrexone.** Patients are ineligible for naltrexone if they have poor liver function or a history of liver disease, have recent prescribed or nonprescribed opioid use, and, for women, are pregnant or not using adequate birth control (Rohsenow, 2004). Absolute contraindications to naltrexone use include acute hepatitis, liver failure, active opioid withdrawal, and the current use of methadone or opioid-containing medications prescribed to manage pain and treat serious medical conditions, such as heart disease, severe arthritis, sickle cell anemia, and recurrent congestive heart failure (CSAT, 1998). A relative contraindication applies to patients who have an anticipated need for opioids to treat an identified medical problem, because use of naltrexone can impede the effectiveness of prescription and over-the-counter analgesics, cough medicines, and pain medications that contain opioids (CSAT, 1998).

**Patients appropriate for naltrexone.** Current research suggests that the patients most likely to benefit from naltrexone are those who have close relatives with alcohol problems, have particularly strong urges to drink, or have limited cognitive abilities (Rohsenow, 2004). Naltrexone is also well tolerated in older patients (Oslin et al., 1997a). People with lower blood concentrations of the drug may benefit from a larger dose, and those with good results on naltrexone may benefit from longer maintenance (Rohsenow, 2004).

### *Research needs*

More research is needed on which subgroups of patients are most likely to respond well to naltrexone, as well as to other pharmacotherapies. In a recent controlled trial in Germany, Kiefer, Helwig, Tarnaske, Otte, and Wiedemann (2005a) looked at the response to naltrexone and acamprosate by patients who had (1) low versus high baseline somatic distress, depression, and anxiety, (2) low versus high baseline craving, and (3) typological differentiation according to the subtypes proposed by Cloninger and Lesch (Lesch & Walter, 1996). A comparison of the course of abstinence rates indicated that naltrexone was effective particularly in patients with high baseline depression, whereas acamprosate was mainly efficacious in patients with low baseline somatic distress. Baseline craving showed no predictive value. Naltrexone revealed best treatment effects in Lesch's types III and IV typology, whereas acamprosate was mainly effective in type I (Kiefer et al., 2005a).

Some researchers hope that it may become possible to choose therapy based on identification of genetic subtypes of the specific molecular targets for drugs. For example, because a family history of alcohol problems is a predictor of naltrexone response, it is hypothesized that a gene variation of the OPRM1 may increase an individual's susceptibility to substance dependence, as well as increase the response to naltrexone. To test this, a recent randomized study of patients with alcohol dependence examined the association between their treatment outcomes and two specific polymorphisms of the gene encoding the OPRM1. In subjects of European descent, individuals with one or two copies of the Asp40 allele who were treated with naltrexone had significantly lower rates of relapse and a longer time to return to heavy drinking than those homozygous for the Asn40 allele (Oslin et al., 2003). If these results are replicated, then gene testing may be a feasible and cost-effective way to identify individuals who are most likely to respond to naltrexone treatment.

Research by McGeary and colleagues (2006) found that, among non-treatment-seeking heavy drinkers, all of naltrexone's moderating effects on craving and on a cue-elicited urge to drink could be accounted for by Asn40Asp polymorphisms in the OPRM1 gene. However, in a study of veterans being treated for alcohol dependence, Gelernter and colleagues (2007) found no significant interactions between the OPRM1 Asn40Asp polymorphisms and the response to naltrexone treatment. Oslin, Berrettini, and O'Brien (2006) reviewed the current research agenda and the biological correlates of the receptor genes that have been demonstrated to predict clinical response to naltrexone in individuals who are dependent on alcohol.

### *Extended-Release Injectable Naltrexone*

On April 13, 2006, FDA approved the marketing application of Alkermes, Inc., for its extended-release injectable form of naltrexone with the trade name Vivitrol® (formerly Vivitrex®). Vivitrol is a once-monthly, single-dose 380 mg intramuscular injectable medication that uses a proprietary Medisorb® drug delivery technology. Vivitrol became commercially available on June 13, 2006, through a limited network of specialty pharmacy providers.

A second company, DrugAbuse Sciences, also has an injectable naltrexone formulation called Naltrel in Stage III clinical trials. A third injectable formulation, Depotrex®, is under development.

The extended-release injectable formulation of naltrexone was developed to address the problem of compliance with oral naltrexone. The long-acting injectable formulation offers a number of advantages. An intramuscular injection is needed monthly instead of daily, which ensures that patients are exposed to the medication for at least the first month. This monthly, extended-release injection eliminates the need for daily self-dosing and reduces the opportunity for patients to discontinue their medication impulsively. Any discontinuation in therapy would come to the attention of the physician or healthcare provider who is administering the injections. The long-acting formulation also produces a more consistent and predictable drug blood level than oral naltrexone (Dunbar et al., 2006). The injectable form eliminates first-pass metabolism, while reducing the repetitive peak-to-trough plasma naltrexone levels associated with daily oral naltrexone administration (Dunbar et al., 2006; Johnson et al., 2004).

### *Research on injectable naltrexone*

Several formulations of injectable naltrexone have been tested in pilot studies and clinical trials since 1998, and all studies have shown the injectable long-acting formulation to be safe, well tolerated, and effective in reducing heavy drinking days and other measures of problem drinking. Although most studies involved small numbers of subjects, developers of the two investigational formulations have published multicenter, randomized, placebo-controlled clinical trials (Garbutt et al., 2005; Kranzler et al., 2004). Studies done to date include the following:

- **Preliminary studies.** In a 12-week study of an injectable naltrexone formulation (Depotrex) combined with 8 weekly coping skills sessions, the 15 patients on 206 mg of daily naltrexone had fewer drinking days than 5 patients on placebo, supporting continued research on the sustained-release drug (Kranzler, Modesto-Lowe, & Nuwayser, 1998). An 8-week study of the same injectable formulation among 12 subjects who were heroin dependent showed that both low- (192 mg) and high-dose (384 mg) injections were safe and effective and produced long-lasting antagonism to the effects of heroin (Comer et al., 2002). Few adverse effects were reported except for mild discomfort at the injection site, and blood plasma levels remained above 1 ng/ml for 3 to 4 weeks after the injection.
- **DrugAbuse Sciences Naltrexone Depot Study Group.** This group conducted the first multicenter study of injectable naltrexone (Naltrel) for alcohol dependence, randomly assigning 315 patients either to an intramuscular injection of naltrexone monthly for 3 months or to placebo; all subjects received five sessions of manual-guided MET (Kranzler et al., 2004). The medication was well tolerated, with approximately 74 percent of subjects receiving all injections. For those taking injectable naltrexone, there was a significant advantage over placebo in time to first drinking day, fewer drinking days during treatment, and a significantly greater abstinence rate than for the placebo group (18 vs. 10 percent). Earlier studies, including a 6-week, open-label trial of one 300 mg injection among 16 subjects, combined with weekly individual counseling sessions, found no serious adverse events and a significant reduction in the number of drinks per day, heavy drinking days, and the proportion of drinking days compared with baseline (Galloway, Koch, Cello, & Smith, 2005; Modesto-Lowe, 2002).
- **Vivitrex® Study Group.** This group conducted a 6-month, double-blind, placebo-controlled trial of long-acting injectable naltrexone, using two different doses, at 24 U.S. public hospitals, private and VA clinics, and tertiary care medical centers. Adults who were actively drinking were randomized to naltrexone treatment or placebo, and 624 received at least one injection. All subjects received 12 sessions of a low-intensity psychosocial intervention. Compared with placebo, the high (380 mg) dose resulted in a 25-percent decrease in the event rate of heavy drinking days, whereas the low (190 mg) dose resulted in a 17-percent decrease. The long-acting naltrexone was well tolerated, and there was no evidence of hepatotoxicity (Garbutt et al., 2005). An earlier 16-week, multisite pilot study had shown the formulation to be both safe and well tolerated (Johnson et al., 2004).

### *Injectable naltrexone use in primary care*

Now that it has been approved for marketing by FDA, injectable naltrexone is available as a treatment option that can be used by primary care practitioners and addiction specialists. In the multisite trial, the efficacy of the 380 mg dose was evident in the first month after the initial injection and was maintained over the 24-week treatment period (Garbutt et al.,

2005). Unlike patients in the oral naltrexone trials, the majority of patients were actively drinking when they started injectable naltrexone treatment. However, the FDA Center for Drug Evaluation and Research (CDER) analysis of the study data concluded that injectable naltrexone was effective *only* in those who were abstinent at baseline. CDER's analysis emphasized the proportion of patients who did not relapse to heavy drinking (FDA CDER, personal communication, 2008).

**Adverse events.** In patients using oral naltrexone, high urinary levels of 6-ß-naltrexol have been associated with adverse events, such as headache, anxiety, nausea, and spontaneous erection (King, Volpicelli, Gunduz, O'Brien, & Kreek, 1997). In a multicenter study, at least 15 percent of individuals withdrew from oral naltrexone treatment because of adverse events, particularly nausea (Croop, Faulkner, & Labriola, 1997). In contrast to oral naltrexone, plasma levels of extended-release naltrexone remain relatively constant among patients taking the injectable formulation, which may be one reason for its milder adverse effects. The lack of first-pass metabolism with injectable formulations, with reduced levels of 6-ß-naltrexol, may also contribute to its improved adverse-event profile (Johnson, 2006). The peak plasma concentration of injectable preparations exceeds that of oral naltrexone during the days immediately following the injection. The higher tolerability of injectable naltrexone may be because such peaks occur daily with oral therapy but only early in treatment with the injectable formulations (Johnson, 2006). The following side effects were observed in the clinical trials of injectable naltrexone:

- **Vivitrol.** High doses (400 mg) of Vivitrol seemed to be safe and well tolerated in the 16-week clinical trial, with the four most common side effects among 40 subjects being nausea, headaches, nonspecific abdominal pain, and pain at the injection site. Two subjects dropped out from adverse effects—one from induration at the injection site and one from an allergic reaction resulting in angioedema (Johnson et al., 2004). In the longer 24-week clinical trial, subjects who received the high (380 mg) dose of Vivitrol were significantly more likely to report nausea, fatigue, decreased appetite, dizziness, and pain at the injection site than those in the low (190 mg) dose or placebo groups (Garbutt et al., 2005). Among subjects in the high-dose Vivitrol group, 14.1 percent discontinued treatment compared with 6.7 percent of those in both the low-dose and the placebo groups. Two of the high-dose subjects dropped out because of serious adverse events—allergic-type eosinophilic pneumonia and interstitial pneumonia—which resolved following medical treatment. The most frequent reasons for dropping out of the study were nausea, injection site reactions, and headaches (Garbutt et al., 2005).
- **Naltrel.** In general, the first 12-week clinical trial showed Naltrel to be safe and well tolerated at an initial dose of 300 mg (one 150 mg injection in each buttock), with subsequent doses being only 150 mg (Kranzler et al., 2004). Side effects, including upper abdominal pain, chest pain, and injection site reactions, were significantly more common in the group taking Naltrel than in those taking placebo. Reasons for discontinuing treatment were similar in the Naltrel and placebo groups, although 13 subjects taking Naltrel (8.2 percent) dropped out of treatment, compared with 6 subjects (3.8 percent) in the placebo group. No serious adverse events were reported in a subsequent 6-week, open-label trial. Sixteen subjects, followed for 6 weeks after a single 300 mg dose of Naltrel intramuscularly, reported 198 side effects. The 17 side effects rated as severe included nausea, flatulence, gastrointestinal pain, fatigue, lethargy, somnolence (two reports), depression,

irritability, headache (four reports from three participants), back pain, injection site mass, injection site pain, and an elevated GGT level (Galloway et al., 2005).

In light of one diagnosed and one suspected case of eosinophilic pneumonia in the Vivitrol trials, the manufacturer recommends that physicians consider a diagnosis of eosinophilic pneumonia in any patient receiving injectable naltrexone who develops progressive dyspnea and hypoxemia, as well as the possibility of eosinophilic pneumonia in patients who do not respond to antibiotics.

**Conditions excluding treatment with injectable naltrexone.** More research is needed to determine whether injectable naltrexone is associated with unexpected adverse or allergic reactions because three subjects in the Vivitrol trials had angioedema or pneumonia, an allergic-type reaction rate of 1:218. The Vivitrol manufacturer states that patients should not be actively drinking at the time Vivitrol is initially administered and that the medication is contraindicated in patients who have previously exhibited hypersensitivity to naltrexone, polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent.

Injectable naltrexone is a potent opioid antagonist. Contraindications to the oral form of naltrexone also pertain to the injectable formulations, including the following:

- In patients with acute hepatitis or liver failure and patients with active liver disease, injectable naltrexone must be carefully considered, given naltrexone's hepatotoxic effects. Use of injectable naltrexone should be discontinued in the event of symptoms or signs of acute hepatitis.
- In patients who are receiving opioid analgesics, patients with current physiologic opioid dependence, and patients in acute opioid withdrawal.
- In individuals who have failed the naloxone challenge test or have a positive urine screen for opioids.

There appears to be at most a fivefold margin between a safe dose of naltrexone and a dose that can cause hepatic injury. Injectable naltrexone at recommended doses does not appear to be a hepatotoxin.

**Patients appropriate for injectable naltrexone.** In reviewing the clinical evidence on injectable naltrexone, Johnson (2006) concludes that injectable naltrexone could benefit individuals who have failed at outpatient treatment using adjunctive medication, as well as other target populations. Such patients with alcohol dependence include the following:

- Patients who show low compliance with medication resulting from nonspecific factors, such as memory impairment
- Patients who experience marked or prolonged side effects from taking oral naltrexone
- Individuals who experience relatively low therapeutic effects from oral naltrexone, suggesting that a trial with an injectable preparation be done to rule out fluctuating blood levels of naltrexone as a possible cause
- Individuals who expect to be in situations where oral naltrexone might be unavailable or difficult to obtain if lost, such as overseas travelers or military personnel on short assignments

- Individuals detoxified in hospitals and awaiting referral to outpatient treatment so that medication can be available to these patients during the hiatus between detoxification and treatment
- Individuals with co-occurring alcohol and psychiatric disorders, for whom the injectable form would reduce the need for additional pills
- Offenders in forensic facilities or drug courts who could be offered the option of imprisonment or supervised treatment with injectable preparations; clear guidelines and protocols must guide the ethical use of injectable naltrexone in forensic settings.

As reported in the section on oral naltrexone, research demonstrates that people with a family history of alcoholism seem to respond best to this medication. The trials on injectable naltrexone have not explored the connection between such characteristics in men and women and the efficacy of the injectable formulation.

Estimates of efficacy—with a small to medium effect size—seem to be comparable in men taking Vivitrol or Naltrel (Johnson, 2006). However, the potential benefit of injectable naltrexone for women is unclear. The multisite clinical trials showed that injectable naltrexone can reduce heavy drinking in men, but no significant effects were shown in women. Injectable naltrexone seems to effectively reduce relapse and promote abstinence among individuals who are alcohol dependent, but the two published trials did not explore the effect of gender on treatment outcomes.

**Injectable vs. Oral Naltrexone**

No direct studies have compared the efficacies of oral and injectable naltrexone. The decision on which form of naltrexone to prescribe is likely to be driven by patient characteristics, history, and preferences.

Johnson (2006) delineates five important considerations that need to be resolved if injectable naltrexone is to be used fully in the treatment of alcohol dependence:

1. **Training of healthcare providers.** Providers need training in proper administration of the injections, which will reduce the likelihood of local site reactions and of resulting noncompliance by patients.
2. **Establishment of precedents in psychiatry for initiating an intramuscular rather than an oral medication.** Plausible guidelines might include the use of an injectable preparation after a trial of oral naltrexone has failed (presumably because of low compliance) or after a trial of oral naltrexone has shown no untoward side effects or adverse reactions for the patient. To what extent patients in real-world medical clinics will accept voluntary naltrexone injections is unknown.
3. **Cost arrangements.** Uneven insurance coverage across the United States has hindered the widespread use of oral naltrexone and can be a potential problem for injectable naltrexone. Injectable naltrexone could be limited to patients who have private insurance policies or self-pay.
4. **Flexible planning for adequate psychosocial support and monitoring of patient care.** Injectable naltrexone preparations have been tested only in conjunction with psychosocial support, which will be particularly important for patients coming in monthly for injections. An adequate standard of patient care will require a flexible approach that can provide such features as initial heightened support to establish a firm therapeutic alliance and a safety net in case of relapse.
5. **Attention to emerging knowledge about combining other medications with injectable naltrexone.** Preliminary studies suggest that adding other medications may augment the efficacy of naltrexone. If these studies are confirmed, the injectable form of naltrexone will offer important advantages, such as a lowered risk of kinetic interactions, enhanced patient compliance, and a potential for increased pharmacodynamic response against a platform of stable naltrexone levels in the blood.

### *Research needs*

The Vivitrol trial, which represents one of the largest samples ever treated with a medication for alcohol dependence, shows that this formulation could improve intervention strategies for alcohol dependence because it can provide a predictable pharmacological foundation for treatment. In addition, it has the clinical benefit of providing a firm basis for combination with other treatments, including psychotherapy, other medications, or both. Additional research will resolve the following issues raised by the multisite trial:

- **Better understanding of the effects of injectable naltrexone on women.** Treatment effects were highly significant among men taking 380 mg injectable naltrexone but not significant in women. Because only a small number of women were included in the Vivitrol study, they may not be representative of women with alcohol dependence in general. Also, women's typical heightened response to psychosocial interventions may obscure the medication effects (Garbutt et al., 2005). A recent study found that drinking outcomes with oral naltrexone seemed to be superior for women compared with men (Kiefer, Jahn, & Wiedemann, 2005b). In light of this finding, it has been suggested that the injection delivery method may inhibit its effectiveness for women. The injections may have more frequently been delivered subcutaneously rather than intramuscularly in women, thereby slowing absorption (Johnson, 2006). Recent research on the efficacy of medications injected intramuscularly in the buttocks showed that the higher percentage of body fat in women frequently causes injections into fat rather than into muscle, which can be prevented through use of longer needles. More research is needed.
- **More knowledge about treatment duration and special populations.** Additional research is needed to determine the optimal duration of treatment with long-acting naltrexone, as well as indicators that treatment can be discontinued. The usefulness of injectable naltrexone for special populations, such as people with a major mental disorder or those in the criminal justice system, is yet to be examined.

