Advances in the Treatment of Alcohol Dependence

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the series of planning teleconferences "Advances in the Treatment of Alcohol Dependence," which was held in February, March, and April 2007. This report was prepared by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Cephalon, Inc.*

The planning teleconference series was chaired by ***Richard N. Rosenthal****, M.D., from the Department of Psychiatry, Columbia University College of Physicians and Surgeons, and the Department of Psychiatry, St. Luke's-Roosevelt Hospital Center, New York, N.Y. The faculty were* ***Kathleen T. Brady****, M.D., Ph.D., from the Clinical Neuroscience Division, Department of Psychiatry, Medical University of South Carolina, Charleston;* ***Petros Levounis****, M.D., M.A., from the Department of Psychiatry, St. Luke's-Roosevelt Hospital Center, and the Addiction Institute of New York, N.Y.; and* ***Mark L. Willenbring****, M.D., from the Division of Treatment and Recovery Research, the National Institute on Alcohol Abuse and Alcoholism, the National Institutes of Health, Bethesda, Md.*

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Approximately 18 million adult Americans, who represent 8.5% of the population, suffer from alcohol abuse or dependence each year, with men affected slightly more frequently than women.[1] Richard N. Rosenthal, M.D., noted that the prevalence of alcoholism is similar to rates of other chronic diseases, such as diabetes, depression, and asthma.[2–5] Additionally, alcohol abuse and dependence are associated with more than 100,000 annual deaths and up to 40% of annual hospitalizations.[1,6] Despite the high prevalence of alcohol dependence and abuse and the availability of 4 medication formulations approved by the U.S. Food and Drug Administration (FDA) for the treatment of these disorders, the National Institute on Alcohol Abuse and Alcoholism reported that only about 1% of afflicted individuals receive alcohol-specific treatment.[1]

The Armamentarium for Treating Alcohol Dependence and Its Impact on Clinical Practice and Patient Outcomes

Dr. Rosenthal provided a neurobiological background for a discussion of current medications approved for the treatment of alcohol dependence and stated that the goal of pharmacologic treatment is to prevent patients from relapsing to their previous drug-taking behavior.

Triggers for Relapse

Dr. Rosenthal identified 3 major biological mechanisms derived from animal models that have been shown to be associated with relapse of drug-seeking behavior: drug re-exposure, conditioned cue re-exposure, and nonspecific stress.[7–9] In animals that have been trained to self-administer substances of abuse and have subsequently had this reward mechanism extinguished, the reward extinction model states that drug re-exposure is a sufficient stimulus to reinstate drug-seeking and drug-delivering behavior.[7] Similarly, conditioned cues have been shown to be associated with the ingestion of alcohol, and craving and dysphoria are often elicited by exposure to these cues.[9] Finally, nonspecific stress, which is usually defined physiologically as that which raises serum cortisol levels, increases relapse rates as well.[8] Because these triggers for relapse cannot always be avoided, patients need pharmacologic and/or psychosocial interventions to help prevent relapse. Pharmacologic treatments work within the context of the neurobiology of alcohol dependence.

The Neurobiology of Alcohol Dependence

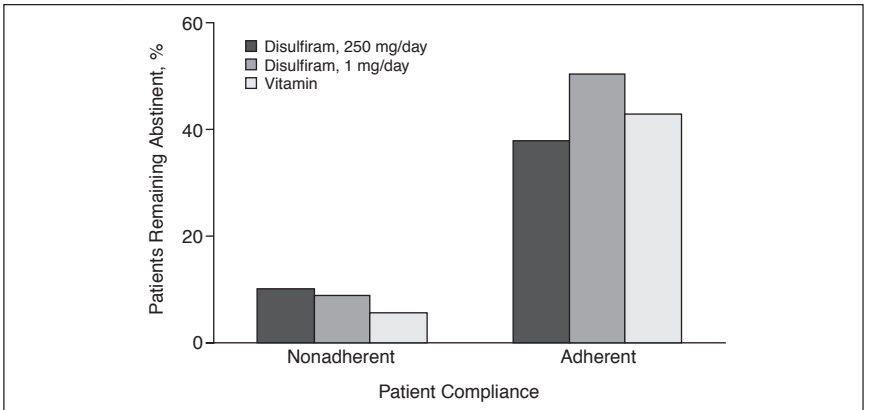
Several neurotransmitter systems are involved in the reward system in alcohol dependence, including the corticotropin-releasing factor, endogenous opioid, γ-aminobutyric acid (GABA), glutamate, serotonergic, dopaminergic, and endocannabinoid systems. Dr. Rosenthal stated that the GABA, glutamate, and endogenous opioid systems are most directly relevant to the newer FDA-approved medications for alcohol dependence treatment.

GABA system. The GABA system is the primary inhibitory neurotransmitter in the central nervous system,[10] and within this system, $GABA_A$ receptors are the most prevalent types.[11] Most sedatives, such as barbiturates, benzodiazepines, and alcohol, interact

with the GABA system, activating $GABA_A$ and therefore decreasing cell excitability.[11] Because GABA neurotransmitters are widely distributed throughout the brain, several alcohol-induced inhibitory behaviors ensue when alcohol potentiates the GABA receptors, similar to the mechanism of action of benzodiazepines.[11,12] For example, Dr. Rosenthal commented that inhibiting GABA receptors in the cerebellum leads to incoordination, whereas in other areas of the brain, this inhibition can cause sedation and anesthesia.[11,12] When chronically exposed to alcohol, the brain decreases GABA receptor sensitivity through a conformational change as a compensatory strategy to maintain the GABAergic tone at a normal level of functioning, which may contribute to the excitatory components of withdrawal syndrome.[12,13] Thus, administering cross-tolerant medications, such as benzodiazepines, during the withdrawal period from alcohol is a reasonable treatment intervention.[12]

