ABSTRACT

This paper reviews various pharmacologic strategies for the treatment of alcohol dependence based on what has been learned of the neurobiology of this condition. Aspects of treatment are twofold, focusing initially on acute withdrawal management followed by abstinence maintenance treatments. Specific strategies discussed include deterrence, reward reduction, and treatment of comorbid psychiatric disorders. The benefits and side effects of disulfiram, naltrexone, acamprosate, and selective serotonin reuptake inhibitors (SSRIs) are considered, as these are the most commonly prescribed agents. Focal points to guide future therapeutic directions include increased attention to behavioral strategies underpinning medication use, increased attention to combinations of medications versus monotherapy, and increased attention to individual differences among patients.


In the previous article, the neurobiologic bases for various pharmacotherapeutic agents set the stage for understanding how these medications may be put into action in the realm of patient care. For many years, much of the focus in drug development was centered on the issue of detoxification—getting the patient to withdraw from alcohol with the assistance of pharmacotherapy. More recently, scientists and clinicians have begun turning their attention toward using medications for maintaining in addition to establishing abstinence. The former is a more challenging task. Here we will explore various approaches to assisting patients to remain alcohol free once they have undergone detoxification, a process that will be discussed in depth later in this issue (see page 60). There are 3 basic strategies to abstinence maintenance treatments for alcohol dependence: deterrence, reward reduction, and treatment of comorbid psychiatric disorders. We begin with the oldest—and probably least appealing—method, which is deterrence.

ALCOHOL DETERRENCE—DISULFIRAM

For about 50 years (until 1994), disulfiram was the only medication approved by the US Food and Drug Administration (FDA) for the treatment of alcohol dependence. Disulfiram works by causing unpleasant physical side effects in individuals when they drink alcohol in the presence of the drug. Specifically, it can cause flushing, hypotension, nausea, and vomiting. From a behavioral perspective, the therapeutic rationale for using disulfiram is to punish the behavior of drinking alcohol, which leads to the person drinking less and avoiding alcohol to avoid these unpleasant effects. In the meantime, it gives the alcohol-dependent person an opportunity to develop alternative...
behaviors, coping skills, and relapse-prevention skills to be able to sustain alcohol avoidance over the long term.

In practice, however, punishment is difficult to enforce. Individuals stop taking their medications and at times develop a variety of techniques to conceal this fact from their caretakers and therapists. In response, a variety of compliance enhancement techniques have been developed to assist patients in taking the disulfiram, including using sustained-release medication implants, writing treatment contracts whereby the alcohol-dependent person agrees to be observed while taking the medication, or providing incentives. These incentives may be psychosocial, such as therapy to help patients remain with their families; economic, such as paying cash or promising continued employment if employment is at risk; or legal, as in granting probation instead of incarceration if the patient is in trouble with the law due to drinking. If the patient is also engaged in methadone treatment for opiate dependence, disulfiram may be mixed with the methadone, ensuring the patient will take the disulfiram with the daily methadone dose. Despite compliance enhancements, punishment is not the ideal means of assisting individuals in their attempts to remain alcohol free. It is preferable to decrease the pleasurable “reward” gained from drinking alcohol, and this is the goal of newer treatments.

**Reward-Reduction Treatments**

Now that we are gaining a better understanding of the biologic bases for alcohol addiction and the importance of modulating the effects of dopamine for regulating alcohol consumption, pharmacotherapy that reduces the reinforcing aspects or the pleasurable aspects of drinking alcohol is a much more appealing tactic that will engage more people in treatment and enhance motivation to remain in treatment. The therapeutic rationale for this type of treatment behaviorally is to decrease the reinforcing effects of alcohol, to promote the extinction of drug-associated cues, and to develop coping and relapse-prevention skills.