## *Acamprosate*

Acamprosate calcium delayed-release tablets were approved by FDA on July 29, 2004, for treating AUDs in patients who have completed withdrawal from alcohol. Acamprosate, manufactured by Merck KGaA and marketed by Forest Laboratories, Inc., under the brand name Campral®, became available to U.S. physicians, patients, and pharmacies on January 11, 2005. The FDA-approved labeling for acamprosate, which is available at the FDA's Web site (http://www.fda.gov), recommends that acamprosate be used in conjunction with "a comprehensive management program that includes psychosocial support." FDA approval was based on short- and long-term efficacy and safety data from four double-blind, placebo-controlled randomized trials comparing Campral plus psychotherapy with placebo plus psychotherapy (Forest Laboratories, Inc., 2005). In the three 90- to 360-day trials, which required patients to be abstinent before starting the medication, a greater percentage of those taking acamprosate rather than placebo remained abstinent.

The mechanism of action by which acamprosate maintains abstinence from alcohol is not completely understood, but it differs from the modes of naltrexone or disulfiram. Whereas naltrexone blocks the endogenous opioid reward system, acamprosate is believed to act on neurotransmitter systems in the brain that have been altered by alcohol abuse, returning them from a hyperactive to a normal state. Acamprosate has a structure similar to GABA. It is an inhibitory modulator of NMDA-type excitatory amino acid receptors, perhaps acting indirectly via metabotropic glutamate receptors. It is hypothesized that acamprosate

interacts with the glutamate neurotransmitter system thereby regulating the glutamatergic system, which reduces symptoms of withdrawal (reviewed by Litten et al., 2005; Myrick & Anton, 2004). Acamprosate thus may block protracted withdrawal symptoms that could contribute to relapse (Myrick & Anton, 2004). According to De Witte, Littleton, Parot, and Koob (2005), emerging evidence suggests that acamprosate interacts with excitatory glutamergic neurotransmission in general and as an antagonist of the metabotropic glutamate receptor subtype 5 in particular—which provides a unifying, satisfactory hypothesis to explain the diverse neurochemical effects of this medication.

Because of acamprosate's poor absorption, the recommended dose of Campral is two 333 mg tablets taken three times daily to provide a daily 2 g dose (Forest Laboratories, Inc., 2005; Sofuoglu & Kosten, 2004). Recent U.S. trials have used Campral at an exploratory level of 3 g per day; acamprosate remained safe and well tolerated in a broadly inclusive sample of subjects (Anton et al., 2006; Mason et al., 2006).

### *Research on acamprosate*

Over the past 15 years, the safety and efficacy of acamprosate for alcohol dependence have been well established in multiple double-blind, placebo-based trials (Mason, 2005). Overall, in numerous European trials, acamprosate has been consistently associated with greater beneficial effects than placebo on the following measures of alcohol abstinence: greater rates of complete abstinence, longer times to first drink, and/or an increased duration of cumulative abstinence (Mason, 2005). Surprisingly, two recent well-designed, multisite studies of U.S. patients have not shown the level of efficacy for acamprosate that is consistently demonstrated among European patients (Anton et al., 2006; Mason et al., 2006). In addition, a recent study in Australia found that use of acamprosate did not further improve the significant change that outpatients reported in their subjective health status and psychological well-being as a result of receiving CBT alone for their alcohol dependence (Feeney, Connor, Young, Tucker, & McPherson, 2006b).

Acamprosate has been used in conjunction with psychosocial or behavioral counseling to promote abstinence in 26 countries, producing an extensive body of data. By 2000, acamprosate had been studied in 17 randomized, placebo-controlled clinical trials performed in 11 European countries and South Korea and covering approximately 5,000 male and female outpatients. Reviews and several meta-analyses have been done on these trials, which all support the therapeutic effect of acamprosate (Mann, 2004; Mason, 2001; Soyka & Chick, 2003). Outcomes of the clinical trials of acamprosate at a dose of 1,998 mg per day are listed in Exhibit 2 (Mann, 2004).

**Exhibit 2**
**Published Placebo-Controlled Clinical Trials of Acamprosate 1,998 mg/day in Alcohol Dependence[a]**

| Study | Country | No. of Patients | Duration (mo)[b] | Outcome Measure | Result[c] |
|---|---|---|---|---|---|
| Chick et al., 2000 | Britain | 581 | 6/1.5 | %A | No effect |
| Lhuintre et al., 1990 | France | 569 | 3/3 | GGT | Decreased |
| Paille et al., 1995 | France | 538 | 12/6 | %A | Increased |
| Whitworth et al., 1996 | Austria | 448 | 12/12 | TFD | Increased |
| Tempesta et al., 2000 | Italy | 330 | 6/3 | %A | Increased |
| Tempesta et al., 2000 | Italy | 330 | 6/3 | CAD | Increased |
| Tempesta et al., 2000 | Italy | 330 | 6/3 | TFD | Increased |
| Barrias et al., 1997 | Portugal | 302 | 12/6 | %A | Increased |
| Barrias et al., 1997 | Portugal | 302 | 12/6 | CAD | Increased |
| Gual & Lehert, 2001 | Spain | 288 | 6/none | CAD | Increased |
| Sass et al., 1996 | Germany | 272 | 11/11 | TFD | Increased |
| Sass et al., 1996 | Germany | 272 | 11/11 | %A | Increased |
| Sass et al., 1996 | Germany | 272 | 11/11 | CAD | Increased |
| Geerlings et al., 1997 | Benelux region[d] | 262 | 6/6 | CAD | Increased |
| Geerlings et al., 1997 | Benelux region[d] | 262 | 6/6 | %A | No effect |
| Geerlings et al., 1997 | Benelux region[d] | 262 | 6/6 | TFD | Increased |
| Poldrugo, 1997 | Italy | 246 | 6/6 | CAD | Increased |
| Poldrugo, 1997 | Italy | 246 | 6/6 | %A | Increased |
| Poldrugo, 1997 | Italy | 246 | 6/6 | TFD | Increased |
| Pelc et al., 1997 | Belgium/France | 188 | 3/none | CAD | Increased |
| Pelc et al., 1997 | Belgium/France | 188 | 3/none | %A | Increased |
| Namkoong et al., 2003 | South Korea | 142 | 2/none | TFD | No effect |
| Namkoong et al., 2003 | South Korea | 142 | 2/none | CAD | No effect |
| Roussaux et al., 1996 | Belgium | 127 | 6/none | %A | No effect |
| Besson et al., 1998 | Switzerland | 110 | 12/12 | %A | Increased |
| Besson et al., 1998 | Switzerland | 110 | 12/12 | CAD | Increased |
| Pelc et al., 1992 | Belgium | 102 | 6/6 | CAD | Increased |
| Pelc et al., 1992 | Belgium | 102 | 6/6 | %A | Increased |
| Pelc et al., 1992 | Belgium | 102 | 6/6 | TFD | Increased |
| Lhuintre et al., 1985 | France | 70 | 3/none | %A (GGT & MCV) | Increased |
| Ladewig et al., 1993 | Switzerland | 61 | 6/6 | %A | No effect |
| Ladewig et al., 1993 | Switzerland | 61 | 6/6 | CAD | Increased |

a Studies are ranked by size.
b Duration of treatment/duration of additional followup beyond trial treatment period.
c The results of the studies are identified as "increased" or "decreased" only when the intergroup difference was statistically significant at the level of 0.05.
d Belgium, The Netherlands, and Luxembourg.
CAD = cumulative abstinence duration.
GGT = gamma glutamyltransferase levels.
MCV = mean corpuscular volume.
TFD = time to first drink.
%A = percentage of patients remaining abstinent at study end.

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The European acamprosate studies varied in duration from 3 months to more than a year. In 13 of 15 studies, subjects treated with acamprosate had a higher rate of treatment completion, longer time to first drink, and higher abstinence rates compared with subjects treated with placebo (Mason, 2001). In the combined studies, the abstinence rate at the end

of treatment in the acamprosate groups was 35 percent versus 21 percent in the placebo groups.

One review of the clinical data concluded that there was some evidence in three studies (those of Chick, Pelc, and Paille and their colleagues) that acamprosate could reduce craving (Mann, 2004). However, other reviewers consider it inaccurate to refer to acamprosate as an anticraving agent; they believe the evidence supports its efficacy only as a medication to prevent relapse, possibly by blocking prolonged withdrawal symptoms (Mason, 2001). Mann (2004) also concluded that, for three studies that failed to show beneficial effects of acamprosate over placebo, the possible reasons were that patient numbers were too small, a 2-month treatment period was used rather than the longer treatment periods used in the other studies, and acamprosate was not started until 25 days after patients had been weaned from alcohol, by which time many subjects were no longer abstinent.

In a recent meta-analysis of 16 studies, the relative benefit of remaining continually abstinent for 6 months after detoxification was quantified as 1.47 for subjects treated with acamprosate compared with subjects receiving placebo (Mann, Lehert, & Morgan, 2004). This meta-analysis also suggested that the relative benefit attributable to acamprosate may increase over time.

### *Acamprosate use in primary care*

Current data suggest that acamprosate may be equally useful in primary care and in specialized substance abuse treatment settings (Mann, 2004). A number of Phase IV studies of acamprosate have been made under naturalistic practice conditions that basically confirm the abstinence rates found in the placebo-controlled trials (Pelc et al., 2002; Soyka, Preuss, & Schuetz, 2002). A pragmatic trial in France compared results when 149 general practitioners, who were accustomed to managing patients in their practice, added acamprosate to standard treatment. A very high percentage of patients successfully completed the 1-year followup period (348 of 422 patients or 82.5 percent). The duration of abstinence compared well with the clinical trials: 0.67 for standard care and 0.81 for acamprosate. In clinical practice, this means that patients taking acamprosate could be expected to remain abstinent for 23 percent longer on average than patients on standard care and to experience about 2 months more abstinence during a 1-year treatment period (Kiritze-Topor et al., 2004). However, the principal finding was that adjunctive therapy with acamprosate was associated with a significantly better outcome in patients' quality of life, based on social, medical, and economic measures.

The first U.S. study to evaluate the clinical efficacy of acamprosate compared the safety and effects of the standard 2 g dose, an exploratory 3 g dose, or placebo in a double-blind, 6-month trial conducted among 601 volunteers in 21 outpatient clinics across the United States (Mason et al., 2006). All patients received the drug or placebo plus eight concomitant sessions of brief, manual-guided counseling (http://www.alcoholfree.info). The main outcome measure was the percentage of alcohol-free days over the 6-month period. Surprisingly, the percentage of abstinent days did not differ significantly across groups in the a priori analysis (54.3 percent for placebo, 56.1 percent for 2 g acamprosate, and 60.7 percent for 3 g). However, the researchers used standardized assessments to characterize the subjects at baseline according to such potential covariates as baseline goal of total abstinence, alcoholism severity, stage of readiness to change, treatment exposure, and such

psychological precedents as psychiatric hospitalizations or suicide attempts. Analysis of these covariates showed that acamprosate was associated with a significantly higher percentage of abstinent days than placebo in the subgroup of patients who had a baseline goal of abstinence (58.1 percent for placebo, 70.0 percent for 2 g acamprosate, and 72.5 percent for 3 g). Researchers concluded that acamprosate has an appreciable treatment effect among patients who have abstinence as a treatment goal.

In the COMBINE study, all groups showed substantial reduction in drinking. This multisite, U.S. study used a 3 g daily dose of acamprosate. However, the study found no evidence of efficacy for acamprosate and no evidence of incremental efficacy for combinations of naltrexone, acamprosate, and combined behavioral intervention (Anton et al., 2006). The lack of acamprosate efficacy was unexpected, given the positive results of many previous trials (Anton et al., 2006). The substantial improvement shown by all COMBINE groups, possibly in part as a result of the attention within the study itself (the "Hawthorne effect"), may have lessened the study's power to show an impact from the acamprosate.

**Adverse events.** The international and U.S. clinical trials demonstrated a favorable safety and tolerability profile (Garbutt, West, Carey, Lohr, & Crews, 1999; Mason, 2001). Side effects are generally mild, with the most frequent side effect being short-term diarrhea that is dose related and transient (Boothby & Doering, 2005). Very few patients drop out of treatment because of adverse effects. There is no risk of alcohol interactions with acamprosate, and there is no abuse potential (Mason, 2001). Participants in the first U.S. multisite trial experienced no deaths or serious drug-related adverse events (Mason et al., 2006). The COMBINE trial, using acamprosate at a 3 g dosage, found no problems with either adverse events or medication adherence (Anton et al., 2006).

**Conditions excluding treatment with acamprosate.** Acamprosate is contraindicated in patients with severe renal impairment and requires a dose reduction for patients with moderate renal impairment (Forest Laboratories, Inc., 2005). However, this medication may be particularly useful in patients with hepatic impairment and/or liver disease (Scott, Figgitt, Keam, & Waugh, 2005).

**Patients appropriate for acamprosate.** Mason and colleagues (2006) suggest that their U.S. multisite trial was "perhaps the most definitive evidence to date that acamprosate is not an effective treatment for alcohol dependence in non-motivated and non-abstinent populations."

Acamprosate is a proven effective intervention for treatment of alcohol dependence. However, acamprosate prevents lapses or relapses only in a minority of patients. Two important questions, therefore, are (1) whether acamprosate is more effective when combined with particular types of psychosocial treatment and (2) whether specific subgroups of patients respond particularly well to acamprosate.

Three Phase IV studies failed to find any significant differences in outcome among various psychosocial treatment groups, which included individual therapy, group therapy, brief therapy, and CBT. A pooled analysis of seven trials, covering 1,485 patients, was unable to identify a positive predictor of efficacy with acamprosate treatment, suggesting that acamprosate can be considered a potentially effective pharmacotherapy for all patients

(Verheul, Lehert, Geerlings, Koeter, & van den Brink, 2005). The variables looked at, none of which predicted efficacy with acamprosate, included family history of alcoholism, late age of onset, female gender, high physiological dependence, serious anxiety symptomatology, and severe craving at baseline.

Soyka and Chick (2003) recommend that patients be given an initial prescription trial of acamprosate and, if they manage to abstain, they should continue receiving the drug for 1 year. Both the European and U.S. studies suggest that treatment needs to be initiated as soon as possible after the period of alcohol withdrawal, once the patient has achieved abstinence (Soyka & Chick, 2003). Acamprosate should not be stopped if the patient lapses because this medication appears to have a small effect in reducing drinking following a relapse (Chick, Lehert, & Landron, 2003).

### *Research needs*

More research is needed to understand the different outcomes of the international versus the U.S. trials on efficacy of acamprosate. Understanding why the research results are discrepant can have important clinical implications. A number of possible reasons have been postulated for the failure of U.S. studies to show the efficacy for acamprosate shown in nearly all international studies:

- Differences in U.S. and European drinking patterns
- Length of clinical trials (European trials are generally longer than U.S. trials)
- More standardized, manual-based psychosocial treatments in U.S. trials, which may result in more consistently improved patient outcomes that reduce the perceived effect of the added medication (Mason et al., 2006)
- Differences in length of pretreatment abstinence preceding the medication (COMBINE required only 4 days of abstinence, achieved primarily on an outpatient basis, whereas most positive studies of acamprosate have a longer pretreatment abstinence period established during inpatient treatment) (Anton et al., 2006).

## Combined Medication Therapy

Currently, much scientific and clinical interest focuses on combining therapeutic agents to treat alcohol dependence. This interest is predicated on the hypothesis that multiple neurochemical pathways may be deranged as either “state” or “trait” effects of the drinking behavior, so combining effective medications that work at different neurotransmitters may produce a synergistic or at least added response (Johnson & Ait-Daoud, 2000). Knowledge is growing about how the various neurotransmitters interact in the brains of people who are alcohol dependent, as well as how this interaction may vary in different stages of the addiction. In the meantime, practical trials are being conducted that combine medications that have some demonstrated effectiveness in clinical settings, such as naltrexone and acamprosate. These trials will help determine the treatment response to combination therapies, as well as delineate the subgroups of patients most positively affected by the various combinations.

The treatment field has considerable interest in the use of therapeutic medications alone or in combination to treat patients who have co-occurring alcohol and mental disorders. The rate of substance use is higher among patients who have psychotic-spectrum mental illnesses, such as schizophrenia, schizoaffective disorder, and bipolar disorder. In a recent review of the small but growing body of literature on the use of disulfiram and naltrexone for alcoholism in patients with co-occurring mental disease, Petrakis, Nich, and Ralevski

(2006a) concluded that the literature supports the use of these medications for patients with co-occurring psychotic-spectrum disorders. Recent research on pharmacological treatment for such patients includes the following:

- A 12-week randomized clinical trial of disulfiram and naltrexone each alone and in combination was conducted on individuals with Axis I disorders and alcohol dependence who were receiving intensive psychosocial treatment. Compared with controls on placebo, patients with psychotic-spectrum disorder had better alcohol outcomes on an active medication, but no clear advantage was seen for disulfiram, naltrexone, or the combination. Retention rates and medication compliance were high, exceeding 80 percent (Petrakis et al., 2006a).
- Both disulfiram and naltrexone were effective and safe in a subgroup of 93 veteran outpatients in this randomized trial who had posttraumatic stress disorder (PTSD) and co-occurring alcohol dependence. Patients had better alcohol outcomes with naltrexone, disulfiram, or the combination than they did on placebo; their overall PTSD psychiatric symptoms also improved (Petrakis et al., 2006b).
- A 16-week, open-label pilot study of naltrexone with 34 outpatients who had bipolar disorder and alcohol dependence found that the medication was well tolerated. Patients showed significant improvement on rating scales for depression and mania, and days of alcohol use and craving decreased significantly (Brown, Beard, Dobbs, & Rush, 2006).

### *Disulfiram Combined With Acamprosate*

Concomitant administration of disulfiram with acamprosate may improve the effectiveness of acamprosate. Besson and colleagues (1998) conducted a double-blind study of 118 patients who were randomly given acamprosate or placebo, with both groups stratified for voluntary, concomitant use of disulfiram. Treatment lasted for 360 days, with a 360-day followup. The subgroup that received both medications had better outcomes with regard to duration of its cumulative abstinence than did the subgroups on one or no medication. No adverse interaction occurred in patients taking concomitant disulfiram and acamprosate, with diarrhea being the only significant treatment-induced effect.

### *Acamprosate Combined With Naltrexone*

Since 1995, an extensive body of clinical trial data indicates that both acamprosate and naltrexone are effective in the treatment of alcohol dependence. Clinical trials with acamprosate demonstrate that this drug significantly increases the proportion of patients who remain abstinent after acute detoxification (Mann et al., 2004; Mason, 2001). For naltrexone, the most reproducible finding is that it reduces relapse into heavy drinking (Kranzler & Van Kirk, 2001; Streeton & Whelan, 2001). Some studies show that naltrexone reduces craving and the desire to drink in social drinkers and in people with alcohol dependence who are both abstinent and nonabstinent (Kiefer & Wiedemann, 2004).