Glutamate system. As the corollary to the GABA system, the glutamate system is the primary excitatory neurotransmitter in the central nervous system, and the *N*-methyl-D-aspartate (NMDA) receptor, which binds glutamate, is the most sensitive receptor to alcohol.[10,12,14] NMDA receptors contribute to neurologic plasticity, that is, adaptiveness to environmental and genetic influences by learning and memory formation,[15] and, upon activation, NMDA receptors allow positive ion influx and transmit fast-traveling excitatory impulses.[12,14] Dr. Rosenthal stated that during chronic alcohol exposure, the brain upregulates through increasing the number of NMDA receptors,[16] which contributes to the development of tolerance to alcohol.[10,13,15,16] When chronic alcohol administration ceases, NMDA receptors remain upregulated, and the resulting excessive glutamate-induced excitation corresponds to the hyperexcitatory symptoms of alcohol withdrawal, including hallucinations, hyperactivity, and seizures.[10,12,16–18] Additionally, this high glutamate activity increases the risk of excitotoxic cell death, possibly resulting in cognitive deficits that are seen over time as sequelae of alcohol dependence.[18]

Figure 1. Relationship Between Disulfiram Compliance and Alcohol Abstinence in Alcohol-Dependent Patients[a]



[a]Data from Fuller et al.[23]

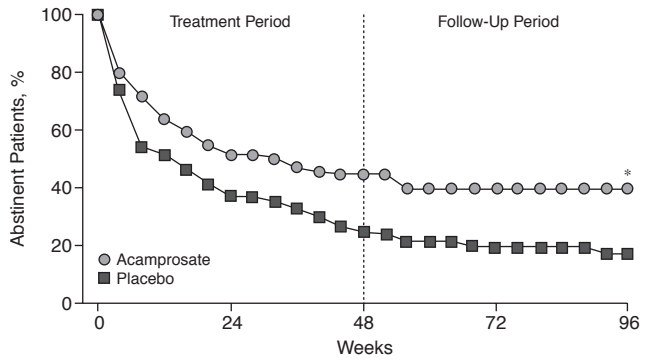
Endogenous opioid system. Alcohol consumption is associated with an increased release of endogenous opioids, which are thought to play a large role in the reward system through an increase of dopamine release in the nucleus accumbens.[19–21] The 3 major opioid peptides, β-endorphins, enkephalins, and dynorphins, bind to the μ-, δ-, and κ-opioid receptors, respectively.[19–21] Upon alcohol ingestion, β-endorphins are increased, which is hypothesized to mediate the euphoric effect produced by alcohol.[19,21]

Pharmacotherapy for Alcohol Dependence

Disulfiram. Mechanism of action. Approved by the FDA in 1951, disulfiram does not work within the context of the GABA, glutamate, or endogenous opioid systems but rather is an aversive agent. Disulfiram inhibits the metabolism of acetaldehyde into acetate by blocking the enzyme aldehyde dehydrogenase, an action which precipitates the accumulation of acetaldehyde when alcohol is consumed.[22] This build-up of acetaldehyde causes unpleasant stereotypic reactions such as tachycardia, flushing, sweating, shortness of breath, nausea, and vomiting, all of which are strong deterrents to drinking alcohol.[22] A caveat to these aversive responses to disulfiram is that alcohol is contained in products other than alcoholic beverages, such as aftershave, mouthwash, and some over-the-counter medications.[22] Therefore, Dr. Rosenthal emphasized that patients must be aware of the ingredients of products that they come in contact with to avoid accidental exposure.

Efficacy. Fuller et al.[23] examined abstinence rates and drinking days for 605 alcoholic men from 9 Veterans Administration medical centers who were treated daily with 250 mg of disulfiram (the standard dosage), 1 mg of disulfiram (a low dosage that would not elicit an alcohol-disulfiram reaction), or a vitamin (the no-disulfiram control group). Patients' self-reports were substantiated by blood and urine toxicology analyses as well as family and friend interviews. Among subjects who drank and completed assessments, men treated with 250 mg/day of disulfiram had fewer drinking days per year (49.0) than those taking 1 mg/day of disulfiram (75.4) or vitamin (86.5). Although no differences were shown in abstinence in the general pool, 20% of those patients who were adherent reduced their alcohol consumption (Figure 1). Dr. Rosenthal explained that despite the similar abstinence rates between the placebo and medication groups, the fact that those who were

Figure 2. Continuous Abstinence Rates for the 48-Week Treatment Period and the 48-Week Follow-Up Period for Patients Receiving Acamprosate or Placebo[a]



[a]Adapted with permission from Sass et al.[30]
*p = .003 vs. placebo.

adherent to treatment did not drink alcohol illustrates the effectiveness of disulfiram as a psychological deterrent to alcohol ingestion.[24] Thus, disulfiram operates through aversive contingency rather than neuromodulation, and its efficacy is dependent on patients' adherence with the medication.[24] As with any chronic illness, treatment is only effective if patients are compliant, and noncompliance has been a problem with this medication.[6,25,26]

Safety and tolerability. Disulfiram has been shown to cause hepatitis, and therefore, the liver function of all patients taking this medication should be monitored regularly to detect any abnormalities.[22] Additionally, Dr. Rosenthal stressed that this medication is contraindicated for women who are pregnant and for patients with ischemic heart disease.[22] Disulfiram may also inhibit the metabolization of other drugs, causing drug-drug interactions with anticoagulants, anticonvulsants (phenytoin), and antituberculosis agents (isoniazid) and prompting the need to monitor potential increases in high blood disulfiram levels in patients who are on these medications.