**Opioid Antagonists—Naltrexone**

Naltrexone is the only other FDA-approved medication for the treatment of alcohol dependence. Naltrexone is a well-known entity in the addiction treatment community, because it has been used for many years as a therapy for opiate dependence.1 This experience tells us that this medication has very few serious side effects when used over extended treatment periods;2 and it has no independent psychoactive effects.3 Further, naltrexone does not interact with alcohol in a negative way; using naltrexone will not make people who continue to drink while taking the drug more impaired or more intoxicated. It also has few drug interactions with other medications commonly prescribed to alcohol-dependent patients, including antidepressant and anxiolytic medications.4 Thus, naltrexone is a relatively safe medication for alcohol-dependence treatment. Is it effective?

**Table 1. Relapse with Naltrexone Treatment**

<table>
<thead>
<tr>
<th>Alcohol Consumption</th>
<th>Naltrexone (n = 35)</th>
<th>Placebo (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sampled (n)</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Relapsed (n) (≥5 drinks/1 occasion)</td>
<td>8</td>
<td>19</td>
</tr>
</tbody>
</table>

Data from Volpicelli et al.5

**Figure. Naltrexone Treatment: Relapse Rates**

Adapted with permission from Volpicelli et al. Naltrexone in the treatment of alcohol dependence. Arch Gen Psychiatry. 1992;49:876-880.6
Volpicelli and colleagues conducted a double-blind, placebo-controlled study in 70 male alcohol-dependent patients. The results revealed that, although approximately the same numbers of subjects from both the study group and placebo group sampled alcohol initially, those taking naltrexone were much less likely to relapse (as defined by drinking 5 or more drinks on 1 occasion; Table 1/Figure). Furthermore, other data collected from several early randomized placebo-controlled clinical treatment trials indicated that naltrexone reduced drinking days, number of drinks per occasion, cravings for alcohol, and likelihood that a “slip” would lead to a relapse (Table 2) perhaps because there is a self-reported decrease in the “high” that the individual experiences when drinking alcohol. The results of more recent clinical trials are mixed (Table 2). In particular, a large study by Krystal et al in 2001 of 627 veterans with severe chronic alcohol dependence failed to reveal any benefit of naltrexone over placebo after 12 months of therapy.

Meta-analyses of naltrexone’s efficacy for treatment of alcohol dependence, however, have been positive, particularly when the individual is compliant with the medication regimen. According to Volpicelli’s research, in which he used the BRENDA model (see page 65) of counseling to enhance compliance in study subjects, naltrexone has a significant benefit compared with placebo when medication compliance is over 90%. One of the issues that may interfere with compliance for any medication is its side effects. For naltrexone, these are generally not serious but may be somewhat common and include gastrointestinal upset, nausea, vomiting, headache, fatigue, insomnia, and dizziness. Another impediment to medication compliance is remembering and being motivated to take the medication on a daily basis. To overcome this obstacle, researchers are developing depot naltrexone, which seems to be well tolerated, effective (as defined as increased cumulative days abstinent, increased time to relapse, increased likelihood of attaining total abstinence compared with placebo) and long lasting, requiring only once-monthly injections.

Meta-analyses of naltrexone studies find significant effects on drinking outcomes, but the effect size is small to medium. Given the variability in medication response, a better understanding of outcome predictors is needed to determine who will most benefit from its use. For example, it would appear that naltrexone works best for those who are compliant with their medication and who have high alcohol craving at baseline. It also may be more effective for those with a positive family history of alcoholism and for those who receive more intensive psychosocial treatment (eg, cognitive behavioral therapy compared with brief interventions).

**Glutamate/NMDA Antagonists—Acamprosate**

Acamprosate is widely used in Europe for the treatment of alcohol dependence but has not yet been approved in the United States because findings from a multisite clinical trial performed here were unequivocal in substantiating its overall effectiveness. Although its exact mechanism of action is not clearly defined, it is believed that acamprosate plays a role in alcohol intoxication and the development of physical dependence. In meta-analyses of double-blind European studies (N >3000), acamprosate increased and maintained abstinence, although, like naltrexone, it had only a small-to-medium effect size (Table 3). Side effects are similar to those experienced with naltrexone and include nausea, vomiting, diarrhea, and headache. Acamprosate is not substantially metabo-