However, each drug has been shown to be effective in only 20 to 50 percent of unselected patients with alcoholism (Kreek et al., 2002). Because the two drugs have different pharmacological mechanisms of action and appear to act on different behavioral aspects of alcohol dependence, combining these drugs might provide greater benefit than either provide alone.

Kiefer and Wiedemann (2004) reviewed three preclinical and four clinical studies published since 2000 on the pharmacologic aspects of combined treatment. Their meta-analysis

concluded that the combination of acamprosate with naltrexone seems to be both safe and effective, with no negative effects on safety or cognitive function (Kiefer & Wiedemann, 2004). The available data show no severe adverse events during the combined treatment, with diarrhea and nausea being the most significant side effects. The clinical data showed that combined treatment was superior to both placebo and therapy with acamprosate alone. The synergistic effect of combined treatment remained after 12 weeks of drug-free followup (Kiefer & Wiedemann, 2004). A recent 12-week, single-site study in Australia found that the combination of acamprosate and naltrexone, with CBT, was superior to either medication alone for alcohol abstinence (Feeney, Connor, Young, Tucker, & McPherson, 2006a). Naltrexone alone with CBT was slightly less effective on all measures than the combined medication. Studies suggest the following explanations for a potentiated effect from the combined drugs:

- The administration of acamprosate with naltrexone unexpectedly—and significantly—increased the rate and extent of absorption of acamprosate by about 33 percent (Johnson et al., 2003b; Mason et al., 2002). This suggests that combination treatment may make acamprosate more available systemically with no decrease in tolerability, which may provide clinical advantages.
- Some patient subgroups may respond preferentially to the anticraving effects of either drug—either being "reward cravers" (naltrexone) or "relief cravers" (acamprosate) or because of other as yet undetermined factors (Kiefer & Wiedemann, 2004). Pharmacological anticraving treatment may also be more effective with patients who have early-onset alcohol dependence (Johnson, Ait-Daoud, & Prihoda, 2000). Larger prospective studies need to evaluate whether any factors can predict a positive response to anticraving treatment.
- The combination of naltrexone and acamprosate may produce a more incisive anticraving effect in patients than either drug alone. Such a synergy could result from two drugs interfering with two distinct biological aspects of the craving process—reward and relief craving. If this is true, then it would be unlikely that distinct groups would respond preferentially to either drug (Keifer & Wiedemann, 2004).

Although more testing is needed, the results to date suggest that some patients could benefit from combined acamprosate–naltrexone therapy (Kiefer & Wiedemann, 2004). The combined treatment could benefit particularly those patients who have had an inadequate response to either naltrexone or acamprosate alone (Kiefer & Wiedemann, 2004).

### *The COMBINE Clinical Trial*

So far, only a limited number of controlled clinical trials have been conducted on combination treatments. Both researchers and practitioners have been eagerly awaiting results from the COMBINE study, NIAAA's sophisticated, 11-site combination therapy trial with almost 1,400 subjects in the context of primary care and other nonspecialty treatment settings. In addition to comparing the efficacy of naltrexone and acamprosate separately and together for 16 weeks, the study also looked at these pharmacotherapies in combination with different intensities of behavioral interventions. (Note: The behavioral interventions integrate successful elements of those evaluated in NIAAA's Project MATCH.) The COMBINE study had two pilot studies, which showed the safety and feasibility of the approach (COMBINE Study Research Group, 2003).

This randomized clinical trial was conducted from January 2001 to January 2004 among volunteers who were recently alcohol abstinent (median age 44 years) and who had a *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1994) diagnosis of primary alcohol dependence. Eight groups of patients received medical management combined with 16 weeks of naltrexone (100 mg/day), acamprosate (3 g/day), both medications, and/or placebos—both with and without a combined behavioral intervention (CBI). Patients were evaluated at 16 weeks and for up to 1 year after treatment, looking at the percentage of days they were abstinent from alcohol and the time elapsed to their first heavy drinking day. Results were as follows:

- All groups showed substantial reductions in drinking.
- A significant interaction was found in those receiving naltrexone + a behavioral intervention. Patients receiving (1) naltrexone + medical management, (2) CBI + medical management + placebos, or (3) naltrexone + CBI + medical management had a higher percentage of days abstinent (80.6, 79.2, and 77.1, respectively) than the 75.1 percent among those who received placebos and medical management only.
- Naltrexone reduced the risk of a heavy drinking day, which was most evident in those receiving medical management but not CBI.
- Acamprosate, unexpectedly, showed no significant effect on drinking versus placebo, either by itself or with any combination of naltrexone, CBI, or both. This result was unexpected, because the study hypothesis and an earlier COMBINE single-site study had supported the combined use of acamprosate and naltrexone (Kiefer & Wiedemann, 2004). However, because all groups in this study, including the control groups, showed significant reductions in drinking, the power necessary to detect a statistically significant difference between groups may have been lost. As Johnson (2006) points out, pharmacotherapy trials increasingly demonstrate that the greatest treatment effect comes from being enrolled in a study irrespective of the treatment condition; this can make any statistically significant difference between the active medication and placebo groups seem relatively small clinically.

A major finding of the COMBINE study was that patients who received medical management with naltrexone or with behavioral intervention or the combination of both fared better on drinking outcomes than those on acamprosate. Other significant findings included the following:

- Medical management in primary care settings can be an effective means of treating alcohol-dependent populations. Most COMBINE groups received a nine-session medical management intervention that focused on enhancing medication adherence and abstinence, using a model that could be adapted by primary care settings. In the context of medical management, naltrexone yielded outcomes similar to those from behavioral treatment provided by substance abuse treatment specialists. Unexpectedly, the patients who received medical management and placebo showed a positive effect over and above that seen in patients who received only specialist-delivered behavioral therapy.
- At 1 year after treatment, the COMBINE study found that the differential effects of treatment still persisted, but these effects were only marginally significant. These results suggest that a number of individuals require either prolonged or intermittent care. This tends to validate previous research suggesting that useful approaches for those who do well during initial treatment would be (1) continued naltrexone and medical monitoring, (2) the continuation of behavioral intervention, or (3) both

continued naltrexone–medical monitoring and behavioral intervention (Anton et al., 2006).

## Research on Promising Drugs

People who develop chronic alcoholism, either because of being genetically at risk or because of sustained, persistent heavy use, ultimately develop brain changes (Anton, 2002). Neuroadaptive changes, or sensitized changes, mean that the brains of people with alcohol dependence are definitely different, both from the brains that they had before they started drinking heavily and from the brains of social drinkers. Through medication, physicians can affect alcoholism in three major areas: (1) reward or reinforcement, (2) protracted withdrawal, and (3) disorder or impulse control (Anton, 2002).

Current research on drugs could potentially be effective in each of these areas. For example, nalmefene and ondansetron are drugs being tested that may work on the patient's reward system. The selective serotonin reuptake inhibitors (SSRIs) and buspirone work on serotonergic systems, trying to stabilize affective or impulsive conditions that may work, along with the reward mechanisms, to increase a person's risk of relapse to persistent alcohol use (Anton, 2002). A second rationale for the use of serotonergic drugs in alcohol pharmacotherapy is that studies have clearly shown that serotonin modulates the mesolimbic dopamine transmission. It has been suggested that serotonin-dependent activation of dopaminergic neurons in the ventral tegmental area contributes to the reinforcing effects of alcohol consumption (Tambour & Quertemont, 2007).

Because of the increased understanding of the neurobiology of alcoholism, researchers can study combinations of agents that act on different neurotransmitter systems and can potentially enhance the effect of either medication alone. There is particular interest in potential combinations of naltrexone with other drugs for specific conditions. Some preliminary reports suggest that combining naltrexone with ondansetron may be of some use (Ait-Daoud, Johnson, Prihoda, & Hargita, 2001). Some pharmacologic agents now being studied include the following:

- **Opiate receptor antagonists.** Nalmefene, which may have a profile similar to naltrexone, shows promising activity in single-site pilot studies (Mann, 2004), but a multisite study found no evidence of superior efficacy outcomes with nalmefene treatment over placebo (Anton et al., 2004). A 2005 meta-analysis of the available research concluded that the evidence on nalmefene was insufficient at that time to warrant use (Srisurapanont & Jarusuraisin, 2005). However, a Finnish multisite, randomized double-blind study recently found that targeted nalmefene was more effective than placebo at reducing heavy drinking among 403 subjects in alcohol treatment centers and private general practices (Karhuvaara et al., 2007). This study is described above in Updated Findings From the Literature, October 2007.
- **Serotonergic agents.** SSRIs have not proved to have much effect on drinking behavior when used alone, but they might be effective in combination with other drugs. Some studies suggest that SSRIs may be useful in reducing alcohol use among people with Type A alcoholism, as classified by Babor and colleagues (Myrick & Anton, 2004) and that SSRIs may be just as effective for treating depression in people who are alcohol dependent as in those without alcohol problems (Anton, 2002). The serotonin type-3 antagonist ondansetron has shown promise in subjects with early-onset alcohol dependence but needs more extensive study (Anton & Swift,

2003). Some preliminary reports also suggest that combining naltrexone with SSRIs may be of some use.

- **Anticonvulsant agents.** Double-blind, placebo-controlled trials of carbamazepine, divalproex, and topiramate have shown positive effects on several measures of drinking behavior and craving among patients. In 2007, the anticonvulsant drug topiramate was reported to be a safe, consistent, and efficacious treatment for alcohol dependence in a large, multisite study (Johnson et al., 2007) done to replicate and extend an earlier small, double-blind, placebo-controlled trial. The positive findings of this large, multisite trial of topiramate are described above in Updated Findings from the Literature, October 2007.

## Extent of Pharmacotherapy Use by Medical Care Providers

Only a small percentage of practitioners use the available pharmacotherapies for treating addiction. This pattern of underuse is found in every professional group studied, including general practitioners, family physicians, VA physicians, and addiction psychiatrists (Petrakis, Leslie, & Rosenheck, 2003; Thomas et al., 2003). For example, one study found that addiction specialists were prescribing naltrexone to only 3 to 13 percent of their patients (Mark, Kranzler, & Song, 2003b). If pharmacotherapies are to be used at an optimum level, then medical administrators and specialty treatment programs will need to address the reasons for physicians' reluctance to use these medications. Reasons for nonuse tend to be the same across studies and include the following:

- Lack of awareness about the medication (pharmaceutical companies have not provided information about drugs for addiction—to professionals or consumers—as they have for other medications)
- Lack of knowledge about efficacy of the drug in practice, as well as a perceived lack of evidence that the drug would be effective
- The time required for patient management
- Lack of reimbursement and inability of patients to pay for the drug (Mark et al., 2003a).

When physicians have more information about a drug, they prescribe it more (Mark et al., 2003b). A drug such as naltrexone is used more often when the treatment organization in which physicians work promotes its use (Thomas et al., 2003). In addition, several studies indicate that patients have better outcomes when the physician believes that a medication will be effective. Several studies, particularly those pertaining to methadone or buprenorphine, reported that training of physicians resulted in much more positive attitudes about treating patients who are drug dependent and about the value of pharmacotherapy (McCarty, Rieckmann, Green, Gallon, & Knudsen, 2004).

Although substance use disorders constitute one of the most significant public health issues in the United States, there is evidence that physicians frequently do not appropriately screen, diagnose, provide treatment interventions, or make referrals to specialists for patients with these disorders (AMA Council on Medical Education, 2007). Physicians receive little or no training on treating addictions during medical school. In 2005–2006, just 46 percent of U.S. medical schools offered both required and elective course hours on the topic of substance abuse, and the mean number of course hours required was less than 16 (AMA Council on Medical Education, 2007). It is becoming increasingly important that physicians gain more professional knowledge in this area.

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Whitworth, A. B., Fischer, F., Lesch, O. M., Nimmerrichter, A., Oberbauer, H., Platz, T., et al. (1996). Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. *Lancet, 347,* 1438–1442.

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# Section 2—Annotated Bibliography

**Reference:** Anton, R. F., Moak, D. H., Latham, P., Waid, L. R., Myrick, H., Voronin, K., et al. (2005). Naltrexone combined with either cognitive behavioral or motivational enhancement therapy for alcohol dependence. *Journal of Clinical Psychopharmacology, 25*(4), 349–357.
**Purpose:** Compare the effectiveness of naltrexone and placebo when specifically combined with either cognitive-behavioral therapy (CBT) or motivational enhancement therapy (MET) in outpatients with alcoholism.
**Conclusions:** Naltrexone was superior to placebo in reducing relapse and craving, especially when combined with CBT.
**Methodology:** Outpatients who had maintained abstinence before study enrollment and met the study inclusion/exclusion criteria were given a baseline assessment over a 5–10-day period. Study participants were randomly assigned to one of four study groups: CBT plus placebo, CBT plus naltrexone, MET plus placebo, and MET plus naltrexone. Participants in the CBT groups had therapy weekly for 12 weeks, whereas those in the MET groups met 4 times in 12 weeks.
**Summary of Results:** A total of 160 outpatients were randomized into 1 of 4 study groups. Compliance, study retention, and characteristics of study participants were similar across the study groups. Fewer patients relapsed (38 percent) in the CBT/naltrexone group than in the other groups ($p < 0.05$). The percentage of days abstinent was highest in the CBT/naltrexone group (91 percent vs. 79 percent in the CBT-only group [$p < 0.05$]). Naltrexone, independent of therapy group, slowed the time to the first relapse ($p = 0.05$), and the time to successive relapses was significantly prolonged for the CBT/naltrexone group ($p = 0.02$ for third relapse and $p = 0.01$ for fourth relapse). The obsession factor decreased more in subjects treated with naltrexone ($F_{1,146} = 3.95$, $p = 0.049$). Gamma glutamyl transpeptidase decreased significantly more in subjects treated with naltrexone ($F_{2,149} = 10.41$, $p < 0.0001$).

**Reference:** Anton, R. F., O'Malley, S. S., Ciraulo, D. A., Cisler, R. A., Couper, D., Donovan, D. M., et al., & COMBINE Study Research Group. (2006). Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence: The COMBINE study, A randomized controlled trial. *JAMA, 295*(17), 2003–2017.
**Purpose:** Study whether medications for alcohol are effective without specialist intervention and whether combining different medications improves efficacy.
**Conclusions:** Patients receiving medical management had better outcomes with either combined behavioral intervention (CBI) or naltrexone. Acamprosate was ineffective with or without CBI. The combined use of naltrexone and acamprosate was not more effective than naltrexone or CBI alone.
**Methodology:** Random assignment of 1,383 study participants into 9 study groups for 16 weeks of outpatient treatment occurred after a baseline assessment and abstinence for at least 4 days. Eight study groups received medical management and, of these, four received CBI and four did not. Within each grouping of four, one received placebo, one naltrexone, one acamprosate, and one naltrexone and acamprosate combined. The ninth study group received CBI alone without pills or medical management.

**Summary of Results:** Adverse events such as nausea ($p < 0.001$), vomiting ($p < 0.001$), diarrhea ($p < 0.001$), decreased appetite ($p = 0.002$), and somnolence ($p = 0.003$) differed significantly, with higher percentages in the combined medication groups. Internal study validity was high, and all groups showed substantial reduction in drinking. For percentage of days abstinent through end of treatment, none of the main effects of acamprosate, naltrexone, and CBI were significant; however, the two-factor interaction was significant (naltrexone/no CBI [80.6] vs. placebo/no CBI [75.1] [$p = 0.009$]). For percentage of participants with 1 or more heavy drinking days during treatment, only the main effect of naltrexone versus placebo was significant (68.2 percent vs. 71.4 percent, $p = 0.02$).

**Reference:** Anton, R. F., & Swift, R. M. (2003). Current pharmacotherapies of alcoholism: A U.S. perspective. *American Journal on Addictions, 12*(Suppl 1), S53–S68.
**Purpose:** Review current knowledge about the newest medications being used to reduce alcohol consumption and craving and prevent relapse in patients in the United States.
**Conclusions:** Medications should be used as part of a comprehensive treatment plan that addresses the psychological, social, and spiritual needs of the patient.
**Methodology:** Eleven naltrexone studies were reviewed. Several studies were reviewed for all other medications.
**Summary of Results:** Craving is likely to have a neuroanatomical basis; the effects of medications on craving are varied. Disulfiram has limited acceptance and may be most effective among older, motivated individuals who receive supervised medication administration. Naltrexone has been shown to reduce relapse and heavy drinking and modestly increase abstinence; it may work best with relapse prevention therapy. Enhancing adherence is key to the use of medications. A naltrexone monthly injection has been developed to increase adherence. Acamprosate is well tolerated and has been shown to reduce relapse and increase days of abstinence. Patients taking selective serotonin reuptake inhibitors report a decreased desire and liking for alcohol. People with Type A alcoholism (later onset and less severe dependence) appeared to benefit from fluoxetine compared with placebo. Low doses of ondansetron moderately reduced alcohol consumption in males who are alcohol dependent. Lithium has not been shown to reduce drinking. Carbamazine has been reported to reduce alcohol withdrawal and may reduce rebound drinking. Multiple medications administered together or in sequence may be required to obtain optimal treatment effectiveness. Medications must be cost effective to be used in alcoholism treatment programs.

**Reference:** Boothby, L. A., & Doering, P. L. (2005). Acamprosate for the treatment of alcohol dependence. *Clinical Therapeutics: International Peer-Reviewed Journal of Drug Therapy, 27*(6), 695–714.
**Purpose:** Review the existing data on the pharmacokinetics and efficacy of acamprosate.
**Conclusions:** Evidence shows moderate efficacy of acamprosate. The combination of acamprosate, naltrexone, and psychosocial treatment has superior efficacy.
**Methodology:** The study reviewed articles from 1966 to 2005 in MEDLINE, International Pharmaceutical Abstracts, Current Contents, Cumulative Index to Nursing, and Allied Health Literature.
**Summary of Results:** Thirty-two articles were reviewed. According to the evidence, acamprosate is an analog of taurine and gamma-aminobutyric acid (GABA); it acts on GABA and glutaminergic receptors in the nucleus accumbens; and it suppresses the excitatory neurochemical process that occurs with chronic alcohol use. The percentage of treatment subjects who achieved abstinence ranged from 18 to 61.