Acamprosate. Mechanism of action. Dr. Rosenthal reported that acamprosate is not active at $GABA_A$ receptors and is a weak inhibitor of presynaptic $GABA_B$ receptors in the nucleus accumbens.[27,28] However, this agent does inhibit glutamate overactivity by reducing the release of glutamate from the presynaptic nerve terminal and reducing the overactivation of postsynaptic NMDA receptors.[29] This inhibition of the glutamatergic transmitter system may reduce vulnerability to relapse, possibly by blocking cue-induced craving or by blocking the relief of dysphoric states that are normally relieved by alcohol consumption.[13,29]

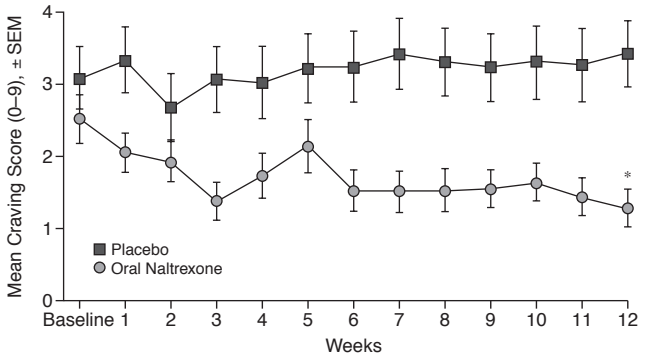
Efficacy. Dr. Rosenthal went on to discuss studies that have shown that acamprosate is effective in treating patients with alcohol dependence. For example, after a 48-week trial of newly detoxified alcohol-dependent patients who received routine counseling and either acamprosate or placebo, Sass et al.[30] reported a significant difference in continuous abstinence rates between patients who received acamprosate and those who received placebo (43% vs. 21%, respectively; $p = .005$), as well as number of days abstinent (224 days vs. 163 days, respectively; $p < .001$). The discontinuation rates were 41% for patients taking acamprosate and 60% for those taking placebo. An additional 48-week follow-up period of patients no longer taking study medication showed that more acamprosate-treated patients remained abstinent than placebo-treated patients (Figure 2).[30] Similarly, metaanalyses[31,32] found that patients treated with acamprosate had significantly higher continuous abstinence rates compared with patients treated with placebo ($p = .08$ and $p < .001$, respectively).

Safety and tolerability. Dr. Rosenthal reported that as a relatively safe and well-tolerated medication, acamprosate does not induce or inhibit hepatic microsomal enzymes. It may be coadministered with other medications typically given to alcohol-dependent patients, such as anxiolytics, hypnotics and sedatives (including benzodiazepines), or nonopioid analgesics, and no drug-drug interactions occur with alcohol, disulfiram, or diazepam.[33–36] Because this agent is primarily eliminated via the kidneys, the dosage of acamprosate should be lowered from two to one 333-mg tablet 3 times a day for individuals who have moderate renal impairment (creatinine clearance = 30–50 mL/min), and this agent is contraindicated for those who have severe renal impairment (creatinine clearance ≤ 30 mL/min).[33,35] Side effects of the medication include asthenia, nausea, pruritis, flatulence, and diarrhea, although loose stools have been shown to decrease over long-term exposure to acamprosate.[32,33]

Although suicidal ideation, suicide attempts, and completed suicides are infrequent overall with acamprosate,[33] adverse events of a suicidal nature were more common in clinical trials[33,34] in acamprosate-treated patients than placebo-treated patients (1.4% vs. 0.5%, respectively, for ≤ 6 months; 2.4% vs 0.8%, respectively, for 1 year); no difference was reported between the groups for completed suicides. Nonetheless, Dr. Rosenthal emphasized that suicidality and depression are important safety issues to monitor when administering acamprosate, as with any psychoactive medication in alcohol-dependent patients.

Naltrexone. Mechanism of action. Naltrexone binds all of the endogenous opioid receptors but has the most robust effect as a μ-receptor antagonist, thereby inhibiting the positive reinforcement of increased β-endorphins during alcohol use.[19,22,37,38] Through this

Figure 3. Mean Craving Scores for Alcohol-Dependent Patients Treated With Naltrexone Versus Placebo[a]



[a]Reprinted with permission from Volpicelli et al.[44]
*Oral naltrexone significantly decreased mean craving scores compared with placebo ($p < .01$).

interference, naltrexone is hypothesized to reduce alcohol craving, decrease alcohol consumption, and reduce relapse rates by reducing the priming effect of alcohol re-exposure during abstinence.[39–43] Naltrexone is available in both oral and extended-release injectable forms; Dr. Rosenthal focused on the oral form.

Efficacy. In a 12-week trial by Volpicelli et al.,[44] 23% of patients treated with oral naltrexone relapsed to heavy drinking versus 54% of patients treated with placebo (Figure 3). Naltrexone reduced the time to relapse ($p < .01$), reduced the mean number of drinking days ($p < .025$), and decreased craving scores ($p < .01$) compared with placebo. A meta-analysis[45] of 27 randomized controlled trials found that short-term (< 12 weeks) treatment with oral naltrexone decreased rates of relapse to heavy drinking by 36%, decreased rates of return to any drinking, and lowered the risk of treatment withdrawal. Medium-term treatment yielded no benefit for prevention of relapse to heavy drinking but did increase time to first drink and decrease alcohol craving.[45] Not enough data are available on prolonged treatment. Meta-analyses[32,46] have indicated variable effects of oral naltrexone in helping patients to maintain complete abstinence but have shown moderate effects in decreasing patients' number of heavy drinking days.

Safety and tolerability. The main side effect caused by oral naltrexone is nausea, and dysphoria has also been reported,[44,47] although Volpicelli et al.[44] found no psychiatric symptoms or mood changes. High doses of this medication may cause reversible increases in liver function enzymes in certain individuals, prompting the FDA to include a black box warning in the prescribing information; however, this warning stipulates that under the correct dosages, these effects are unlikely to occur.[48] Finally, Dr. Rosenthal recommended that, when prescribing naltrexone, clinicians should screen patients for opioid abuse to avoid inducing withdrawal in opioid-dependent patients. Additionally, clinicians should be cautious in giving opioid analgesia to patients whose opioid receptors are blocked.

Although oral naltrexone has a favorable side effect profile, Dr. Rosenthal noted that compliance remains an issue,[32] as is the case with any medication. For this reason, naltrexone for extended-release injectable suspension may be a useful alternative to oral medication; its efficacy, safety, and tolerability are discussed in the next section of this ACADEMIC HIGHLIGHTS.

Conclusion

Alcohol dependence is a neurobiological disease affecting several neurotransmitter systems that offer different treatment targets for medication. Dr. Rosenthal stated that pharmacologic interventions that modify these neurotransmitters or their receptors have shown promise in treating alcohol dependence. Further, the optimal treatment of alcohol dependence may be achieved by integrating pharmacologic therapies with psychosocial interventions.