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**Table 2. Naltrexone Study Summary**

<table>
<thead>
<tr>
<th>Naltrexone Study</th>
<th>Additional Therapy</th>
<th>Slowed Relapse</th>
<th>Drinking Reduction</th>
<th>Craving Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OLDER STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volpicelli et al 1992</td>
<td>Intensive multimodality</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>O'Malley et al 1992</td>
<td>Supportive/coping skills</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Volpicelli et al 1997 (treatment completers)</td>
<td>Relapse prevention</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Anton et al 1999</td>
<td>Cognitive-behavioral</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>RECENT STUDIES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chick et al 2000 (compliant patients only)</td>
<td>12-step facilitation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Morris et al 2001</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Guardia et al 2002</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Krystal et al 2001</td>
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lized in the liver and thus has the advantage of being safe for use in individuals with liver disease.25

**MANAGEMENT OF COMORBID PSYCHIATRIC DISORDERS**

Deterrence and reward reduction are 2 approaches to pharmacologically reducing alcohol’s grip upon an individual. A third equally important strategy is the treatment of comorbid psychiatric conditions, because patients with psychiatric disorders are at high risk for developing alcohol dependence, and those with alcohol dependence often have comorbid psychiatric illnesses. A reduction in psychiatric symptoms (usually mood/anxiety disorders) and/or treatment for other substances of abuse via the effective use of pharmacotherapy will improve the individual’s overall functioning and may reduce the drive to self-medicate with alcohol.

Kessler and colleagues conducted a household survey in 1997 and found that respondents with a history of alcohol abuse or dependence were at elevated risk for having at least 1 other lifetime psychiatric diagnosis. Among women, the most common comorbidities were anxiety and mood disorders, whereas among men, drug abuse and antisocial personality disorders were more prevalent.26 This has implications for alcohol treatment, because alcohol-dependent patients with psychiatric disorders are at increased risk for noncompliance, relapse, psychosocial and interpersonal problems, more severe psychiatric symptoms, and suicide.27

Studies have been conducted examining the effects of selective serotonin reuptake inhibitors (SSRIs) on patients who suffer from both depression and alcohol abuse/dependence. From these data, it appears that when the antidepressant medication successfully treated the depression, there was also a decrease in drinking (Table 4).28-31 Likewise, studies have demonstrated a positive effect on drinking behavior when an antianxiety agent, the 5-HT1 serotonin agonist buspirone, was administered to individuals suffering from anxiety (Table 5).32-35 Furthermore, buspirone has a lower addiction risk for alcohol-dependent patients compared with benzodiazepines, another family of drugs commonly used in the treatment of anxiety disorders. In one randomized, 12-week,
placebo-controlled trial by Kranzler and colleagues including 61 anxious alcoholics (all of whom also received weekly relapse-prevention psychotherapy), positive effects were noted with buspirone compared with placebo therapy. Specifically, buspirone was associated with greater retention in the 12-week treatment trial, reduced anxiety, a slower return to heavy alcohol consumption, and fewer drinking days during the follow-up period 6 months posttreatment.\textsuperscript{35} Thus, multiple studies examining the use of medications to treat comorbid psychiatric conditions seem to optimistically point toward assisting in the reduction in alcohol-related symptoms, in retention of patients in treatment, and in a reduction in the incidence of relapse.

**Conclusion**

The field of pharmacotherapy for alcoholism is still in its infancy, although substantial progress has been made in the past decade. Research is now being driven by an understanding of how alcohol’s effects (intoxication, reward, and withdrawal, for example) are modulated by specific areas of the brain and by specific neurotransmitters. As we learn more, we become more sophisticated in drug development as well as in learning how to combine various drugs for maximum benefit. We also learn how individual differences between patients may influence prescriptive practices. For example, we are beginning to gain an understanding as to how different individuals require different therapies based on their genetic predisposition or psychiatric comorbidity. Finally, we are paying increased attention to how different individuals require different therapies based on their genetic predisposition or psychiatric comorbidity.

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