**Reference:** Bouza, C., Magro, A., Muñoz, A., & Amate, J. M. (2004). Efficacy and safety of naltrexone and acamprosate in the treatment of alcohol dependence: A systematic review. *Addiction, 99,* 811–828.
**Purpose:** Determine the efficacy and safety of naltrexone and acamprosate in treating alcohol dependence.
**Conclusions:** Acamprosate appears to fit well within a classic therapeutic framework with a goal of abstinence, whereas naltrexone seems more useful when the goal is controlled consumption. Both drugs appear to be safe.
**Methodology:** This study was a literature review of 33 studies that measured relapse and abstinence rates. All studies were published, randomized, controlled clinical trials, comparing naltrexone or acamprosate with a placebo or control group. All studies were on adults who were alcohol dependent. The review included studies in which the analysis and data presented were comparable with one another.
**Summary of Results:** The acamprosate-versus-placebo trials included 4,000 subjects who were alcohol dependent who had undergone detoxification. As shown on the seven studies that supplied data, acamprosate doubled the cumulative days of abstinence. Naltrexone studies included 3,205 participants. These studies showed a favorable effect on time to relapse, percentage of drinking days, number of drinks per drinking day, days of abstinence, and total consumption of alcohol during treatment.

**Reference:** Brewer, C., Meyers, R. J., & Johnsen, J. (2000). Does disulfiram help to prevent relapse in alcohol abuse? *CNS Drugs, 14*(5), 329–341.
**Purpose:** Review published clinical studies in which disulfiram administration was supervised to assess whether disulfiram successfully prevents relapse to alcohol abuse.
**Conclusions:** All but one of the controlled studies reviewed demonstrated positive outcomes from supervised disulfiram administration to prevent relapse to alcohol abuse. Patients who benefit the most from supervised disulfiram therapy are those who have a history of repeated nonpharmacological treatment failure, who have numerous drinking triggers, and who face serious consequences if they relapse.
**Methodology:** MEDLINE was searched for all studies between 1966 and 1999 in which disulfiram administration was directly supervised at least weekly. Thirteen controlled and five uncontrolled studies were reviewed and summarized.
**Summary of Results:** Supervised disulfiram use is more effective in preventing relapse to alcohol abuse than unsupervised use. In several studies, the supervised group experienced reduced drinking, prolonged remissions, reduced absenteeism at work, improved treatment retention, and improved compliance with other therapy. A few studies compared supervised disulfiram with acamprosate or naltrexone. The effectiveness of acamprosate was increased in one study by combining it with supervised disulfiram. In another study, the disulfiram group did significantly better on all measures of both cocaine and alcohol use than did the naltrexone group. Disulfiram has a deterrent effect because of the disulfiram–alcohol reaction; patients surrender control over their urge to drink by taking the medication. Administration can be monitored by a spouse, family member, employer, partner, landlord, health professional, therapist, or probation officer. Failure of compliance is detected by the monitor and reported quickly to a health professional who can intervene before the patient resumes drinking. Supervised disulfiram therapy should continue for at least 6 months.

**Reference:** Buonopane, A., & Petrakis, I. L. (2005). Pharmacotherapy of alcohol use disorders. *Substance Use & Misuse, 40,* 2001–2020.

**Purpose:** Provide an overview of the literature on the epidemiology, gender, and psychiatric comorbidity of alcohol use disorders; issues in neurobiology; and future treatment directions for alcohol pharmacotherapy.
**Conclusions:** Alcohol pharmacotherapy research has resulted in new pharmacological interventions; however, barriers still exist to their use. More research and clinical guidelines are needed to identify subgroups of patients who may benefit from the use of specific medications or combinations of different treatments acting on different neurotransmitters.
**Methodology:** Medications used clinically for the treatment of alcoholism are reviewed in detail. These include disulfiram, naltrexone, acamprosate, and serotonergic agents.
**Summary of Results:** The epidemiology of alcoholism in the United States reveals that almost 14 percent of Americans have alcohol use-related problems in their lifetimes. Women have higher rates of alcohol-related morbidity and mortality despite ingesting smaller daily amounts of alcohol. All patients, but especially women with alcohol use disorders, have high rates of comorbid psychiatric or mood disorders. An overview is given of the effect of alcohol on a variety of neurotransmitters such as dopamine, glutamate, gamma-aminobutyric acid, ß-endorphin, serotonin, cannabinoids, and neuropeptides. Medications that interact with these neurotransmitters are reviewed. Of these medications, naltrexone, acamprosate, and serotonergic agents are reviewed in detail. Future directions for treating alcohol dependence include the use of anticonvulsants and the opioid antagonist nalmefene, which is less hepatotoxic than naltrexone. Future research may indicate that the use of combinations of medications rather than the use of a single medication may achieve better results with alcoholism treatment.

**Reference:** Chick, J. (1999). Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Safety, 20*(5), 427–435.
**Purpose:** Review the literature on the safety of disulfiram when used to treat alcohol dependence.
**Conclusions:** Although disulfiram may cause hepatotoxicity, fatal hepatitis is a rare consequence of disulfiram use. Occasional, dose-related cases of psychosis and confusional states, peripheral neuropathy, and optic neuritis have been reported. Medical supervision of patients taking disulfiram should be at least monthly for the first 6 months and continue throughout the course of drug therapy.
**Methodology:** The literature on the safety of disulfiram was reviewed by searching MEDLINE and the Adis International database from 1966 to 1998. A manual search was conducted of the *Quarterly Journal of Studies on Alcohol, British Medical Journal*, and *Journal of the American Medical Association* from 1950 to 1966. All studies were included, although many reported on individual cases.
**Summary of Results:** Disulfiram may cause hepatotoxicity at the recommended dosage level of 250 mg/day and may rarely cause fatal hepatitis. The risk of fatal hepatitis caused by disulfiram has been estimated at 1 in 30,000 patients per year and may be more likely when disulfiram is continued after jaundice develops. Because the onset of hepatitis is rapid, frequent monitoring of liver function tests may not detect it. An occasional confusional state (beginning with fatigue and forgetfulness) or psychosis was reported particularly with the use of high doses (500 mg/day or more) of disulfiram. Neuropathy is a rare and reversible event, peaking 1 year after starting treatment. Common but less serious adverse effects include tiredness, headache, sleepiness, and an unpleasant “garlic-like” breath odor. Patients and their families should be advised of possible adverse effects of disulfiram.

**Reference:** Chick, J., Gough, K., Falkowski, W., Kershaw, P., Hore, B., Mehta, B., et al. (1992). Disulfiram treatment of alcoholism. *British Journal of Psychiatry, 161*, 84–89.
**Purpose:** Assess the efficacy of disulfiram in outpatient treatment of alcohol dependence.
**Conclusions:** Disulfiram improves treatment outcomes for people with alcohol dependence in outpatient treatment.
**Methodology:** This randomized, partially blind clinical trial enrolled 126 patients who had relapsed after previous treatment and were attending treatment at an outpatient alcoholism clinic. Exclusion criteria were pregnancy; cardiac disease; psychosis; habitual drug abuse; and high levels of serum bilirubin, aspartate aminotransferase, or alanine aminotransferase. Subjects were randomized to either a 200 mg tablet of disulfiram or 100 mg of vitamin C for 6 months. Outcome measures were blood tests, medical and psychiatric history, compliance (monitored by self-report, the clinician, and an informant), alcohol consumption, alcohol dependence (using the Severity of Alcohol Dependence Questionnaire), and alcohol-related health and social problems.
**Summary of Results:** Subjects were mostly unemployed males. The mean age was 43. Change in weekly consumption before and after treatment was significant, according to patient (M = 44, 95 percent CI = 14-79, $P < 0.01$) and assessor (M = 31, 95 percent CI = 6-63, $P \leq 0.05$) measures. Change in amount consumed in the past 6 months was also significant, comparing pretreatment and posttreatment, according to patient (M = -1702, 95 percent CI = -2016 to -290, $P < 0.01$), informant (M = -1636, 95 percent CI = -2052 to -238, $P \leq 0.05$), and assessor (M = -1124, 95 percent CI = -1620 to -84, $P \leq 0.05$) measures. There were no treatment differences at month 5 in amount of days since last drink (7.77 days for disulfiram vs. 3.65 days for vitamin C). Alcohol dependence scores fell from pretreatment to posttreatment for patients in both groups (disulfiram mean change with treatment: -8.3, SD = 15.8 vs. vitamin C mean change with treatment: -10.8, SD = 16.9). Alcohol-related problems were not significantly different between the treatment and control groups ($P = 0.06$).

**Reference:** Chick, J., Lehert, P., Landron, F., & Plinius Maior Society. (2003). Does acamprosate improve reduction of drinking as well as aiding abstinence? *Journal of Psychopharmacology, 17*(4), 397–402.
**Purpose:** Determine the impact of acamprosate on patients in abstinence-oriented treatment who relapse.
**Conclusions:** Acamprosate helps control the drinking of patients in abstinence-oriented treatment who relapse.
**Methodology:** Secondary data were analyzed from 15 placebo-controlled clinical trials on acamprosate for patients in abstinence-oriented treatment. Outcomes were median drinks per drinking day (quantity) and per week (frequency). Total consumption was calculated using the values for quantity and frequency.
**Summary of Results:** Patients using acamprosate had lower quantities, lower frequencies, and less consumption than patients receiving placebo. This was true for four different treatment periods: 30 days ($P = 0.006$, 0.101, $< 0.001$), 90 days ($P = 0.005$, 0.027, 0.001), 180 days ($P = 0.004$, 0.005, $< 0.001$), and 360 days (0.074, 0.245, $< 0.001$).

**Reference:** De Sousa, A., & De Sousa, A. (2004). A one-year pragmatic trial of naltrexone vs. disulfiram in the treatment of alcohol dependence. *Alcohol & Alcoholism*, *39*(6), 528–531.
**Purpose:** Compare effectiveness of naltrexone and disulfiram in treating alcohol dependence.

**Conclusions:** Disulfiram appears to control drinking more effectively.
**Methodology:** The study included 100 men who were alcohol dependent (per DSM-IV) from stable family environments. Family members agreed to support and monitor compliance. Subjects with other substance dependence (other than nicotine) or comorbid psychiatric disorder were excluded. Subjects were told that relapse or noncompliance would result in exclusion from the trial. Subjects received a daily dose of either naltrexone or disulfiram. Subjects knew which group they were in and were told what to expect from their treatment. They were seen weekly for 3 months, then every other week until the end of 1 year. Cumulative days of abstinence, days to first relapse, drinks per week, drinks per occasion, craving measures, and serum gamma glutamyl transpeptidase (GGT) were measured regularly. Chi-squared test and t-test were used in statistical analysis.
**Summary of Results:** Time to first relapse was greater for disulfiram than for naltrexone: relapse occurred at a mean of 119 days with disulfiram and 63 with naltrexone ($p = 0.02$). Fourteen percent of the disulfiram group relapsed, compared with 56 percent of the naltrexone group ($p = 0.0009$). Twice as many disulfiram patients remained abstinent as naltrexone patients. Naltrexone patients had lower craving levels. Mean serum GGT was 117 U/I with naltrexone and 85 U/I with disulfiram ($p = 0.038$).

**Reference:** De Witte, P., Littleton, J., Parot, P., & Koob, G. (2005). Neuroprotective and abstinence-promoting effects of acamprosate. *CNS Drugs, 19*(6), 517–537.
**Purpose:** Evaluate multiple lines of recent (since 2000) evidence on the effects of acamprosate on the glutamatergic system, revealing the underlying biology of alcohol dependence and the abstinence-promoting benefit of acamprosate.
**Conclusions:** There is strong evidence that acamprosate has a normalizing effect on glutamatergic hyperactivity.
**Methodology:** An extensive literature review was conducted on excitatory amino acid receptors; excitatory amino acids in alcohol withdrawal; excitatory amino acids in alcohol dependence; excitatory amino acids and the neurotoxicity of ethanol; and excitatory amino acid, ethanol, and acamprosate in humans. References list 121 sources.
**Summary of Results:** Extrapolating from review findings on the role of the glutamatergic system in alcohol dependence and the effect of acamprosate on the glutamatergic system, the authors conclude that acamprosate should reduce craving and reduce the quantity and severity of relapses caused by dysphoria. Cues for alcohol consumption that contribute to alcohol dependence may be extinguished or prevented by acamprosate. Acamprosate's action of inhibiting glutamatergic transmission is likely to ease the severity of withdrawal syndrome. Finally, acamprosate is likely to protect against neuronal loss during withdrawal and rehabilitation.

**Reference:** Dunbar, J. L., Turncliff, R. Z., Dong, Q., Silverman, B. L., Ehrich, E. W., & Lasseter, K. C. (2006). Single- and multiple-dose pharmacokinetics of long-acting injectable naltrexone. *Alcoholism: Clinical and Experimental Research, 30*(3), 480–490.
**Purpose:** Evaluate the pharmacokinetics and tolerability of long-acting naltrexone in a sample of healthy people.
**Conclusions:** Long-acting naltrexone, in single and multiple doses, had adequate pharmacokinetics and was well tolerated among healthy subjects.
**Methodology:** This single-center, randomized, double-blind, parallel-group study (two panels) enrolled healthy, nonsmoking men and women ages 18–50. Exclusion criteria included a history of alcohol or opioid dependence or both, potential for use of narcotic analgesia during the study, and women who tested positive for pregnancy. One group

received a 50 mg dose of oral naltrexone and, after a 7-day intermission, a 190 mg (n = 12) or 380 mg (n = 12) injection of long-acting naltrexone or placebo (n = 4). A second group received a daily 50 mg dose of oral naltrexone for 5 days and, after a 7-day intermission, one 380 mg (n = 12) injection of long-acting naltrexone or placebo (n = 2) per week for 4 weeks. Blood samples were obtained and analyzed for naltrexone and the metabolite 6-ß-naltrexol. Outcomes for pharmacokinetics were dose proportionality, time dependency, accumulation, and achievement of a steady state. Outcomes for tolerability were reported to the investigator, who evaluated their intensity.
**Summary of Results:** Twenty-one subjects, with equal distributions of males and females, ranging in age from 20 to 49 years (μ = 36.9, SD = 7.9) completed the trial. Pharmacokinetics of single and multiple doses of long-acting naltrexone were adequate and consistent (naltrexone: $AUC\infty$ = 1.975, 90 percent CI = 1.756-2.222; $C_{max}$ = 1.455, 90 percent CI = 0.991-2.135; AUC = 1.124, 90 percent CI = 0.982-1.287; $t_{1/2}$ = 0.951, 90 percent CI = 0.772-1.172; accumulation = 1.134, 90 percent CI = 0.048-1.226. 6-ß-naltrexol: $AUC\infty$ = 1.843, 90 percent CI = 1.590-2.137; $C_{max}$ = 1.565, 90 percent CI = 1.075-2.279; AUC = 0.896, 90 percent CI = 0.754-1.065; $t_{1/2}$ = 0.908, 90 percent CI = 0.755-1.092; accumulation = 1.114, 90 percent CI = 1.043-1.191). Naltrexone was well tolerated by participants. Mild events reported by participants were nausea (n = 5), somnolence (n = 4), and dizziness (n = 2).

**Reference:** Fuller, R. K., Branchey, L., Brightwell, D. R., Derman, R. M., Emrick, C. D., Iber, F. L., et al. (1986). Disulfiram treatment of alcoholism: A Veterans Administration cooperative study. *JAMA, 256*(11), 1449–1455.
**Purpose:** Identify the effectiveness of disulfiram for treatment of alcohol dependence among men seeking treatment.
**Conclusions:** Disulfiram is useful in reducing drinking days among men who are unable to achieve total abstinence.
**Methodology:** This controlled, blinded, multicenter study recruited men seeking treatment at nine Veterans Administration medical centers, who met National Council on Alcoholism criteria for alcoholism. Exclusion criteria were living alone, presence of a medical condition that contraindicated treatment with disulfiram, history of destructive behavior, uncooperativeness, psychoactive drug abuse, abstinent for more than 1 month, and place of residence more than 80 km from the hospital. Subjects were randomized to one of three conditions: 250 mg of disulfiram, 1 mg of disulfiram (a control for the threat of the disulfiram–alcohol reaction), and no disulfiram (a control for the counseling that all received). The first two conditions were double blind, and the third was single blind. All groups received counseling. The treatment period was 1 year. The outcome measures were abstinence, time to first drink, and number of drinking days.
**Summary of Results:** There were no differences among study groups on abstinence (P = 0.25) and time to first drink (P = 0.26). Subjects who reported drinking and completed all assessments in the 250 mg disulfiram group reported significantly fewer drinking days (49 ±8 days, P = 0.05) compared with subjects in the other treatment conditions. Subjects who were compliant, regardless of treatment condition, were more likely to be abstinent than those who were not compliant (43 percent vs. 8 percent, P < 0.001).
**Reference:** Fuller, R. K., & Gordis, E. (2004). Does disulfiram have a role in alcoholism treatment today? *Addiction, 99,* 21–24.
**Purpose:** Review the efficacy and safety of disulfiram over the past 55 years.
**Conclusions:** Disulfiram has a role in alcoholism treatment for the patient who is struggling to achieve sobriety and where medication administration can be supervised. Side

effects are usually minor, and serious adverse reactions are uncommon, although monitoring for hepatotoxicity should be done.
**Methodology:** A review of research studies and clinical experience with disulfiram over the past 55 years was organized to include the efficacy of disulfiram, dosage, side effects and adverse reactions, acamprosate and naltrexone combined with disulfiram, antidepressants and disulfiram, and patients who may benefit from disulfiram.
**Summary of Results:** Effectiveness of disulfiram is limited unless the medication administration is supervised. The dose needs to be sufficient to cause a disulfiram–alcohol reaction after alcohol ingestion, but not too high to risk toxicity. It is suggested to begin with the 250 mg daily dose for all patients. The most common side effect, of short duration, is drowsiness, which can be managed by having the patient take the dose in the evening. There can also be a rare but potentially fatal hepatotoxicity at a rate of 1 per 25,000 patients. Liver function tests are recommended at baseline, 2-week intervals for 2 months, and 3–6-month intervals after that. When administered in clinical trials in combination with acamprosate and naltrexone, all medications were well tolerated and effective. Further research is needed on the effectiveness of disulfiram in combination with other pharmacotherapies. Disulfiram in combination with monoamine oxidase inhibitors is not safe, and it should not be used with tricyclic antidepressants. Supervised disulfiram is useful in the treatment of patients who have difficulty with treatment but are motivated to remain in treatment.