Novel Administration Method for Medication Treatment of Alcohol Dependence

Kathleen Brady, M.D., Ph.D., focused her presentation on the extended-release injectable suspension preparation of naltrexone and explored the efficacy, safety, and tolerability of this formulation. As Dr. Rosenthal explained earlier, naltrexone is an opioid μ-receptor antagonist, which means it should reduce the positive reinforcing effects of alcohol[42,43] and thus decrease relapse.

Compliance Problems With Oral Naltrexone

Dr. Brady stated that oral naltrexone is more efficacious when people are compliant with the daily dosing regimen required. Seven of the 27 placebo-controlled trials in the Cochrane review[45] evaluated the efficacy of the drug as a function of adherence. In 4 of those 7 trials, the likelihood of returning to drinking was significantly reduced (relative risk [95% CI] = 0.87 [0.76 to 1.00]) in short-term naltrexone treatment compared with placebo, but positive effects of naltrexone were found only when patients were divided into adherent versus nonadherent groups. In 2 of the 7 studies, reductions in drinking were found in adherent sub-

Table 1. Barriers to Medication Adherence in Patients With Alcohol Dependence

Patients' beliefs about efficacy of medication[49,50]
Cognitive problems[49]
Denial or poor insight into illness[49,51]
Motivational and/or mood problems[49]
Poor social support[49,52]
Medication side effects[49,50,53]

jects in both the placebo and the naltrexone group. Dr. Brady reiterated that while naltrexone has preferential efficacy compared with placebo,[44] patients who were adherent, whether they were taking placebo or naltrexone, were more likely to have reductions in drinking.[45]

Dr. Brady listed potential barriers to medication adherence in alcohol-dependent patients (Table 1).[49–53] Patients' beliefs about the efficacy of medications are one potential barrier to adherence.[49,50] Some recovery support groups are ambivalent about the use of medications or believe individuals should achieve recovery without medication. Another barrier may be cognitive problems; alcohol has major effects on cognition. Many alcohol-dependent people have been drinking for years, and they may have developed memory impairments that interfere with their ability to comply with medication regimens.[49] Additionally, denial and poor insight into illness are core features of alcohol dependence that can deter adherence.[49,51] Poor motivation and/or mood problems can be other potential barriers to compliance.[49] Depression is commonly comorbid with alcohol dependence,[54] and often patients have a sense of hopelessness that can translate into noncompliance. People with alcohol dependence may also have poor social support.[49,52] Often, their social support networks have been eroded by their substance use. Finally, Dr. Brady noted that, although medication side effects may be minimal, if a patient is already ambivalent about taking medication and has denial and/or mood problems, any adverse effects can often cause noncompliance.[49]

Naltrexone for Extended-Release Injectable Suspension in the Treatment of Alcohol Dependence

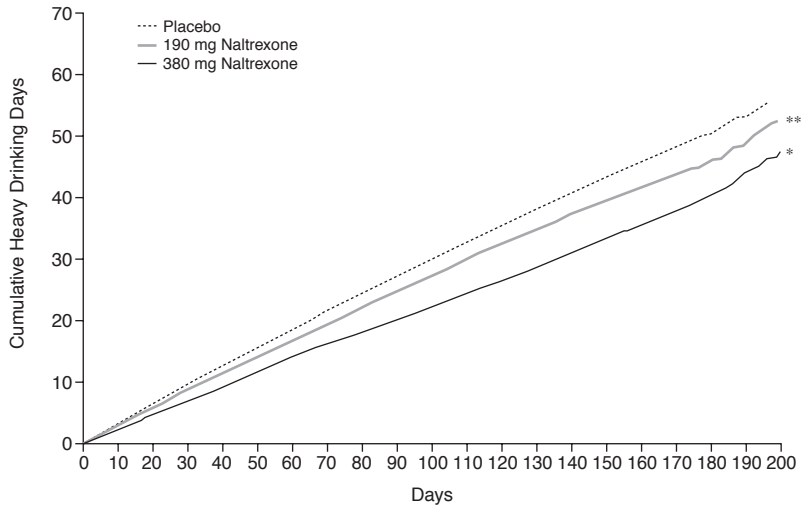
Does long-acting medication improve adherence? Dr. Brady addressed this empirical question by using antipsychotics as a model. Antipsychotics are used to treat mental illnesses with some features similar to those of alcohol dependence, such as denial of illness and cognitive problems, which can interfere with medication adherence. Although the question of improvement in compliance has not been directly answered, global improvement has been shown in patients taking depot formulations of the medications compared with the oral formulations.[55] A review[56] showed that depot antipsychotic medications were significantly superior in both reducing relapse rates ($p = .0002$) and reducing hospital days compared with oral formulations. Dr. Brady stressed that direct conclusions about compliance with naltrexone could not be drawn from the antipsychotic medication studies, but because depot forms of antipsychotic agents have been helpful in improving outcomes in schizophrenia, the same might be true of long-acting injectable medications for alcohol dependence.

Efficacy. Dr. Brady explained that a sustained-release injectable formulation of naltrexone in polymer microspheres comprised of poly (DL-lactide-co-glycolide) has been developed by DrugAbuse Sciences but is not yet FDA-approved. Kranzler et al.[57] conducted a 3-month, randomized, placebo-controlled multicenter trial of this formulation. Of the 315 patients treated in the study, 158 received a 300 mg injection of the naltrexone depot for the first month and then 150 mg injections during the second and third month. No significant difference in cumulative heavy drinking days was found between the groups; of the patients receiving naltrexone depot, 23% reported no heavy drinking compared with 16% of patients receiving placebo injections. The difference was significant ($p = .003$) between the 2 groups for time to first drinking day; the median time to first drinking day with naltrexone was 5 days compared with 3 days in the placebo group. The naltrexone-treated group also had a significantly higher ($p = .048$) abstinence rate (18%) compared with the placebo-treated group (10%).

Dr. Brady cited a study[58] that described the pharmacokinetics of an FDA-approved extended-release injectable suspension of naltrexone. Subjects in one group ($N = 28$) were given a single 50-mg dose of oral naltrexone followed by a single intramuscular injection of 190 mg, a single intramuscular injection of 380 mg of naltrexone (FDA-approved dose), or placebo. Another group ($N = 14$) was given a 50-mg oral naltrexone dose for 5 days followed by an injection of 380 mg of naltrexone or placebo every 28 days (total of 4 doses). The oral and intramuscular doses were separated by a 7-day washout period. Plasma concentrations of naltrexone were sustained in all patients for at least 1 month. The long-acting injectable formulation reduced fluctuations in plasma concentrations on a daily basis compared with the oral naltrexone and did not result in meaningful drug accumulation. The sustained-release formula of naltrexone reduced first-pass elimination, unlike the oral administration, so that there was greater exposure to naltrexone itself and lower exposure to the 6β-naltrexol metabolite, which is a weaker μ antagonist.

Dr. Brady then relayed the details of a double-blind, randomized, placebo-controlled, multicenter study conducted by Garbutt et al.[59] on the effects of the FDA-approved naltrexone for extended-release injectable suspension on alcohol-dependent patients. The 6-month study treated 624 patients, all meeting the DSM-IV criteria for alcohol dependence and having had at least 2 episodes of heavy drinking per week in the past 30 days. The patients were randomly assigned to receive a 380-mg naltrexone injection, a 190-mg naltrexone injection, or a matching volume injection of a placebo at 4-week intervals, and all re-

Figure 4. Change in Mean Heavy Drinking Event Rate By Treatment Group[a]



[a]Reprinted with permission from Garbutt et al.[59]
*p < .03 vs. placebo.
**p = .07 vs. placebo.

ceived 12 sessions of low-intensity psychosocial intervention. The mean event rate of heavy drinking days, which was the primary efficacy measure, was 25% lower in patients receiving the 380-mg injection (p = .03 vs. placebo) and 17% lower in patients receiving the 190-mg injection compared with placebo (p = .07 vs. placebo) (Figure 4). The median heavy drinking days per month was approximately 19 prior to treatment, approximately 6 for the group receiving placebo injections, approximately 5 for the group receiving 190-mg naltrexone injections, and approximately 3 for the group receiving 380-mg naltrexone injections. Benefits were observed both in patients who were drinking at the time they entered the study and in the abstinent patients, but the group with lead-in abstinence experienced a significantly greater benefit (p < .005).

Safety and tolerability. Dr. Brady reported that, in the study conducted by Garbutt et al.,[59] patients who received naltrexone injections mainly complained of nausea, headache, or fatigue. Some patients experienced pain at the injection site. Dropout rates were 14.1% in the group receiving the 380-mg naltrexone injection and 6.7% in the groups receiving the 190-mg naltrexone injection or placebo. Medication was generally very well tolerated, with a favorable liver enzyme profile.

In a different study, Kranzler et al.[57] reported no serious adverse events with this medication; however, common adverse events included headache, nausea, and fatigue. Injection site reactions caused 7 naltrexone-treated subjects and 6 placebo-treated subjects to discontinue treatment. Administration of the injections was problematic (an inability to extrude the microcapsules through the lumen of the needle) in 24.7% of naltrexone injections and 18.5% of placebo injections. Discontinuation due to an adverse event other than an injection-site reaction occurred in 4 (2.5%) of the naltrexone group and 2 (1.3%) of the placebo group.

Dr. Brady stated that some individuals may experience reversible increases in liver function enzymes, and the FDA has required a black box warning for doses higher than what is typically used in alcohol-dependent patients. Dr. Brady seconded Dr. Rosenthal's emphasis on the importance of screening patients for opiate abuse before starting them on naltrexone treatment. Because naltrexone is an opiate antagonist, beginning naltrexone treatment while a patient is using other opiates will precipitate withdrawal. Dr. Brady recommended conducting a urine screen for opiates and giving an oral dose of naltrexone before an intramuscular injection to avoid exposure to large doses of the opiate antagonist until the patient is clear of any opiates. Naltrexone contraindications include patients who may require opioid treatment for a chronic or acute pain condition or even for those who have an episodic medical disorder such as sickle cell anemia or intermittent pain requiring opioid analgesics. Naltrexone is also contraindicated for women who are pregnant or breastfeeding.

Conclusion

Dr. Brady concluded that naltrexone for extended-release injectable suspension is efficacious, safe, and well-tolerated. This preparation of naltrexone also eliminates the need for daily dosing that is required with the oral medication, which can improve compliance and optimize outcomes in the treatment of alcohol dependence.

Integrating Psychotherapy and Pharmacotherapy in the Treatment of Alcohol Dependence

Although medications now exist to effectively treat alcohol dependence, Petros Levounis, M.D., M.A., emphasized that psychosocial interventions continue to play the primary role in helping patients who struggle with alcoholism.

To examine psychosocial therapies for alcohol dependence, Dr. Levounis cited Project MATCH (Matching Alcoholism Treatment to Client Heterogeneity)[60] as the definitive study in assessing the effectiveness of the following 3 interventions: cognitive-behavioral therapy (CBT), motivational enhancement therapy (MET), and twelve-step facilitation therapy

(TSF). All of these therapies were found to be equally effective in helping patients abstain from alcohol during the 3-year study period,[60–62] with preliminary results from a 10-year follow-up[63] showing sustained improvements in abstinence and drinking intensity. Additionally, Dr. Levounis said that contingency management, a psychosocial intervention not examined by Project MATCH, is also effective for the psychotherapeutic management of alcohol dependence.[64]

Table 2. Motivational Enhancement Therapy: Stages of Change[60,70]

Stage of Change	Patient Action
Precontemplation	Not considering changing harmful behaviors
Contemplation	Beginning to recognize a problem, consider behavioral changes, and examine the means to complete those modifications
Preparation/determination	Deciding to change the harmful behaviors
Action	Changing the harmful behaviors (approximately 3 to 6 months)
Maintenance	Continuing to practice productive behaviors
Relapse	Reverting back to the harmful behaviors

Cognitive-Behavioral Therapy

According to the Project MATCH definition,[60,65] CBT for alcohol dependence is derived from social learning theory and its basic principles, which focus on reciprocal determinism. This concept states that behaviors are influenced by intrapersonal and interpersonal experiences and perceptions, and, in turn, these behaviors influence the environment; one impacts, transforms, and determines the other.[66,67] As a result, the patient who struggles with alcohol dependence essentially struggles with difficulties or problems associated with such exchanges.[65]

At the core of CBT is functional analysis: the identification of specific thoughts, feelings, and behaviors that the patient has before, during, and after using alcohol.[68] In practice, Dr. Levounis stated that clinicians should ask patients to recall and recount in detail the events leading up to drinking alcohol, including detailing their thoughts and feelings as well as the actions that they took to become inebriated. This process of relapse recall helps patients recognize their automatic thoughts surrounding alcohol use and prepares patients for the next step of CBT—skills training.