**Reference:** Garbutt, J. C., Kranzler, H. R., O'Malley, S. S., Gastfriend, D. R., Pettinati, H. M., Silverman, B. L., et al. for the Vivitrex Study Group. (2005). Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: A randomized controlled trial. *JAMA, 293*(13), 1617–1625.
**Purpose:** Identify the efficacy of long-acting naltrexone.
**Conclusions:** Long-acting naltrexone treatment is an effective and safe treatment for adults with alcohol dependence.
**Methodology:** Subjects were outpatient adults with an alcohol dependence diagnosis who also reported a minimum of two weekly episodes of heavy drinking during the month before screening. Exclusion criteria were clinically significant medical conditions; major depression with suicidal ideation; psychosis; bipolar disorder; past-year dependence on benzodiazepines, opioids, or cocaine; inpatient substance abuse treatment for more than 7 days during the month before screening; use of opioids, oral naltrexone, or disulfiram during the 2 weeks before screening; and use of benzodiazepines the week before the first administration of study naltrexone. Subjects were randomized to 380 mg of naltrexone, 190 mg of naltrexone, or placebo. All subjects received 12 therapy sessions of the Biopsychosocial, Report, Empathy, Needs, Direct Advice, and Assessment model. Treatment was administered monthly, during a 24-week period. The event rate, defined as the frequency and pattern of heavy drinking (≥ 5 standard drinks for men and ≥ 4 for women) during treatment, was the primary outcome of interest. The event rate of risky drinking (> 2 drinks for men and > 1 for women) was a secondary outcome.
**Summary of Results:** Naltrexone was more effective than placebo in reducing the rate of heavy drinking. The subjects who took 380 mg of naltrexone experienced a reduction in heavy drinking that was 25 percent (P = 0.03) greater than the reduction among placebo subjects, and subjects taking 190 mg experienced a 17 percent (P = 0.07) greater reduction. Differences in risky drinking among the three groups were not significant (380 mg vs. placebo: hazard ratio = 0.90, 95 percent CI = 0.76-1.07, P = 0.23; 190 mg vs. placebo: hazard ratio = 0.95, 95 percent CI = 0.81-1.13, P = 0.58). The most common minor adverse events

reported by subjects were nausea (380 mg = 33 percent, 190 mg = 25 percent, placebo = 11 percent), headache (380 mg = 22 percent, 190 mg = 16 percent, placebo = 16 percent), and fatigue (380 mg = 20 percent, 190 mg = 16 percent, placebo = 11 percent).

**Reference:** Garbutt, J. C., West, S. L., Carey, T. S., Lohr, K. N., & Crews, F. T. (1999). Pharmacological treatment of alcohol dependence: A review of the evidence. *JAMA, 281*(14), 1318–1325.
**Purpose:** Assess the efficacy of five categories of drugs used to treat alcohol dependence: disulfiram, opioid antagonists naltrexone and nalmefene, acamprosate, various selective serotonin reuptake inhibitors (SSRIs), and lithium.
**Conclusions:** Efficacy trials examine how a health intervention works in an ideal treatment setting, whereas effectiveness studies focus on the effect of an intervention in everyday settings. Disulfiram shows limited efficacy and is not used frequently, although it may still have some value. Newer medications such as naltrexone and acamprosate are more likely to be used at increasing rates but will require more study to determine effectiveness. At this time, use of the SSRIs fluoxetine, citalopram, buspirone, and ondansetron or lithium for patients with primary alcohol dependence does not appear to be supported by efficacy data.
**Methodology:** The article reviews and analyzes data from 41 studies and 11 followup or subgroup evaluations, including 11 disulfiram studies, with 1 subgroup publication; 1 nalmefene article; 3 naltrexone studies, with 5 subgroup publications; 9 acamprosate articles; 9 serotonergic studies not restricted to comorbid populations, with 1 subgroup study; and 3 serotonergic agent studies restricted to persons with co-occurring depression or anxiety, with 1 subgroup analysis. One article discussed both fluoxetine and acamprosate. Inclusion criteria included males and females older than 18 who were alcohol dependent, excluding pregnant women; location of study (United States, Canada, Europe, Latin America, Asia, Australia/New Zealand); double- or single-blind randomized control trial; prospective and retrospective controlled studies; sample size of more than 10; and inpatient and outpatient settings from 1966 to December 1997. Additional criteria required inclusion only of studies that provided standard alcohol outcomes: drinking days, return to drinking, time to first drink, episodes of heavy drinking, craving, and relapse.
**Summary of Results:** Oral disulfiram outcome measures and results vary, providing modest evidence that the drug reduces drinking frequencies without significantly enhancing abstinence rates. Naltrexone had a positive effect on abstinence only when combined with psychosocial therapies. In two trials, relapse rates at the end of the trials were higher for the placebo groups (54 percent and approximately 80 percent) than for the naltrexone groups. In another trial, end-of-study relapse rates for all subjects were 53 percent and 35 percent for placebo and naltrexone patients, respectively; however, for compliant patients, the figures were 52 percent and 14 percent, respectively. The most reliable finding in the acamprosate trials has been its effect on drinking frequency; nondrinking days were typically increased by 30 to 50 percent. Several studies also found that acamprosate approximately doubled abstinent rates, although the majority of patients returned to drinking while taking acamprosate. Subjects followed up for almost a year after trial completion who were taking acamprosate showed a greater number of cumulative nondrinking days and a higher abstinence rate than did those receiving placebo. Acamprosate continued to exert a positive effect on abstinence rates but not on the number of nondrinking days. The literature did not allow the authors to evaluate the important question of efficacy of pharmacotherapy when combined with varying types and intensities of psychosocial therapies.

**Reference:** Johnson, B. A., Ait-Daoud, N., Aubin, H. J., van den Brink, W., Guzzetta, R., Loewy, J., et al. (2004). A pilot evaluation of the safety and tolerability of repeat dose administration of long-acting injectable naltrexone (Vivitrex) in patients with alcohol dependence. *Alcoholism: Clinical and Experimental Research, 28*(9), 1356–1361.
**Purpose:** Obtain descriptive data to support the safety and tolerability of long-acting injectable naltrexone.
**Conclusions:** Long-acting naltrexone was well tolerated and safe.
**Methodology:** This double-blind, placebo-controlled, randomized trial was conducted at two U.S. and two European sites. Subjects were men and women, older than age 18, who met criteria for alcohol dependence according to the DSM-IV. Exclusion criteria were medical conditions requiring immediate treatment, other Axis I diagnoses, treatment with naltrexone 10 days before the study, intolerance to naltrexone, opioid use 2 weeks before screening, and other medical treatments for alcohol dependence. Subjects were randomized to receive 400 mg of naltrexone or placebo once a month for 4 months. Both groups received psychosocial support. Outcome measures for safety were adverse events, site assessments, laboratory tests, and physical examination. Outcomes for pharmacokinetics were plasma levels of naltrexone and 6-ß-naltrexol and alcohol consumption.
**Summary of Results:** Thirty subjects (22 male and 8 female), mainly White non-Hispanic (63.3 percent), and ranging in age from 26 to 58 ($\mu$ = 42.6, SD = 9.2), completed the trial. Among treatment condition subjects, days of abstinence (39.2 percent vs. 69.4 percent), drinks per drinking day (7.4 percent vs. 3.8 percent), and number of heavy drinking days (45.3 percent vs. 15.4 percent) improved from preintervention to postintervention. Treatment-condition subjects improved on all measures compared with subjects receiving placebo: days of abstinence (69.4 percent vs. 62.6 percent), drinks per drinking day (3.8 percent vs. 6 percent), and number of heavy drinking days (15.4 percent vs. 23.4 percent). Plasma levels of naltrexone (average $\mu$ = 1.33ng/ml, SD = 1.74 ng/ml) and 6-ß-naltrexol were relatively constant ($\mu$ = 3.03g/ml, SD = 3.29 ng/ml). No major adverse events were reported. Minor events occurring in as much as 10 percent of subjects were headaches, dizziness, somnolence, nausea, abdominal pain, dry mouth, vomiting, injection site pain, fatigue, and decreased appetite.

**Reference:** Kiefer, F., Helwig, H., Tarnaske, T., Otte, C., Jahn, H., & Weidemann, K. (2005). Pharmacological relapse prevention of alcoholism: Clinical predictors of outcome. *European Addiction Research, 11*, 83–91.
**Purpose:** Determine whether somatic distress, depression, anxiety, craving, or typological differentiation (early- or late-onset dependence) helps predict relapse with use of acamprosate or naltrexone.
**Conclusions:** Different subgroups respond differently to naltrexone and acamprosate. Psychopathology and typological differentiation might be useful in determining appropriate pharmacotheraputic treatments.
**Methodology:** One hundred sixty adult patients meeting the DSM-IV criteria for alcohol dependence, who had been abstinent for 12–15 days, participated in a 3-month double-blind study. Patients kept a daily drinking diary, corroborated by breath alcohol tests and physician evaluation. Patients received acamprosate, naltrexone, acamprosate and naltrexone, or placebo. Researchers applied a median split for the Symptom Checklist-90 sum score, the subscores of somatic distress, depression, and anxiety and for craving followed by t tests for unpaired samples with the abstinence duration as the independent variable.

**Summary of Results:** A total of 46.9 percent (75) of patients were abstinent throughout the treatment period; 42.5 percent (68) relapsed; and 10.6 percent (17) dropped out. Mean numbers of days elapsed before the first drink were placebo, 23.3 ± 26.9; acamprosate, 34.9 ± 32.0; naltrexone, 45.4 ± 32.7; and combined treatment, 54.8 ± 34.4. Mean numbers of days before relapse were placebo, 35.6 ± 33.8; acamprosate, 43.7 ± 32.0; naltrexone, 50.4 ± 34.4; and combined treatment, 58.5 ± 33.8. Naltrexone was more effective for people with addictions who had high depression scores and high somatic symptoms than for those with low depression or somatic symptoms. Acamprosate was more effective on those with low scores of somatic distress than on those with high scores. Relapse prevention was most effective in patients of type II (early-onset) alcohol addiction. Neither treatment enhanced abstinence for people with late-onset alcoholism.

**Reference:** Keifer, F., & Weidemann, K. (2004). Combined therapy: What does acamprosate and naltrexone combination tell us? *Alcohol & Alcoholism*, *39*(6), 542–547.
**Purpose:** Evaluate safety and effectiveness of combined therapy.
**Conclusions:** Combination treatment is well tolerated and more effective than monotherapy.
**Methodology:** A literature review of three preclinical and four clinical studies was conducted.
**Summary of Results:** The preclinical studies used mice and rats. All found combination therapy to be effective, but with differing results that may have been caused by procedural differences. The human studies found that the combination therapy is safe, although side effects of both drugs were present. One of the clinical reviews examined data from a study in progress: Data were available for 108 of a planned 1,374 subjects. In this study, it was found that the amount of time before the first relapse was longer in the group on combined therapy than for those on acamprosate alone. The proportion of patients who had relapsed by the end of the study period and the amount of time until the first drink were also better for the combination group. This study also found that the incidence of diarrhea and nausea was greater among the combination group. The authors of this review give three hypotheses regarding the greater efficacy of combination therapy: first, that different subgroups may respond better to one drug or the other; second, that a synergistic effect produces a stronger anticraving effect; and third, that a pharmacokinetic interaction enhances bioavailability of one or both drugs.

**Reference:** Killeen, T. K., Brady, K. T., Gold, P. B., Simpson, K. N., Faldowski, R. A., Tyson, C., et al. (2004). Effectiveness of naltrexone in a community treatment program. *Alcoholism, Clinical and Experimental Research, 28*(11), 1710–1717.
**Purpose:** Determine the efficacy of naltrexone among people diagnosed with alcohol dependence seeking treatment at a community program.
**Conclusions:** Naltrexone might have some benefits for people diagnosed with alcohol dependence who continue to drink until right before beginning treatment.
**Methodology:** This randomized trial recruited patients entering community treatment for a DSM-IV alcohol disorder. Patients were randomized to one of three groups over 12 weeks: 50 mg of naltrexone and treatment as usual, placebo and treatment as usual, or treatment as usual. Outcome measures included the Time Line Follow-Back for self-reported drinking, the Addiction Severity Index for psychosocial functioning, the Obsessive Compulsive Drinking Scale for alcohol craving, the Alcohol Dependence Scale for alcohol severity, and a symptom checklist for adverse effects and liver enzymes.

**Summary of Results:** There were no significant differences between the treatment groups on any outcome. Posthoc analyses showed differences among patients who drank during the 2 weeks after signing the consent form and before starting the medication. Those receiving naltrexone had significantly fewer abstinent days ($p = 0.01$) compared with those who received treatment as usual. There were no significant differences between those in the naltrexone treatment and those receiving placebo.

**Reference:** King, A. C., Schluger, J., Gunduz, M., Borg, L., Perret, G., Ho, A., et al. (2002). Hypothalamic-pituitary-adrenocortical (HPA) axis response and biotransformation of oral naltrexone: Preliminary examination of relationship to family history of alcoholism. *Neuropsychopharmacology, 26*(6), 778–788.
**Purpose:** Learn (1) the acute neuroendocrine and mood response to naltrexone in healthy subjects, (2) the mood response to naltrexone related to family history of alcoholism, and (3) the association of serum naltrexone and 6-ß-naltrexol levels with HPA axis and subjective response after taking naltrexone.
**Conclusions:** This study provides evidence that cortisol and adrenocorticotropic hormone (ACTH) elevations from oral naltrexone result from opioid antagonist disinhibition in the central nervous system.
**Methodology:** Subjects were 17 healthy, social drinkers ages 23 to 47. Exclusion criteria included any current or history of substance dependence, psychiatric or medical disorders, and uncertainty about biological family history of alcohol dependence. The testing was a 2-day inpatient trial, during which subjects stayed in a low-stress environment and were provided regular meals. Baseline blood samples were followed immediately by a 50 mg dose of naltrexone. Subjects completed several different questionnaires as a baseline, then at 90 and 240 minutes after naltrexone administration, focusing on mood, side effects, and alcohol urges. The study was double blind—neither the study nurse nor the subject was aware of the capsule contents. However, to measure biotransformation, all subjects received naltrexone on day 1 and placebo on day 2. Samples were analyzed for cortisol, ACTH, naltrexone, and 6-ß-naltrexol levels.
**Summary of Results:** Baseline ACTH and cortisol levels were similar between naltrexone and placebo sessions. Naltrexone increased levels of ACTH ($p < 0$ .05) and cortisol ($p < 0.05$). Mood changes after naltrexone administration compared with placebo were few. Naltrexone decreased vigor ratings at both 90- and 240-minute intervals ($p < 0.05$). For side effects, there was no difference between naltrexone and placebo. Groups with family history of alcoholism (FH+) responded differently from those without (FH-) in terms of ACTH ($p < 0.05$) and cortisol ($p < 0.05$). The FH+ group had increases in these neuroendocrine parameters many hours after taking medication, whereas the FH- group did not show neuroendocrine changes over time. The FH+ group did not show the normal decline in cortisol or ACTH in the naltrexone session. The FH+ group had more sensitivity to mood effects after the naltrexone dose. There was an inverse relationship ($p = 0.08$) between naltrexone and 6-ß-naltrexol levels.

**Reference:** Kranzler, H. R., Armeli, S., Tennen, H., Blomquist, O., Onken, C., Petry, N., et al. (2003). Targeted naltrexone for early problem drinkers. *Journal of Clinical Psychopharmacology*, *23*(3), 294–304.
**Purpose:** Evaluate efficacy of naltrexone treatment for early problem drinkers.
**Conclusions:** Naltrexone was better than placebo in reducing the frequency of heavy drinking during the treatment period.

**Methodology:** A total of 153 subjects ages 18 to 60 participated in an 8-week trial. Patients were excluded, for among other reasons, if they had a current DSM-IV diagnosis of moderate or higher severity alcohol dependence. Half were given placebo. The placebo group and naltrexone group were each divided into two groups, one on a *daily* schedule and the other on a *targeted* schedule. The *daily* group members received doses enough for each day and were told to take one a day; the *targeted* group members were given seven doses for the first week, but doses were decreased so that during the last week, patients received zero pills. The targeted group members were instructed to take a pill if they anticipated a high-risk situation. Patients could choose a goal of abstinence or nonhazardous drinking. Biweekly counseling sessions emphasized problemsolving, interpersonal skills, and ways of coping with cravings. Patients underwent a battery of assessments. Among them was the Drinker Inventory of Consequences, which was used as a pretreatment and end-of-treatment evaluation. Subjects kept nightly diaries of alcohol and medication intake.
**Summary of Results:** Analyses were completed on 150 subjects. The majority (84 percent) of patients were lifetime alcohol dependent as defined by DSM-IV. Eighty-six percent of subjects completed the 8-week treatment. Compliance was 86 percent. Eleven patients discontinued pills because of various adverse effects. The overall likelihood of drinking on any given day during the study was 0.62 compared with 0.86 during the 3 months before treatment. Subjects with fewer drinking days in the pretreatment period ($p = 0.001$), a treatment goal of abstinence ($p < 0.001$), or greater lifetime alcohol dependence ($p = 0.035$) had fewer drinking days during treatment. In the *targeted* schedule group, the effect of tablet taking had a significant ($p < 0 = 0.001$) influence: subjects tended not to drink heavily on days they took a tablet (naltrexone or placebo). Other characteristics of patients who were less likely to drink heavily were being women ($p < 0.001$), fewer heavy drinking days in pretreatment period ($p < 0.001$), a treatment goal of abstinence ($p = 0.001$), greater lifetime alcohol dependence symptoms ($p = 0.05$), and lower overall study compliance ($p < 0.001$). The decreased risk of heavy drinking among patients in the *targeted* schedule group declined as the number of available tablets declined to fewer than three per week.

**Reference:** Latt, N. C., Jurd, S., Houseman, J., & Wutzke, S. E. (2002). Naltrexone in alcohol dependence: A randomised controlled trial of effectiveness in a standard clinical setting. *Medical Journal of Australia, 176,* 530–534.
**Purpose:** Study whether naltrexone given in a standard medical clinical setting, with or without psychosocial interventions, is effective in treating alcoholism.
**Conclusions:** Naltrexone was significantly more effective than placebo in preventing relapse in a standard medical outpatient clinic for 3 months. The effect was most marked during the first 6 weeks, suggesting a rapid onset. Ongoing monitoring of depression among patients who are alcohol dependent is advised.
**Methodology:** Patients with alcohol dependence were recruited at four hospitals in Australia. Exclusion criteria included pregnant women or women not protected by contraception, use of opioids, significant liver disease, any concomitant major medical or psychiatric illness, untreated major depression, or a recent suicide attempt. Of the 164 patients assessed, 107 were enrolled in the study and randomly assigned, 56 to the naltrexone (50 mg/day) group and 51 to the placebo group. Study participants received a full history and clinical examination at baseline and were followed up by a physician at 1, 2, 3, 4, 6, 8, and 12 weeks. Optional counseling was offered to all study participants. Compliance with treatment was assessed by attendance at followup, pill counts, and random breath tests. Relapse rates were defined as drinking to previous heavy levels.