Skills training is designed to teach patients skills to manage the events and situations that commonly induce drinking behaviors through problem-solving, role playing, and homework exercises.[65] To implement skills training, Dr. Levounis recommended that clinicians help their patients with cognitive restructuring; that is, teach them to substitute the maladaptive automatic thoughts identified in the functional analysis with more realistic and helpful ideas.[65] For example, a patient who goes to a work-related "happy hour" and immediately feels anxious may think that only a stiff drink can take away the edge (automatic thought), and therefore orders the first double-scotch on the rocks. Instead, she or he could learn to think that reaching out to a friend or two at the happy hour can provide wonderful anxiety relief and comfort (cognitive restructuring). Further, making sure that she or he always arrives at such perceived torturous events with a least one friend at hand (skills training) completes the CBT work in this situation.

Motivational Enhancement Therapy

Based on the work of Miller and Rollnick[69] and specifically developed for Project MATCH,[60,70] MET employs goal-directed, motivational psychology to elicit behavioral changes from patients with alcohol dependence. This 4-session treatment approach relies on patients' responsibility and capability to alter problematic behaviors by using their own resources to initiate and maintain needed lifestyle changes.[60] This psychosocial therapy has been shown to be an effective intervention not only for patients with alcohol dependence but also for patients with obesity or eating disorders as well as other patients who struggle to make lifestyle changes.[71]

The foundation of MET is the concept of natural recovery, a process through which individuals undergo a series of stages of change to make the necessary behavioral modifications to overcome alcohol addiction.[60,72–74] Dr. Levounis explained that the 6 stages of change people experience are precontemplation, contemplation, preparation or determination, action, maintenance, and possibly relapse, which then brings one back to the contemplation stage to begin the cycle again (Table 2).[60,70]

For certain stages of change, individuals accomplish established tasks[70] with specific techniques that have been developed to help them complete these stages. One such technique (and the method predominantly used in MET) is motivational interviewing. Motivational interviewing is an individual-oriented approach that focuses on the rapid change of patients' harmful behavior through the examination of their ambivalence.[60,75] For clinicians, the 5 principles of motivational interviewing are to express empathy, support patients' self-efficacy, avoid argumentation, roll with resistance, and develop discrepancy,[69,76] with the goal of establishing collaborative and friendly patient-clinician partnerships, building patient self-esteem, and encouraging autonomy.[75] Dr. Levounis stated that motivational interviewing aids in identifying the patient's stage of change and helps her or him move to the next stage. Furthermore, motivational interviewing allows a clinician to engage patients in treatment even if their motivation for change is minimal or absent. Dr. Levounis commented that he, like many physicians, used to tell patients to come back for treatment when they were ready to do something about their alcohol usage, which is an unhelpful recommendation that misses prime therapeutic opportunities. Presently,

clinicians do not have to start work at such late stages as preparation or action; using motivational interviewing techniques, clinicians can successfully work with patients who are in the contemplation or ever precontemplation stages of change.

Twelve-Step Facilitation Therapy

Based on the concept that alcohol dependence is a disease, TSF attempts to facilitate the recovery process by actively engaging patients in mutual-help groups (originally called self-help groups). The spiritual belief in a higher power and the support from other group members are considered to be the principal factors for maintaining sobriety.[77]

Alcoholics Anonymous (AA) was the mutual-help group used in Project MATCH[60] and is the largest TSF program to date. Although AA does not keep formal lists of its members, as of January 2005, the General Service Office of Alcoholics Anonymous[78] estimated that approximately 2 million people were members in more than 105,000 groups worldwide. Dr. Levounis noted that the only requirement for membership in AA is the desire to stop drinking alcohol[79]; it is not abstinence or the belief in a higher power or the payment of any dues. Although abstinence is encouraged, relapses are understood as part of the recovery process; the support system within AA is designed to help members work through those difficult times and abstain from alcohol on a day-to-day basis.[79] "Keep it simple," "one day at a time," and "keep coming back; it works if you work it" are well-known AA slogans that underscore the commitment of AA to the alcoholic who is struggling to stay sober. Additionally, those AA members who help other recovering alcoholics are less likely to relapse than if they did not help others.[80]

AA encourages patients to accept their illness of alcoholism, understand that the disease has no cure, admit that they are powerless over the substance, surrender themselves to a higher power, and have faith that this power can restore stability in their lives.[60,78] A common misconception of this tenet is that clients must be religious or believe in God to be a member of AA. Dr. Levounis clarified this idea and stated that the higher power can be anything as long as it is greater than oneself, from God, to nature, to the fellowship of AA; patients establish for themselves what exactly they mean by higher power according to their own individual beliefs and convictions.[81] He added that explaining this misperception about the idea of higher power in AA is often all it takes to change a patient's mind and help her or him participate in TSF mutual-help programs.

Contingency Management

Combining the principles of behavioral pharmacology and operant conditioning, contingency management focuses on the assumption that positively reinforced behaviors are likely to be repeated.[64,82] Therefore, this psychosocial therapy provides incentives or rewards to patients who accomplish desired goals, such as maintaining abstinence,[64] and withholds those rewards when negative behaviors are detected, such as repeatedly receiving positive breathalyzer results.[82,83] Rewards can include money, movie tickets, vouchers for restaurants or discount clothing, or other prizes.[83] Dr. Levounis stated that traditional addiction treatment tends to be punitive in the sense that patients are expected to immediately abstain from all drugs and alcohol upon entering treatment and to continue that abstinence, with negative consequences being enforced if a slip or relapse occurs. Contingency management, on other hand, expects that patients will continue using drugs and/or alcohol even in treatment; if, however, they stop using substances and maintain abstinence, they are rewarded.[82]

To implement contingency management, clinicians should establish concrete incentives, be able to detect patients' use of alcohol, and try to increase other incentives, such as familial or social reinforcement, to counterbalance the patients' craving to drink alcohol.[83] Contracts are often instituted, detailing to patients (1) the intended behavioral changes, (2) how often these behaviors will be evaluated, and (3) the subsequent rewards that will be given as a result of implementing the desired behaviors.[82]

At this point, it is unclear if there is an association between the size of the reward and the duration of abstinence, which could make contingency management a costly intervention.[83] Definite conclusions cannot be reached at this time due to the paucity of studies analyzing alcohol dependence and contingency management.[84]

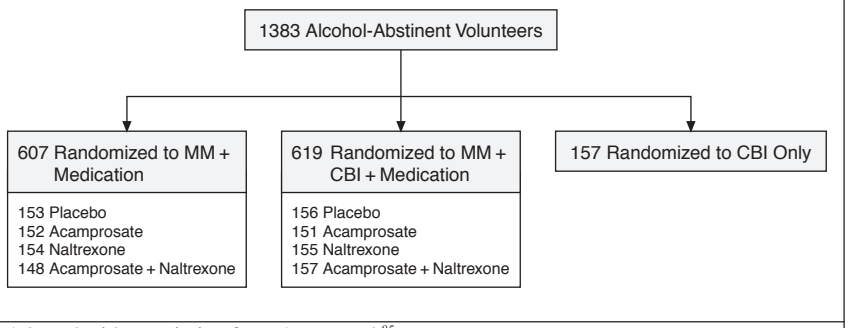
Conclusion

Each of the 4 psychosocial interventions briefly presented by Dr. Levounis has been shown to be effective in helping patients with alcohol dependence.[60–64] As a result, Dr. Levounis recommended implementing psychotherapy and/or mutual-help programs into patients' treatment regimens and suggested that a combination of medication and psychosocial interventions may be the best intervention strategy to optimize patient outcomes. However, Dr. Levounis emphasized that some patients may be inclined to participate in one intervention versus the other and advised that insisting on a combination of therapies to reluctant patients may be futile. Ultimately, clinicians should listen to their patients' preferences and be willing to tailor any treatment plan to their patients' moral, philosophical, and cultural orientations.

The COMBINE Study: Implications for Clinical Practice

As the largest randomized controlled trial to date on treatments for alcoholism, the COMBINE study[85] examined the efficacy of combinations of pharmacologic and behavioral interventions for alcohol dependence, explained Mark L. Willenbring, M.D. The

Figure 5. Treatment Group Randomization for the COMBINE Study[a]



[a]Adapted with permission from Anton et al.[85]
Abbreviations: CBI = combined behavioral intervention; MM = medical management.

2 medication treatments analyzed by this study[85] were acamprosate and oral naltrexone, and the 2 behavioral treatments were medical management (MM) and combined behavioral intervention (CBI).

Study Design

Over the 16-week treatment period, 1383 recently alcohol-abstinent, DSM-IV–diagnosed[86] alcohol-dependent volunteers from 11 U.S. academic sites were assigned to 1 of 9 treatment groups (Figure 5).[85] The sample included 955 men and 428 women, with a mean age of 44 years; 71% had at least 12 years of education, 42% were married, 73% were employed, and 23% were from various ethnic minority groups. On 76 pretreatment characteristics, the only significant between-group difference was the number of DSM-IV alcohol dependence symptoms (5.6 for the MM without CBI group and 5.4 for the MM plus CBI group; $p < .05$). Each participant was assessed 9 times during the treatment period and 3 times during the 1-year follow-up.

Medication. Naltrexone and placebo pills were identical, as were acamprosate and placebo pills, with participants in each group taking the same amount of pills per day (up to 8) over the 16 weeks of treatment. Although clinicians tried to maintain maximum doses of active medication with each patient (naltrexone, 100 mg/day, and acamprosate, 3 g/day), dosage adjustments were made based on individual tolerability.

Medical management. Of the 9 treatment groups, 8 received MM in addition to pharmacotherapy (half of those also had CBI). Dr. Willenbring stated that MM is compatible with primary care or general mental health care in that this counseling strategy does not require special training in addiction treatment and therefore may be provided by any licensed healthcare professional (e.g., nurse, pharmacist, physician). As with depression and smoking, the availability of effective medications for alcohol dependence allows for this disorder to be treated in routine health care settings. In this study,[85] 44 licensed health care professionals provided MM to the treatment sample in 9 sessions. MM began with an average 45-minute introductory visit in which the clinician addressed the diagnosis of alcohol dependence and the consequences of drinking and ended with recommendations to remain abstinent, comply with the medication, and attend support groups in the community. The next 8 sessions consisted of approximately 20-minute visits in which drinking, functioning, medication adherence, and adverse effects were reviewed, and any problems patients encountered during treatment were addressed.

Combined behavioral intervention. Developed specifically for the COMBINE study,[85] CBI is a state-of-the-art intervention that employs all 3 psychosocial interventions analyzed in Project MATCH[60] (CBT, MET, and TSF), as well as support system involvement that was outside of the study parameters. Further, the motivational interviewing technique[87] from MET was used throughout the duration of the study.[85] Unlike MM, CBI was implemented by licensed behavioral health specialists with at least master's degrees in psychology, social work, or counseling. Patients received up to 20 sessions of 50 minutes each that were tailored to their individual needs.