**Summary of Results:** There were no significant differences in patient characteristics between the study groups. The Kaplan-Meier survival curve showed that the relapse rate was significantly lower in the naltrexone group compared with the placebo group (log-rank test, $\chi^2 = 4.15$, $p = 0.042$). There were no significant differences between the naltrexone and the placebo groups in the number of drinking days per week, attendance at the followup clinic or Alcoholics Anonymous meetings, mean alcohol consumption, or mean craving scores. Beck Depression Inventory scores above 20 were more prevalent in the naltrexone group (22 percent) at 3 months compared with the placebo group (3 percent, $p = 0.023$). There was no significant difference in side effects between the two groups, except for an increase in headaches in the placebo group ($p = 0.03$).

**Reference:** Mann, K., Lehert, P., & Morgan, M. (2004). The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: Results of a meta-analysis. *Alcoholism: Clinical and Experimental Research*, *281*(1), 51–63.
**Purpose:** Assess the efficacy of treatment with acamprosate using meta-analytical techniques.
**Conclusions:** Acamprosate significantly improves abstinence rates in subjects who are alcohol dependent.
**Methodology:** Researchers conducted a search of 10 databases, using a number of keywords, and made a manual search of journals, symposia, and conference proceedings. The identified studies were assessed and culled based on design, sample size, randomization methods, blinding, selection and exclusion criteria, outcome criteria, and statistical analysis. Researchers combined the data from these studies with clinical trial data provided by the manufacturer of acamprosate and additional data from some of the studies' authors to undertake a meta-analysis assessing the efficacy of acamprosate in achieving patients' continuous abstinence over 6 months. Researchers undertook numerous sensitivity analyses and adjusted for sample size, DSM-III-R/DSM-IV classification, age, gender, and attrition rates. The 17 studies included in the analysis were placebo-controlled, double-blind trials involving 4,087 patients. Results of studies of less than 6 months in duration were extrapolated using last observation carried forward methodology.
**Summary of Results:** The following table compares the percentage of subjects abstinent after different periods on acamprosate with those on placebo.

| # of Months | Abstinence Rate on Placebo | Abstinence Rate on Acamprosate | p Value |
|---|---|---|---|
| 3 | 33.7 | 45.7 | < 0.0001 |
| 6 | 23.4 | 36.1 | < 0.0001 |
| 12 | 12.6 | 27.3 | < 0.0001 |

The benefit of treatment was not affected by age, severity of dependence, or attrition rates. The studies overall had a high attrition rate, averaging 51 percent.

**Reference:** Mark, T. L., Kranzler, H. R., Song, X., Bransberger, P., Poole, V. H., & Crosse, S. (2003). Physicians' opinions about medications to treat alcoholism. *Addiction, 98,* 617–626.

**Purpose:** Survey physicians who treat substance abuse to learn about their knowledge of, attitudes toward, and use of naltrexone, disulfiram, and acamprosate to treat alcoholism and their opinions about barriers to its treatment with medication.
**Conclusions:** The identification and testing of new medications to treat alcoholism must be accompanied by increased efforts to inform physicians and the public about their value.
**Methodology:** A questionnaire was developed from focus group interviews of physicians and patients that assessed knowledge and use of medications, factors affecting decisions to prescribe, opinions about medications, and opinions about medication attributes. The questionnaire was sent to members of the American Society of Addiction Medicine and the American Academy of Addiction Psychiatry. Incentives to complete the questionnaire were a cover letter, a $50 honorarium check, and a postage-paid, return envelope. Nonrespondents were contacted after 3 weeks and again after 2 months. Questionnaires were received from 1,388 respondents resulting in a response rate of 65 percent.
**Summary of Results:** Most physicians were confident or somewhat confident in their knowledge of naltrexone (86 percent) and disulfiram (92 percent) but not acamprosate (20 percent). Physicians' rating of the effect size of naltrexone was consistent with the clinical literature (14.6 percent vs. 12 percent effect size for promoting abstinence and 18.4 percent vs. 16 percent effect size for reducing heavy drinking). The three top factors influencing physicians to prescribe naltrexone were the patient was willing to comply with the regimen (83 percent), the patient was experiencing craving (79 percent), and the patient was requesting naltrexone (77 percent). To increase the use of medications to treat alcohol dependence, physicians advocated more research to develop new medications (33 percent), more education of physicians about existing medications (17 percent), and increased involvement of physicians in alcoholism treatment (17 percent).

**Reference:** Mason, B. J. (2001). Treatment of alcohol-dependent outpatients with acamprosate: A clinical review. *Journal of Clinical Psychiatry, 62*(Suppl 20), 42–48.
**Purpose:** Review all published, double-blind, placebo-controlled clinical trials of acamprosate among outpatients who are alcohol dependent.
**Conclusions:** Acamprosate can be used for a broad range of patients who are alcohol dependent and being treated with other drugs and with behavioral therapy. Patients treated with acamprosate had a significantly higher rate of treatment completion, longer time to first drink, higher abstinence rate, and/or longer cumulative abstinence duration than patients treated with placebo.
**Methodology:** Of the 16 clinical trials of acamprosate in 11 European countries, 15 have been published and were reviewed. These 15 studies were grouped according to duration of treatment: 4 short-term studies with less than 6 months of treatment, 6 studies with 6 months of treatment, and 5 long-term studies with a year or more of treatment. All 15 studies were double-blind, placebo-controlled clinical trials involving more than 4,500 outpatients with alcohol dependence.
**Summary of Results:** The results of 13 studies found that acamprosate prolongs abstinence and reduces the rate of relapse. Differences in abstinence rates between the acamprosate and placebo groups emerged within the first 30 to 90 days of treatment, were sustained for up to 1 year after treatment, and were maintained for as long as 12 months after treatment. In two studies, there was no significant difference between the acamprosate and placebo groups. Acamprosate is a relapse-prevention drug; it did not reduce craving compared with the placebo. It has minimal pharmacologic effects, does not interact with ethanol or other drugs used to treat alcoholism, can be administered to patients with liver dysfunction, and does not cause acute opioid withdrawal symptoms in

patients using opioids. It can be used in a variety of settings with a range of psychosocial interventions. It appears to be safe and well tolerated with mild diarrhea or loose stool as the only consistent adverse event.

**Reference:** Mason, B. J. (2005). Rationale for combining acamprosate and naltrexone for treating alcohol dependence. *Journal of Studies on Alcohol, Suppl. 15,* 148–156.
**Purpose:** Review the similarities and differences between acamprosate and naltrexone and their interaction and effectiveness when used in combination.
**Conclusions:** Although differing in mechanism of action, acamprosate and naltrexone have good tolerability profiles and may have enhanced efficacy when given in combination.
**Methodology:** The published clinical trials of acamprosate and naltrexone were reviewed for effectiveness. Two published pharmacokinetic and pharmacodynamic drug interaction studies of these drugs were reviewed as was the one single-site clinical trial of acamprosate and naltrexone in combination.
**Summary of Results:** Both drugs have good safety profiles and are acceptable to patients, and neither modifies the properties of alcohol. However, they differ in their mechanism of action. Whereas naltrexone is an opioid receptor antagonist and is contraindicated for patients maintained on methadone, acamprosate is a taurine analog that acts by normalizing the dysregulation of N-methyl-D-aspartic acid-mediated glutamatergic neurotransmission. Although naltrexone has a rapid onset, it does not have any long-term efficacy once discontinued. Acamprosate has a slow onset of action (1 week), but its effect may persist for up to 1 year after discontinuation. Naltrexone has a dose-dependent hepatotoxicity, whereas acamprosate has none. The efficacy of acamprosate, based on published placebo-controlled studies, supports abstinence over a broad range of patients in association with a variety of different psychosocial interventions. The effect of naltrexone may be to reduce consumption by a person who drinks, and its effect on relapse may be dependent on associated psychotherapy (i.e., cognitive-behavioral therapy), especially in patients who are not abstinent. Poor compliance of naltrexone, because of adverse events such as nausea and headache, may cause a decrease in effectiveness. When acamprosate and naltrexone are used in combination, the rate and extent of absorption of acamprosate is increased by an average of 33 percent. Preliminary support for enhanced efficacy of combination treatment relative to acamprosate alone was seen in the single combination clinical trial.

**Reference:** Maxwell, S., & Shinderman, M. S. (2000). Use of naltrexone in the treatment of alcohol use disorders in patients with concomitant major mental illness. *Journal of Addictive Diseases, 19*(3), 61–96.
**Purpose:** Report on the efficacy of naltrexone therapy in patients with co-occurring alcohol dependence and Axis I disorders.
**Conclusions:** Patients with co-occurring disorders had a very positive response to naltrexone therapy.
**Methodology:** The authors reviewed the case records of 72 patients with an alcohol use disorder and at least one Axis I psychiatric disorder, including major depression, schizophrenia, bipolar disorder, schizoaffective disorder, and gender identity disorder. Data collected included diagnoses, medications, and the duration and side effects of and response to naltrexone treatments. During naltrexone therapy, patients continued with any treatment and drugs prescribed for their other disorder. Response to naltrexone was estimated for the first 8 weeks of treatment, based on practitioner notes, patient self-reports, and clinician assessments, as corroborated by case manager reports, urine

toxicologies and Breathalyzers™, and family reports. Responses were categorized as follows: excellent, more than 90-percent reduction in alcohol consumption; very good, 75–90 percent; good, 50–75 percent; fair, 25–50 percent; and poor, less than 25-percent reduction in drinking.
**Summary of Results:** Of the initial 72 patients, 59 completed at least 8 weeks of naltrexone therapy; 97 percent (n = 70) drank alcohol during treatment; 70.8 percent (n = 51) had an excellent response; 11 percent (n = 8) had very good reductions in drinking; 6.9 percent (n = 5) had a good response; 1.4 percent (n = 1) had a fair response; and 2.8 percent (n = 2) had a poor response.

**Reference:** McCaul, M. E., & Petry, N. M. (2003). The role of psychosocial treatments in pharmacotherapy for alcoholism. *American Journal on Addictions, 12,* S41–S52.
**Purpose:** Review seven psychotherapies and their use in combination with pharmacotherapy (naltrexone and acamprosate).
**Conclusions:** Psychotherapy may enhance and extend the effect of pharmacotherapy.
**Methodology:** The seven major types of psychotherapy are reviewed by describing the theoretical basis for each psychotherapy, the evidence supporting the efficacy of each, and when combined with medication the resulting efficacy or interaction of psychotherapy and the medication.
**Summary of Results:** Brief therapeutic interventions in general medical settings have been shown to be effective in reducing alcohol use in those who drink heavily but are not alcohol dependent, especially when combined with naltrexone. Motivation enhancement therapy (MET) has been effective as a four-session manual-guided intervention especially with angry subjects. When MET was used with acamprosate in general healthcare settings, study subjects motivated to abstain had good medication efficacy. Cognitive-behavioral therapy (CBT), effective with patients who abuse substances, has been shown to produce delayed, positive effects after treatment completion. When CBT was used in conjunction with naltrexone, patients were successfully engaged in treatment and medication compliance. Cue exposure therapy (CET) has been shown to reduce the urge to drink and increase the use of coping strategies. When CET was combined with naltrexone, each independently reduced the urge to drink, heavy drinking days, and drinks per drinking day. Behavioral treatments have enhanced compliance with treatment by providing vouchers or cash contingent on naltrexone consumption, thereby increasing treatment retention. Behaviorally based couples therapy when used in conjunction with naltrexone for opioid dependence increased treatment retention and drug-free urine toxicology screens. Twelve-Step therapies, although thought to discourage the use of medication, may be adapted to use with pharmacotherapy and have achieved high rates of alcohol abstinence and low proportions of drinking days.

**Reference:** McCaul, M. E., Wand, G. S., Rohde, C., & Lee, S. M. (2000). Serum 6-ß-naltrexol levels are related to alcohol responses in heavy drinkers. *Alcoholism: Clinical and Experimental Research, 24*(9), 1385–1391.
**Purpose:** Examine the relationship between serum levels of 6-ß-naltrexol and the effects of alcohol.
**Conclusions:** Concentrations of 6-ß-naltrexol may help predict patients' response to naltrexone.
**Methodology:** The study was conducted over a 6-week period with 23 subjects, ages 25 to 60, who reported moderate to heavy alcohol use. The 6 weeks alternated between inpatient stays and outpatient washout periods (time for medication to leave the person's system). All

subjects were on inpatient stay for 3 weeks, in each of which they were subject, at random, to a different dosage of naltrexone: 0, 50, or 100 mg/day. Three alcohol dosages (none, moderate, high) were administered in random order during each week. Alcohol content of drinks and naltrexone doses were concealed to nurses, study assistants, and subjects. Subjects took naltrexone, then had serum drawn 16 hours later to test their levels of 6-ß-naltrexol, the biologically active metabolite of naltrexone. Within half an hour of the serum draw, subjects ingested an alcohol placebo or a moderate or high dose of alcohol. Subjects took a computerized self-assessment, measuring relative levels of sedation, sickness/unpleasantness, and intoxication before and after ingesting the alcohol dose.
**Summary of Results:** At the 100 mg dosage, 6-ß-naltrexol levels varied within and across subjects. There was a positive relationship between subjects' feelings of sedation before drinking and their 6-ß-naltrexol levels ($p = 0.002$). The 6-ß-naltrexol levels appear to affect other baseline measures. Levels of 6-ß-naltrexol were related to subjects' reporting of the pleasant effects of alcohol: when levels were higher, subjects were less likely to report feelings of pleasure and of liking the effects of the beverage/capsule combination.

**Reference:** McKay, J. R. (2005). Is there a case for extended interventions for alcohol and drug use disorders? *Addiction, 100,* 1594–1610.
**Purpose:** Review the evidence for the feasibility and effectiveness of extended interventions for alcohol and drug use disorders.
**Conclusions:** Patients who have failed prior treatments are the best candidates for extended interventions. Most published studies support the effectiveness of using extended interventions.
**Methodology:** Published studies were reviewed if they contained an extended intervention. An extended intervention was defined as a therapeutic protocol that has a planned duration of longer than 6 months. The theoretical rationale for extended intervention is the continued vulnerability to relapse, a function of poor compliance with treatment and continuing care, stress, craving, low motivation, poor self-efficacy, lack of social support, and biological factors such as genetic vulnerability, negative mood states, disturbed sleep, and cognitive impairments. New developments in the design and evaluation of treatments such as adaptive protocols and changing interventions were proposed as well as recommendations for a disease management approach to addictions treatment.
**Summary of Results:** Extended interventions are most appropriate for patients who have not achieved sustained reductions in alcohol or drug use on their own or following brief interventions. Results of studies with long-term behavioral treatments suggest that the 1-year versions of treatment had improved outcomes. Continuing care interventions using home visits, workplace counseling, and behavioral marital therapy sessions were effective in preventing relapse. Extended pharmacotherapy interventions using acamprosate and outpatient therapy were effective; however, a long-term intervention using naltrexone was not. Regular monitoring, such as followup assessments and assessments plus referral to treatment via telephone monitoring and brief counseling, has been studied and found to be effective. Although there is not a lot of evidence, all except two of the behavioral and pharmacological extended interventions reviewed yielded positive effects. The extended intervention needs to be low intensity so that patients participate for long periods.

**Reference:** Monterosso, J. R., Flannery, B. A., Pettinati, H. M., Oslin, D. W., Rukstalis, M., O'Brien, M. D., et al. (2001). Predicting treatment response to naltrexone: The influence of craving and family history. *American Journal on Addictions*, *10,* 258–268.

**Purpose:** Determine the influence of craving levels and family history of alcoholism on efficacy of naltrexone.
**Conclusions:** Naltrexone may be more effective with patients with a strong family history of alcoholism and those with high levels of craving.
**Methodology:** The 183 subjects met the DSM-III-R criteria for alcohol dependence, successfully detoxified for 3 days, in addition to a week placebo lead-in. Exclusion criteria were major psychiatric illness, history of unstable medical condition, use of opioids in the preceding 30 days, significant hepatocellular injury, current disulfiram treatment, comorbid dependence other than nicotine or cannabis, and abstinence from alcohol for more than 28 days. One-third of patients received placebo in this double-blind study. Two-thirds took 50 mg of naltrexone twice daily, except those who suffered nausea, who were directed to take it once daily. All patients received weekly sessions using the BRENDA approach (Biopsychosocial evaluation, Report, Empathy, Needs of patient, Direct advice, Assessment). Assessment instruments included a semistructured interview, a structured interview, and a questionnaire. Variables that differed between treatment groups at a level of $p < 0.05$ were included in analyses as covariates.
**Summary of Results:** The study was completed by 82.1 percent of patients. Excluding retention failures, 78.3 percent of patients were at least 90-percent compliant with the medication regimen. Drinking during the placebo lead-in week was positively associated with clinical deterioration ($p < 0.001$), as was severity of familial alcoholism ($p = 0.003$). Medication was more effective with patients with higher levels of craving ($p = 0.02$). Patients with high familial alcohol problems derived the most benefit from naltrexone therapy.

**Reference:** O'Malley, S. S., Krishnan-Sarin, S., Farren, C., & O'Connor, P. G. (2000). Naltrexone-induced nausea in patients treated for alcohol dependence: Clinical predictors and evidence for opioid-mediated effects. *Journal of Clinical Psychopharmacology*, *201,* 69–76.
**Purpose:** Identify risk factors for naltrexone-precipitated nausea.
**Conclusions:** The risk of nausea associated with naltrexone is significantly predicted by age, gender, intensity of drinking, and duration of abstinence. Moderate to severe nausea is linked to poor compliance with the medication regimen.
**Methodology:** The 120 subjects were men and women from ages 18 to 65 who were alcohol dependent (as defined by DSM-III) with differing intensities of drinking habits. After a period of abstinence of 5 to 30 days, subjects got an initial dose of 25 mg of naltrexone; afterward, they took a daily 50 mg dose for 10 weeks. Subjects were excluded if they experienced one of the following:

- Currently abused or were dependent on substances other than alcohol and nicotine or had an acute major psychiatric illness, a psychotic illness, or cirrhosis
- Had serum glutamic-oxaloacetic transaminase or serum glutamic-pyruvic transaminase more than three times normal levels
- Had elevated bilirubin levels or an unstable medical condition
- Had previously undergone more than five treatments for alcohol dependence
- Were currently using disulfiram
- For women, were pregnant, were nursing, or refused to use a reliable form of birth control.