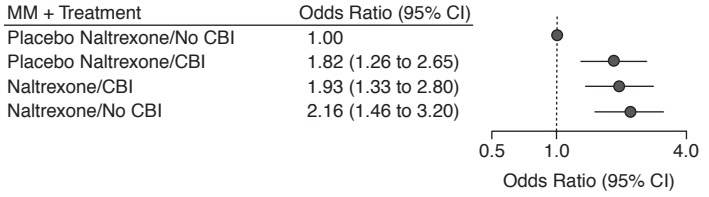
Study Results

Overall, patients taking medication(s) showed a significant increase in days abstinent over the 16-week study period (from 25.2 at baseline to 73.1; $p < .001$) as well as a significant reduction in number of drinks per drinking day (from 12.6 at baseline to 7.1; $p < .03$), thereby reducing drinks per week from 66 to 13. In contrast to previous studies[30–32,88] that have shown an effect for acamprosate-treated patients, the COMBINE study[85] found no difference between acamprosate and placebo with regard to percentage of days abstinent at baseline, endpoint, or at the 1-year follow-up. The naltrexone/MM/CBI group did show a significant difference for percentage of days abstinent ($p = .009$), whereas the naltrexone/acamprosate/MM/CBI group did not.

Similarly, naltrexone and MM had a significant effect at increasing the time to first heavy drinking day (hazard ratio = 0.72; 97.5% CI = 0.53–0.98; $p = .02$) versus placebo and MM.[85] Regarding time to first heavy drinking day in MM groups, Dr. Willenbring noted that patients not receiving naltrexone or CBI had the least improvement, those receiving naltrexone plus CBI or placebo plus CBI had intermediate improvement, and those receiving naltrexone without CBI had the most improvement.

Dr. Willenbring defined good clinical outcome as abstinence or light-to-moderate drinking without any

Figure 6. Odds Ratio for End-Point Good Composite Clinical Outcomes With MM Plus Treatment[a]



[a]Reprinted with permission from Anton et al.[85] Logistic regression model of good clinical outcome at the end of the last 8 weeks of treatment was significant for naltrexone plus CBI (p = .02).
Abbreviations: CBI = combined behavioral intervention; CI = confidence interval; MM = medical management.

alcohol-related problems. In an analysis of endpoint good clinical outcome (Figure 6),[85] a significant interaction was shown between naltrexone and CBI (p = .02), indicating that the presence of naltrexone, CBI, or both improved MM treatment outcomes.

The conclusions from this study[85] indicate that alcohol dependence can be successfully treated with naltrexone and 9 brief sessions of MM. Further, this combination treatment was shown to be as successful as specialty alcohol counseling (CBI), which has been the primary type of treatment offered to alcohol-dependent patients to date. Dr. Willenbring suggested that this finding implies that patients can be given a choice of either medication plus MM or specialty alcohol counseling, which requires a referral.

Tools for Clinicians

To aid clinicians in implementing treatment strategies, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) has developed several tools for use in nonaddiction settings. For example, the free NIAAA publication *Helping Patients Who Drink Too Much: A Clinician's Guide*[89] was recently revised to include COMBINE study results.[85] This publication, available free from NIAAA and online (www.niaaa.nih.gov/guide), features an algorithm decision tree for screening, assessing, and managing patients with alcohol dependence; standard definitions of an alcoholic drink; and prescribing information for medications used to treat alcohol dependence, including dosing information, side effects, contraindications, and important drug-drug interactions. Also included in this guide are a summary folding pocket guide, clinician support and patient education materials, as well as online materials for both clinicians and patients. Of these materials,[89] "Strategies for Cutting Down" is included as a handout for patients that offers recommendations to reduce alcohol ingestion, including keeping track of the number of drinks in one sitting, eating food to absorb much of the alcohol, and knowing how to politely refuse a drink.

An easy-to-use behavioral support program is another important tool provided as part of the 2007 Update to the NIAAA Clinician's Guide.[89] As with other disease management activities, providing support for adherence and self-management is a crucial part of using pharmacotherapy. MM, the brief behavioral platform used successfully in the COMBINE study,[85] has been condensed and is now included with the Guide.[89] Dr. Willenbring stated that MM is most likely to be offered by nurses working with physicians who are prescribing the medication. However, any health care professional or mental health professional, such as a social worker or psychologist, may find this guide beneficial in the treatment of patients with alcohol dependence. This manual has been condensed to facilitate clinicians' ease of use, and each step contains check boxes to document the completion of each step, so that the pages can be used as progress notes for inclusion in the patient's chart.

In addition, 2 tools are provided, each 2 pages long. The first tool is designed for the initial MM session—how to relate the patient's laboratory results to heavy alcohol use, confirm the diagnosis of alcohol dependence, review the consequences of drinking, and recommend abstinence, medication compliance, and TSF. The second tool is for subsequent sessions and includes a questionnaire to update the patient's information, such as drinking status, medication adherence, side effects, medication efficacy, and other treatment received, which is followed by a step-by-step guide for assessing the patient's abstinence and recommendations for each patient outcome (e.g., the patient is not drinking but is not adherent to medication, or the patient is drinking and is not adherent to medication).

Dr. Willenbring noted that in the Guide,[89] abstinence is recommended for patients receiving medication treatment because most studies have required abstinence. Pending further study, he concluded that abstinence should be recommended to patients receiving pharmacotherapy and stressed that if patients are unwilling to abstain, the physician should reconsider whether medication use is still appropriate with a modified goal of reducing alcohol intake.

Conclusion

Dr. Willenbring concluded that an important outcome of the COMBINE trial[85] was that treatment outcomes were at least as good with naltrexone when administered in conjunction with MM as they were with CBI (specialty counseling). He also noted that many patients are likely to find this combination strategy more acceptable and easier than attending a specialty treatment center.

Dr. Willenbring stated that a minority of people with alcohol dependence currently receive professional

treatment, and specialty treatment programs could not accommodate the intensive treatment regimen for everyone with this disorder. Further, patients with alcohol dependence have varying levels of severity and do not all require the same comprehensive treatment. Therefore, by offering pharmacotherapy and brief behavioral support, primary care physicians and psychiatrists can provide patients with access to effective treatment.

***Drug names*:** acamprosate (Campral), diazepam (Diastat, Valium, and others), disulfiram (Antabuse), isoniazid (Laniazid, Nydrazid, and others), naltrexone oral tablet (ReVia and others), naltrexone for extended-release injectable suspension (Vivitrol), phenytoin (Cerebyx, Dilantin, and others).

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

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