After initial testing using several variables, researchers removed those that were found not to affect levels of nausea. The remaining variables were alcohol consumption multiplied by abstinence, alcohol consumption, abstinence, age, and gender.
**Summary of Results:** Of the 120 subjects, 18 had moderate to severe nausea, 10 reported mild nausea, and the remaining 92 experienced nothing unusual. Of the 18 subjects with moderate to severe nausea, 8 discontinued naltrexone because of nausea and other side effects. For those who remained on naltrexone, the nausea subsided within a week for five subjects, subsided within 2 weeks for four, and continued intermittently for one subject. The patients who did not experience moderate to severe nausea were significantly more compliant in taking the daily dose than those who did ($p < 0.05$). Another factor affecting nausea levels was the quantity of alcohol regularly consumed before the abstinence period. Subjects with less nausea had consumed an average of 2.86 drinks per occasion, whereas those with moderate to severe nausea had consumed an average of 5.17.

**Reference:** O'Malley, S. S., Rounsaville, B. J., Farren, C., Namkoong, K., Wu, R., Robinson, J., et al. (2003). Initial and maintenance naltrexone treatment for alcohol dependence using primary care vs. specialty care. *Archives of Internal Medicine, 163,* 1695–1704.
**Purpose:** Study the effectiveness of a primary care approach to the management of alcohol dependence with naltrexone therapy.
**Conclusions:** Naltrexone therapy can be used effectively with a primary care model of counseling to treat patients dependent on alcohol.
**Methodology:** The study compared the effectiveness of a primary care model of counseling and naltrexone therapy with cognitive-behavioral therapy (CBT) and naltrexone therapy for 10 weeks, followed by a random assignment to the same therapy but with or without naltrexone for 6 months. The resulting nested sequence of 3 randomized clinical trials started with 197 patients dependent on alcohol, and 113 "responders" were randomized to the 6-month maintenance phase. Of the 425 eligible patients, 107 were excluded and 121 either declined to participate or dropped out before randomization.
**Summary of Results:** There was no difference between the two groups based on no more than 2 days of heavy drinking during the last 28 days; however, patients in the CBT and naltrexone group were more likely to be abstinent during the last 28 days ($p = 0.02$). Of the patients in the primary care group randomized to receive either naltrexone or a placebo for 6 months of maintenance treatment, the naltrexone group maintained fewer days of heavy drinking and more abstinence than the placebo group (81 percent vs. 52 percent, $p = 0.03$), and the placebo group had a decreased percentage of days abstinent (90 percent vs. 78 percent, $p = 0.02$). There was no difference in study outcomes for the patients in the CBT group randomized to receive either naltrexone or a placebo for 6 months of maintenance treatment.

**Reference:** Ooteman, W., Verheul, R., Naassila, M., Daoust, M., Schippers, G. M., Koeter, M. W. J., et al. (2005). Patient-treatment matching with anti-craving medications in alcohol-dependent patients: A review on phenotypic, endophenotypic and genetic indicators. *Journal of Substance Use, 10*(2–3), 75–96.
**Purpose:** Review the literature on predictors and matching variables of the effectiveness of pharmacological interventions (acamprosate, naltrexone, selective serotonin reuptake inhibitors [SSRIs]) in patients with alcohol dependence to decrease craving and prevent relapse.

**Conclusions:** To better match patients with the optimum pharmacotherapy more research is needed using genetic or endophenotypic variables.
**Methodology:** A search of PubMed, EMBASE, PsychINFO, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, and the Database of Abstracts of Reviews of Effects was conducted in 2004. References were checked to identify trials, reviews, and meta-analyses. Studies were included if they reported data on at least one of the three types of possible anticraving medications (acamprosate, naltrexone, or SSRIs). Studies were reviewed for results that matched specific patients to specific treatment outcomes. The three-pathway (reward, relief, and obsessive) model of craving in patients with alcoholism was used as a theoretical framework.
**Summary of Results:** Limited support was found for the matching hypothesis of the three-pathway model (i.e., naltrexone for reward, acamprosate for relief, and SSRIs for obsessive pathways). Baseline craving and/or familial alcoholism could predict a match between patients with these characteristics and naltrexone. The best match for SSRI treatment could be patients with comorbid mood or anxiety disorders. Patients with early-onset or Cloninger Type II alcoholism may have a poor outcome with SSRI therapy. Promising findings suggest that genotypes may predict the best patient–treatment match. One study found a genetic indicator for naltrexone effectiveness, OPRM1 genotyping, which predicted which patients would have the best response. Combining therapies, such as naltrexone and acamprosate, seems to decrease craving more, perhaps by affecting both the reward and relief pathways at the same time.

**Reference:** Oslin, D. W., Berrettini, W., Kranzler, H. R., Pettinati, H., Gelernter, J., Volpicelli, J. R., et al. (2003). A functional polymorphism of the μ-opiate receptor gene is associated with naltrexone response in alcohol-dependent patients. *Neuropsychopharmacology, 28*(8), 1546–1552.
**Purpose:** Determine the relationship between two polymorphisms of the μ-opiate receptor and treatment outcomes among people with alcohol dependence taking naltrexone or placebo.
**Conclusions:** The study provides evidence of a relationship between the μ-opiate receptor gene and positive treatment outcomes for naltrexone.
**Methodology:** This study reported on three randomized clinical trials of naltrexone and placebo, both with adjunct psychosocial intervention. Subjects were mainly non-Hispanic White and African-American males. Study one randomized subjects to (1) 9 months of 100 mg naltrexone per day, (2) 12 weeks of 100 mg of daily naltrexone and 6 months of placebo, or (3) 9 months of placebo. Study two treatment conditions were 24 weeks of 100 mg of daily naltrexone and one of three psychosocial interventions. Study three treatment conditions were 50 mg daily of naltrexone, nefazodone, or placebo and cognitive-behavioral therapy. Outcome measures were the Addiction Severity Index for severity of alcohol-related problems, the Time Line Follow-Back for alcohol consumption, and relapse to heavy drinking as the main outcome. Blood samples were genotyped using the polymerase chain reaction-restriction fragment length polymorphism method.
**Summary of Results:** Naltrexone subjects with the Asp 40 variant of the μ-opiate receptor gene were less likely to relapse than naltrexone subjects who were homozygous for the Asn 40 allele (Wald = 4.05, 1df, OR = 3.52 [95 percent CI = 1.03-11.96] p = 0.044). Time to first relapse was also longer among naltrexone subjects with the Asp 40 variant (Wald = 4.22, 1df, OR = 2.79 [1.05, 7.41] p = 0.040). Rates of abstinence between these two groups did not differ (Wald = 0.259, 1df, OR = 0.76 [95 percent CI = 0.27-2.16] p = 0.611). There were no significant differences among the placebo subjects.

**Reference:** Petrakis, I. L., Nich, C., & Ralevski, E. (2006). Psychotic spectrum disorders and alcohol abuse: A review of pharmacotherapeutic strategies and a report on the effectiveness of naltrexone and disulfiram. *Schizophrenia Bulletin, 32*(4), 644–654.
**Purpose:** Assess efficacy of naltrexone and disulfiram in patients with co-occurring disorders.
**Conclusions:** Naltrexone and disulfiram can be used to effectively treat individuals with alcohol dependence and comorbid psychotic spectrum disorders.
**Methodology:** A short review of literature was followed by a clinical trial. Data were gathered on 251 subjects, all of whom were diagnosed as alcohol dependent as well as having a major Axis I disorder. Primary outcomes were measures of alcohol use. Detailed self-reports were collected weekly in interviews administered by research personnel. In addition, craving, psychiatric symptoms, and side effects were evaluated. Outcome variables included consecutive days of abstinence, total days abstinent, and the number of heavy (≥ 5 drinks) drinking days.
**Summary of Results:** In the entire sample, subjects significantly decreased alcohol use in all outcome measures. Subjects assigned to either drug had significantly fewer drinking days per week ($p = 0.02$) and more consecutive days of abstinence ($p = 0.04$) than the placebo group. In measures of heavy drinking days and number of days abstinent, there were no significant differences between the treatment groups. Subjects without psychotic spectrum disorders had better results than those with such disorders in terms of consecutive abstinence days, total days of abstinence, and heavy drinking days. There were no measurable effects on psychotic symptoms, and side effects were consistent with other studies and groups.

**Reference:** Pettinati, H. M., O'Brien, C. P., Rabinowitz, A. R., Wortman, S. M., Oslin, D. W., Kampman, K. M., et al. (2006). The status of naltrexone in the treatment of alcohol dependence: Specific effects on heavy drinking. *Journal of Clinical Psychopharmacology, 26*(6), 610–625.
**Purpose:** Reevalute the literature on controlled naltrexone trials focusing on outcomes to reduce heavy drinking versus outcomes to increase abstinence.
**Conclusions:** The majority of clinical trials in the literature favor prescribing naltrexone to reduce heavy drinking, consistent with naltrexone's mechanism of action.
**Methodology:** A search of MEDLINE between 1990 and 2006 was conducted to identify published studies evaluating the use of an opioid antagonist (naltrexone or nalmefene) for the treatment of alcohol dependence. Inclusion criteria were a double-blind, placebo-controlled study design, a sample of at least 20, and outcomes of both abstinence and excessive or heavy drinking. Of the 95 studies identified involving human subjects and randomized controlled trials, 27 met the inclusion criteria.
**Summary of Results:** Naltrexone blocks the ability of ethanol to increase dopamine release in the dopamine reward pathways, thus reducing the pleasurable effects of alcohol and excessive drinking. Nausea and vomiting are the most common side effects (< 15 percent of patients), and potential hepatotoxicity occurred at higher doses (350 mg/d) than the recommended daily dosage of 50 mg. The review of 27 studies revealed that 70 percent (19) favored naltrexone over placebo in reducing heavy or excessive drinking. Only 36 percent (9/25) favored naltrexone over placebo in increasing abstinence. Because naltrexone is specific for opiate receptors, if a patient with alcoholism does not have an endogenous opioid system sensitive to alcohol, naltrexone may not have an effect. Patients who may respond better to naltrexone have a family history of alcoholism, an intense craving for

alcohol, an enhanced opioidergic activity in response to alcohol intake, and/or a genetic polymorphism.

**Reference:** Pettinati, H. M., Volpicelli, J. R., Pierce, J. D., & O'Brien, C. P. (2000). Improving naltrexone response: An intervention for medical practitioners to enhance medication compliance in alcohol dependent patients. *Journal of Addictive Diseases, 19*(1), 71–83.
**Purpose:** Conduct a reanalysis of existing data focusing on patient compliance and relapse rates. Conduct a preliminary analysis of the BRENDA (a focused clinician–patient monitoring of pill taking, patient education, and problemsolving related to daily pill taking and missed doses) intervention designed to improve treatment compliance for clinic patients who are alcohol dependent.
**Conclusions:** Compliance with treatment and medication will improve relapse rates and can be enhanced through a clinician–patient intervention.
**Methodology:** For the first study, two groups of patients dependent on alcohol and/or nicotine completed studies (12-week, double-blind, placebo-controlled studies of naltrexone [50 mg/day] and a mix of group and individual counseling sessions) were grouped together to assess the effect of treatment compliance on relapse rates. Treatment compliance was defined as at least 80-percent attendance at clinic visits and a self-report statement that naltrexone was taken as prescribed. Relapse was defined as drinking at least five drinks during one drinking occasion or a documented breath alcohol level greater than 100 mg/dL. For the second study, the BRENDA intervention was assessed. Treatment completion rates and pill compliance rates, as measured by pill counts, were compared between two groups of outpatients in a 12-week, double-blind, placebo-controlled naltrexone trial; one group received the BRENDA intervention.
**Summary of Results:** For the first study, of 104 compliant patients, only 10 percent of the patients in the naltrexone group relapsed versus 39 percent in the placebo group ($\chi^2 = 12.1$, $df = 1$, $p < 0.001$). Of the 92 noncompliant patients, there was no significant difference in the relapse rates between the two groups. For the second study, of the 100 patients receiving the BRENDA intervention, 83 percent completed treatment compared with 56 percent in the other group ($\chi^2 = 17.4$, $df = 1$, $p < 0.001$) and 77 percent were compliant in taking their medication, compared with 61 percent in the other group ($\chi^2 = 6.03$, $df = 1$, $p < 0.01$).

**Reference:** Ramoz, N., Schumann, G., & Gorwood, P. (2006). Genetic and pharmacogenetic aspects of alcohol-dependence. *Current Pharmacogenomics, 4,* 19–32.
**Purpose:** Review the genetic and pharmacogenetic basis of alcohol dependence and discuss results from the field of pharmacogenetics of alcoholism to improve therapeutic response based on genotype.
**Conclusions:** The current knowledge of genes involved in the neurobiology of alcohol dependence allows for the selection of a sufficient number of candidate genes for pharmacogenetic studies.
**Methodology:** Published studies were reviewed that addressed glutamatergic and opioidergic genes and genes pertaining to pathways known to interact with these neurotransmitter systems. The review is organized into genome-wide scans, candidate genes in the metabolism of alcohol, candidate genes from reward circuits and neurotransmitter systems involved in alcohol, and expression profiles of genes and proteins.
**Summary of Results:** The heterogeneity of alcohol dependence is evident at both the clinical phenotypic and the neurobiological/genetic levels. One strategy to improve

treatment results is the identification of more homogeneous subgroups of patients to receive specific treatments. The heritability rate of alcoholism is estimated at 50–60 percent. Genome scans implicate the involvement of loci on chromosomes 1, 2, 4, 5, 6, 7, 12, 14, 15, 16, and 17. In the metabolism of alcohol, the Lys487 allele, found in 50 percent of Asians, causes a dramatically reduced ability to catabolize the toxic acetaldehyde substrate, resulting in the Flushing Syndrome. In the reward circuits, characterized by dopaminergic activity, genes that may have pharmacogenetic relevancy are the GABRA6 gene (role of benzodiazepine in alcohol withdrawal), SLC6A4 gene (serotonin reuptake inhibitors may reduce alcohol intake in subgroups of patients), CB1 gene (the CB1 agonists modify alcohol consumption in rodents), and the OPRM1 gene (the 118G allele being associated with increased chances of naltrexone efficacy).

**Reference:** Rohsenow, D. J. (2004). What place does naltrexone have in the treatment of alcoholism? *CNS Drugs, 18*(9), 547–560.
**Purpose:** Review 17 studies of naltrexone to investigate its effectiveness and the characteristics of patients who would benefit from it.
**Conclusions:** Because naltrexone has been shown to be effective in most clinical trials, it has a place in therapy, combined with a good behavioral or counseling program. If treatment programs are tailored to individual needs and compliance is maximized, the likelihood of success when using naltrexone is improved.
**Methodology:** A review of 17 studies was completed to investigate the effectiveness of naltrexone and the characteristics of patients who would benefit from using it.
**Summary of Results:** Although a recent multicenter clinical trial of naltrexone did not find any significant differences between groups, other trials have consistently found that naltrexone, in combination with a behavioral treatment or counseling for alcoholism, results in a modest effect size resulting in significantly less severe drinking outcomes. The most beneficial results for naltrexone across studies are the reduction in heavy drinking and the number of drinking days. Naltrexone makes drinking less pleasurable so that patients who have a lapse are less likely to progress to heavy drinking. Naltrexone is best used in patients who are both able and willing to take it. Patients may not take naltrexone if they have a variety of medical conditions, poor liver function or history of liver disease, or any recent opioid use and, for women, if they are pregnant or are not using adequate birth control. Naltrexone may be most effective when combined with a comprehensive treatment program. Benefits of naltrexone include a reduced urge to drink or sense of craving; however, the benefits wear off soon after the drug is discontinued. Future research should focus on an increased drug dosage, increased length of treatment, improved compliance, and matching individuals with the most optimum treatment package.

**Reference:** Rubio, G., Ponce, G., Rodriguez-Jimenez, R., Jimenez-Arriero, M. A., Hoenicka, J., & Palomo, T. (2005). Clinical predictors of response to naltrexone in alcoholic patients: Who benefits most from treatment with naltrexone? *Alcohol & Alcoholism, 40*(3), 227–233.
**Purpose:** Determine whether family history of alcoholism is a clinical marker for outcome of patients treated with naltrexone.
**Conclusions:** Naltrexone might help some men with alcohol abuse improve treatment outcomes.
**Methodology:** This randomized, open-controlled trial compared naltrexone (50 mg/day) plus psychotherapy with psychotherapy alone. Both treatments were administered for 6 months. Male patients were recruited after detoxification (mean days of abstinence = 14.5 days, SD = 7.2) at a hospital in Madrid, Spain. Exclusion criteria were use of opioids in the

year before the trial, a DSM-IV psychiatric disorder (other than alcohol dependence), and a medical condition that would be exacerbated by naltrexone. Predictive variables were alcohol dependence based on DSM-IV criteria, the Severity of Alcohol Dependence Scale, and the Addiction Severity Index; frequency, duration, and intensity of craving; self-report alcohol intake and consumption pattern; biological measurements of alcohol use (aspartate aminotransferase, alanine transaminase, gamma glutamyl transpeptidase, and carbohydrate-deficient transferin); and family history of alcoholism based on interviews with first-degree relatives and, when necessary, the Research-Diagnostic Criteria-Family History. Outcome variables were number of drinking days, number of heavy drinking days (> 5 drinks or 40 g/day), abandonment of treatment, days of continued abstinence, and final abstinence (continued abstinence during the last 28 days of followup).
**Summary of Results:** Patients in the naltrexone group had more days of abstinence in the last 28 days of followup (71 percent vs. 59 percent, P = 0.030), fewer drinking days (2 percent vs. 14 percent, P = 0.007), and fewer heavy drinking days (6 percent vs. 28 percent, P = 0.015). The treatment groups did not differ on abstinence, days of consumption, continuous days in abstinence before first consumption, total consumption, and days of consumption. Treatment with naltrexone was associated with alcohol abuse before age 25 ($X^2 = 4.836$, $P < 0.028$; OR = 2.004, P = 0.014), co-occurring drug use ($X^2 = 12.835$, $P < 0.001$; OR = 6.348, $P < 0.001$), and/or a family history of alcoholism ($X^2 = 5.714$, $P < 0.017$; OR = 2.084, P = 0.010).

**Reference:** Scott, L. J., Figgitt, D. P., Keam, S. J., & Waugh, J. (2005). Acamprosate: A review of its use in the maintenance of abstinence in patients with alcohol dependence. *CNS Drugs, 19*(5), 445–464.
**Purpose:** Review relevant pharmacological data on acamprosate and highlight clinical evidence for its use in the management of abstinent adult patients with alcohol dependence.
**Conclusions:** In several clinical trials of up to 12 months, acamprosate effectively maintained abstinence in patients who were alcohol dependent and had been detoxified, irrespective of disease severity or the type of psychosocial support.
**Methodology:** This review covers the pharmacology of acamprosate, its therapeutic efficacy, and its tolerability, based on published literature.
**Summary of Results:** Acamprosate is thought to modulate the glutamatergic and GABAergic neurotransmitter systems in the central nervous system to restore the normal balance between these two systems. Acamprosate is indicated for the maintenance of abstinence in adult patients with alcohol dependence who are abstinent at treatment initiation. The recommended dosage of acamprosate is two 333 mg tablets three times daily, which may be taken without food. Acamprosate treatment should be accompanied by a comprehensive management program including psychosocial support and should be maintained if the patient relapses. If administered to lactating rats, acamprosate has been found in their milk and has been shown to cross the placental barrier. Acamprosate does not appear to be metabolized, with 99 percent of the drug eliminated unchanged in the urine. As a result, a 50-percent dosage reduction is recommended in patients with moderate renal impairment (creatinine clearance 1.8-3 L/h), and the drug is contraindicated in patients with severe renal impairment. Because acamprosate is not metabolized in the liver, there have been no clinically relevant effects of mild to moderate hepatic impairment on pharmacokinetic values of acamprosate. The most frequently reported adverse event is diarrhea, but it is generally well tolerated in this patient population. Limited data indicate that acamprosate has similar efficacy to naltrexone and that combination therapy with these two drugs provides better efficacy than acamprosate alone.

**Reference:** Soyka, M., & Chick, J. (2003). Use of acamprosate and opioid antagonists in the treatment of alcohol dependence: A European perspective. *American Journal on Addictions, 12,* S69–S80.
**Purpose:** Present the findings of placebo-controlled trials of acamprosate and naltrexone medications that took place in Europe and reflect that perspective and experience.
**Conclusions:** Rates of total abstinence for those using acamprosate were statistically and significantly better compared with those of the placebo groups in the studies reviewed. Rates are measured by time-to-first-drink data compiled in 13 studies (2 studies with fewer than 100 patients were eliminated). For the studies that also measured cumulative abstinence duration (CAD), a beneficial effect was seen in acamprosate use over placebo. It is recommended to begin acamprosate as soon as a patient is near successful detoxification to achieve the best effect. If a patient manages to abstain, the drug should be continued for 1 year. Studies in Germany and Austria followed up on patients after 1 year's treatment and found greater improvement in the acamprosate-treated group. Improvement persisted into the second year of treatment without any indication for sudden relapse on cessation of the drug. Acamprosate appears to have a slight effect in reducing drinking during relapse and should not be stopped if the patient lapses. Results from studies on methadone have been less consistent than those reported for acamprosate; several European studies have been negative or partly negative. The Swedish and Finnish studies did not find naltrexone superior to placebo in their treatment-as-usual groups and groups with supportive therapy. There is evidence from the Swedish study that naltrexone is effective in settings offering coping skills training, that is, an approach that includes training in how to terminate drinking if it starts, rather than focusing on complete abstinence. There has been a trend to offer naltrexone to patients aiming for harm-free drinking rather than abstinence, provided favorable predictors exist for a nonabstinent goal such as low level of dependence and social support. For the Finnish 32-week study, the dropout rate was 16.5 percent in the initial 12-week period and twice that by the end of the study. In the coping skills groups, naltrexone was superior to placebo in terms of percentage of patients never relapsing to heavy drinking (26 percent vs. 3 percent, $p = 0.008$), but in groups receiving supportive therapy, there was no significant difference (8 percent vs. 12 percent). The naltrexone Health Technology Board of Scotland (HTBS) study found an NNT (number needed to treat) of 12.4 for preventing relapse (defined as drinking more than 5 drinks in a day). The study comparing acamprosate with naltrexone (the Hamburg study) found the group with the fewest heavy drinking days was the combined naltrexone and acamprosate, followed by naltrexone on its own, then acamprosate on its own. All were associated with better outcomes than placebo. A Spanish study comparing acamprosate and naltrexone found no significant difference between them in terms of days to first drink. However, with relapse defined as five or more drinks, the time to the first relapse was longer for naltrexone than for acamprosate.
**Methodology:** The clinical studies of acamprosate met the following criteria for review: comparison with placebo, adequate measures of randomization, standard attempts to keep patients and assessors blind to treatment groups, and predefined primary outcome criteria (number of days to the first drink and secondary CAD). Followup rate was not an inclusion criterion. Fifteen studies ($n = 3{,}979$) were selected for analysis and review with two studies eliminated. For naltrexone, European studies that met Cochrane criteria for methodological quality are discussed as well as several reviews and meta-analyses. Swedish and Finnish studies compared the efficacy of naltrexone associated with different psychological treatments. A 32-week Finnish study tested groups of cognitive coping skills or supportive group therapy combined with either naltrexone or placebo but stopped medication at week 13 for all subjects with instructions to take the medication only when there was a risk of

sampling alcohol or when craving threatened to overwhelm. The most extensive meta-analysis was conducted by the HTBS. The HTBS review included 12 positive studies and 5 negative studies (n = 2,113) including a negative Veterans Administration study. In a single center study (Hamburg), the author randomly allocated 160 patients who were detoxified one 50 mg naltrexone daily, two 333 mg acamprosate three times per day, both, or a placebo.
**Summary of Results:** The use of acamprosate is believed to vary within and between countries of Europe. In a survey in Scotland, all National Health Service units specializing in alcohol treatment prescribe it. Although many centers routinely offer a trial of acamprosate to patients who are newly detoxified and aiming for abstinence, naltrexone usage varies. Naltrexone is suggested for patients aiming for abstinence and for patients for whom continued drinking is a therapeutic possibility or an inevitability.

**Reference:** Streeton, C., & Whelan, G. (2001). Naltrexone, a relapse prevention maintenance treatment of alcohol dependence: A meta-analysis of randomized controlled trials. *Alcohol & Alcoholism, 36*, 544–552.
**Purpose:** Review the existing evidence for the efficacy of naltrexone for the treatment of alcohol dependence.
**Conclusions:** Naltrexone is superior to placebo for the treatment of alcohol dependence.
**Methodology:** A literature review of randomized controlled trials published between 1976 and 2001 was indexed in MEDLINE, EMBASE, PsychLIT, and the Cochrane Controlled Trials Registry. Studies were selected according to the following characteristics: enrollment of adult subjects with alcohol dependence in outpatient or inpatient treatment; comparison of a 50 mg dose of naltrexone with placebo or another drug licensed in Australia; collection of data at least on relapse, abstinence, and discontinuation because of adverse events; provision of treatment for at least 3 months; and complete databases. Outcome measures were rates of relapse and abstinence; mean drinking days and number of drinks per drinking day, as measures of efficacy; reports of adverse events; and number of subjects who discontinued treatment because of an adverse event, as measures of safety.
**Summary of Results:** Seven trials were reviewed. All outcomes favored the naltrexone subjects over those receiving placebo: the average relapse rate was 14 percent lower; the average days of drinking was 3 percent lower; and the average abstinence rate was 10 percent greater. There were no differences in the incidence of reporting at least one adverse event or the incidence of discontinuation because of adverse events between the naltrexone and placebo subject groups.

**Reference:** Suh, J. J., Pettinati, H. M., Kampman, K. M., & O'Brien, C. P. (2006). The status of disulfiram: A half of a century later. *Journal of Clinical Psychopharmacology, 26*(3), 290–302.
**Purpose:** Review the history, current status of treatment, and future developments of disulfiram for the treatment of alcohol and cocaine dependence.
**Conclusions:** Supervised disulfiram can be an effective treatment for alcohol use.
**Methodology:** A MEDLINE literature review (1937–2005) on the treatment of disulfiram for alcohol and cocaine dependence was conducted.
**Summary of Results:** Supervised disulfiram can be an effective treatment for alcohol use. Two studies presented conflicting evidence about the efficacy of disulfiram, compared with naltrexone. One study found similar efficacy when comparing disulfiram and acamprosate for treatment of alcohol use. Future efforts should focus on assessing the effectiveness of disulfiram combined with other pharmacotherapies, especially newer ones.

**Reference:** Thomas, C. P., Wallack, S. S., Lee, S., McCarty, D., & Swift, R. (2003). Research to practice: Adoption of naltrexone in alcoholism treatment. *Journal of Substance Abuse Treatment, 24,* 1–11.
**Purpose:** Study factors associated with acceptance of naltrexone and other alcoholism treatment medications by clinicians and attitudes toward the role of medication in therapy.
**Conclusions:** Lack of information about naltrexone, its high cost, and organizational affiliation were important reasons for or against its acceptance.
**Methodology:** A survey was developed, based on a literature review and interviews with clinicians, and disseminated in 1999 in Massachusetts, Tennessee, and Washington State. The survey was based on a conceptual framework and measured clinician characteristics, clinic and patient characteristics, prescribing practices for medications used in alcoholism treatment, and reasons for or against prescribing these medications. The survey was mailed to practicing members of the American Society of Addiction Medicine and/or the American Academy of Addiction Psychiatrists with followup by mail and telephone.
**Summary of Results:** A total of 63 percent of physicians (n = 129) and 65 percent of nonphysician clinicians (n = 1,062) responded. Eighty percent of physicians had some experience prescribing naltrexone; however, only 15 percent prescribed it often. Among nonphysicians, 45 percent had some experience with it, and only 5 percent prescribed it often. Factors associated with prescribing naltrexone among physicians were being in an organization that actively recommends naltrexone ($p < 0.001$) and spending time in research ($p < 0.05$). Having an additional degree or being in recovery ($p < 0.01$) negatively predicted adoption of naltrexone. Among nonphysicians, factors associated with prescribing naltrexone were working in an organization that recommended it ($p < 0.001$), having received marketing information about it ($p < 0.001$), having a high proportion of Medicaid patients ($p < 0.001$), and working in Washington State ($p < 0.05$). Factors associated with not prescribing naltrexone were having a high proportion of self-pay patients ($p < 0.05$) or having a high proportion of State Block Grant patients ($p < 0.05$).

**Reference:** Verheul, R., Lehert, P., Geerlings, P. J., Koeter, M. W., & van den Brink, W. (2005). Predictors of acamprosate efficacy: Results from a pooled analysis of seven European trials including 1,485 alcohol-dependent patients. *Psychopharmacology, 178*(2–3), 167–173.
**Purpose:** Identify the patient characteristics that predict successful treatment with acamprosate for alcohol dependence.
**Conclusions:** Acamprosate is effective for all patients with alcohol dependence.
**Methodology:** The study analyzed data pooled from seven European randomized trials of acamprosate. Independent variables were severity of withdrawal symptoms, family history of alcoholism, age of onset, duration of alcohol dependence, anxiety (using the Hamilton Depression Scale), severity of craving, physiological dependence, and gender. Dependent variables were cumulative abstinence duration (CAD) and continuous abstinence (CA).
**Summary of Results:** Trials initiated treatment approximately 1–4 weeks after the initiation of a detoxification period, for a total time ranging from 3 to 12 months (median = 6 months). A total of 983 subjects were included in the multifactorial analysis. No significant interactions were found between the independent variables demonstrating main effects and the outcome variables: CAD (craving $P = 0.347$ and anxiety $P = 0.829$) and CA (values not reported).

**Reference:** Weiss, R. D. (2004). Adherence to pharmacotherapy in patients with alcohol and opioid dependence. *Addiction, 99,* 1382–1392.

**Purpose:** Review the issues common to medication adherence including reliability of measurement, the complex reasons for nonadherence among patients, and strategies to increase adherence. Address the importance of medication adherence with disulfiram and naltrexone.
**Conclusions:** Nonadherence to medication regimens is a common problem in the treatment of chronic disorders, including substance use disorders. Nonadherence is associated with poor outcomes and increased costs. Improving patient adherence begins with paying close attention to it and using strategies to monitor it closely. The review presents a range of possible reasons for patient nonadherence and discusses in detail interventions the clinician can use in sessions with patients, including psyhosocial strategies and medication prescribing and dosing strategies that enhance adherence. For the treatment of alcohol dependence, ongoing development of long-acting preparations of naltrexone may hold promise for improved treatment results by addressing the limitation of oral naltrexone linked to nonadherence and gastrointestinal side effects.
**Methodology:** A review of the literature of English-language publications was performed that related to medication adherence among patients with alcohol and opioid dependence.
**Summary of Results:** Adherence is a complex issue. A major goal for practitioners should be improving adherence, and more research is needed to identify effective approaches. The authors suggest that treatments that are more efficacious, reduce dose complexity, and diminish side effects should be developed.

# Section 3—General Bibliography


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# Appendix—Methodology

A lengthy and systematic process was used to identify and synthesize the literature and research that support this Treatment Improvement Protocol (TIP). This TIP literature search was built on—and expanded—a short pharmacotherapy literature review covering 2000–2005, which had been completed for the Center for Substance Abuse Treatment as part of the Screening, Brief Intervention, and Referral to Treatment program. The literature search, done through the National Institute of Medicine's PubMed database, encompassed both clinical and administrative topics. For example, it identified articles concerning physicians' use of pharmacotherapy for alcohol problems, as well as such barriers to use as practitioners' attitudes and lack of knowledge about these medications. In addition, the Center for Substance Abuse Research (CESAR) conducted a literature search specific to alcohol-related disorders and acamprosate in April 2005 (for databases used, see the list below). This search identified 83 relevant articles in the period from 2000 to 2005. These preliminary searches, as well as the experience of literature searches done for earlier TIPs, demonstrated that it would not be necessary to conduct a separate literature search dedicated to administrative topics.

The series of comprehensive searches undertaken for this literature review was started in March 2006. The searches covered the period from 2000 to 2006, with selected articles also retrieved from 1998 to 1999, and focused on (1) research literature concerning medications approved by the Food and Drug Administration (FDA) for medical management of alcohol disorders, as well as combined pharmacotherapies, (2) use of these medications in primary care, including adverse events and selection of appropriate patients, and (3) need for further research and knowledge. The searches, conducted by a professional librarian from CESAR, used the following databases:

- **PubMed.** Search terms included
  - Alcoholism/drug therapy
  - Alcohol-related disorders/drug therapy
  - Alcohol-related disorders AND each of the following:
    - Acamprosate/Campral (since April 2005)
    - Naltrexone
    - ReVia
    - Antabuse
    - Disulfiram
    - Odansetron
    - Topiramate
    - Nalmefene
    - Multiple substance abuse
    - Relapse prevention
    - Craving.
- **PsycINFO.** Search paths included
  - (Alcoholism OR Alcohol abuse) AND (Pharmacotherapy OR Drug therapy OR Acamprosate/Campral [since April 2005] OR Naltrexone OR ReVia OR Antabuse OR Disulfiram OR Odansetron OR Topiramate OR Nalmefene) OR Multiple substance abuse OR Relapse prevention OR Craving.

- **ETOH.** (This Alcohol and Alcohol Problems Science Database, sponsored by the National Institute on Alcohol Abuse and Alcoholism, includes articles from 1972 through December 2003 only.) Search terms included
  - Ti Pharmacotherapy OR
  - Kw Drug therapy.
- **Academic Search Elite, CINAHL, Health Source Academic, Psychology and Behavior Science, PsycArticles, Social Science Abstracts, Social Index.** Search terms included
  - Alcoholism AND
  - (Pharmacotherapy OR Drug therapy).

While the TIP on alcohol pharmacotherapies was being developed, Vivitrol® (formerly Vivitrex®), a long-acting injectable form of naltrexone, was in the final stages of approval by FDA. To keep apprised of emerging research and updates on the status of the FDA application, the FDA and the manufacturer's Web sites as well as Web search engines were searched regularly for references to this new medication. In April 2006, a targeted literature search was carried out on long-acting naltrexone, which elicited 24 articles specific to this new form of the drug, including articles on an open-label trial, randomized controlled clinical trials, and a multicenter, randomized, placebo-controlled pilot study.

Using the search strategy developed for the comprehensive review, updates to this literature review were made in October 2006 and in April 2007. An additional update was made in October 2007, after the text for the literature review had been completed; that update appears as a separate section at the beginning of this Web-site literature review. Continuing updates will be made at 6-month intervals as long as the literature review remains available on the Web site of the Substance Abuse and Mental Health Services Administration's Knowledge Application Program (KAP). Exhibit A-1 provides a tabulation of the articles identified during the initial literature search as well as during the updated searches.

**Exhibit A-1**
**Articles Identified in Specific Categories by Year**

| Year of Publication | Reviews, Meta-Analyses, and General Articles | Clinical Trials | Studies and General Articles on 1 or 2 Medications | Total Articles by Year |
|---|---|---|---|---|
| 1998 | 15 | 0 | 5 | 20 |
| 1999 | 18 | 0 | 6 | 24 |
| 2000 | 22 | 30 | 37 | 89 |
| 2001 | 23 | 31 | 42 | 96 |
| 2002 | 15 | 36 | 32 | 83 |
| 2003 | 25 | 28 | 43 | 96 |
| 2004 | 27 | 28 | 38 | 93 |
| 2005 | 35 | 19 | 64 | 118 |
| 2006 | 34 | 14 | 29 | 77 |
| 2007 | 9 | 11 | 22 | 42 |
| **Totals by Category** | **223** | **197** | **318** | **738** |

For each citation found, reference information and abstracts were reviewed by the literature reviewer and TIP editors. The reviewers eliminated any citations that focused on preclinical research, including animal studies, and on medications used for detoxification rather than medical management. Citations were also rejected when they concerned use of medications for mental or physical disorders occurring in conjunction with substance use disorders. For example, articles were omitted that focused on medications to treat depression in people with alcohol use disorders. Citations from foreign sources written in English were included because so much significant research on naltrexone and acamprosate has been done in foreign, particularly European, countries. The foreign literature on acamprosate was particularly crucial because acamprosate had been used in 26 countries (with 17 randomized, placebo-controlled clinical trials) before 2004, when it was approved for use in the United States. Citations addressing the future directions of pharmacologic treatment were also included, such as the promise of genetic-based research and of selected medications now under development.

After references were selected using these search procedures, the bibliographies or citation lists from these references were reviewed to find older, seminal literature appropriate for this topic. Because disulfiram has been used in the United States for more than 55 years, it was especially important to identify seminal research before 2000. Members of the TIP development panel were asked to suggest earlier research and other articles that would be relevant to the TIP, focusing on the disulfiram literature.

Potentially useful books were identified by chapters appearing in the literature searches and by the TIP chair.

Included with the literature review on the KAP Web site is a 50-item Annotated Bibliography that lists many major and seminal articles on the pharmacotherapy of alcohol disorders. This highly selective list covers articles on each medication currently approved for medical management of alcohol disorders. The literature reviewer assembled an initial list of candidates for this Annotated Bibliography, and the TIP consensus panel of experts reviewed the list and recommended additions and deletions. The Annotated Bibliography represents the final selections recommended by the TIP consensus panel. Because the Annotated Bibliography is limited to only 50 citations, many fine articles could not be included.