

*Drug Therapy*ALASTAIR J.J. WOOD, M.D., *Editor***DRUG THERAPY FOR ALCOHOL
DEPENDENCE**

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ALCOHOL dependence is a chronic disorder that results from a variety of genetic, psychosocial, and environmental factors.¹ As defined by the American Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders*, it is characterized by increased tolerance of the effects of alcohol, impaired control over drinking, and continued drinking despite adverse consequences (Table 1).² Alcohol dependence affects nearly 10 percent of the population and results in social problems, considerable morbidity and mortality, and high health care costs.^{3,4}

Alcohol dependence is treated by medical, psychological, and social interventions that reduce or eliminate the desire to drink and the harmful effects of alcohol. Treatment usually consists of two phases: detoxification and rehabilitation. Detoxification ameliorates the symptoms and signs of withdrawal; rehabilitation helps the patient avoid future problems with alcohol. Most rehabilitative treatments are psychosocial, consisting of individual and group therapy, residential treatment in alcohol-free settings, and self-help groups such as Alcoholics Anonymous. Almost all programs advocate complete abstinence from alcohol. Although psychosocial treatments are effective in reducing alcohol consumption and in maintaining abstinence in many patients, 40 to 70 percent of patients resume drinking within a year after treatment.⁵

There is increasing interest in drug therapy for alcohol dependence.⁶⁻⁸ The rationale for such therapy is based on several premises. First, advances in neurobiology have identified neurotransmitter systems

that initiate and maintain the drinking of alcohol; pharmacologic modification of these neurotransmitters or their receptors may modify dependence. Second, new drugs that reduce alcohol consumption in animals may also reduce consumption in humans. Third, the development of drugs for the treatment of addictive disorders, such as nicotine and opioid dependence, suggests that it may be possible to develop drugs for the treatment of alcohol dependence.

In the United States, the Food and Drug Administration (FDA) has approved two drugs, disulfiram (Antabuse, Wyeth-Ayerst, Philadelphia) and naltrexone (ReVia, Dupont Merck, Wilmington, Del.), for the treatment of alcohol dependence. Acamprosate (Campral, Lipha, Lyons, France, and Merck, Darmstadt, Germany), approved in several European countries, is being tested in the United States. Tiapride (marketed by various manufacturers) is also approved in several European countries. Other drugs marketed as mood stabilizers, sedatives, anxiolytics, and antidepressants have been used to treat alcohol dependence. This review discusses the putative mechanisms of action of these drugs and their efficacy.

**THE NEUROBEHAVIORAL ASPECTS
OF ALCOHOL DEPENDENCE**

Alcohol is a drug with complex behavioral effects that can be pleasurable or unpleasant, stimulating or sedating. The predominant effects depend on the dose, the length of time after ingestion, whether ingestion is chronic or intermittent, the drinker's expectations, the setting in which alcohol is consumed, the drinker's personality, and his or her genetic predisposition to alcohol dependence. Alcohol affects several brain neurotransmitters, including dopamine, γ -aminobutyric acid, glutamate, serotonin, adenosine, norepinephrine, and opioid peptides, and their receptors.^{7,8} Several neurobehavioral effects of alcohol have been related to the development of alcohol dependence (Table 2). These effects and their associated neurotransmitters are potential targets for drug therapy to treat dependence.

The pleasurable and stimulant effects of alcohol are mediated by a dopaminergic pathway projecting from the ventral tegmental area to the nucleus accumbens.^{9,10} Repeated excessive alcohol ingestion sensitizes this pathway and leads to the development of dependence.^{11,12} Drugs that target this dopamine system may reduce the reinforcing effects of alcohol and thereby reduce alcohol consumption. Similarly, drugs that increase the aversive effects of alcohol may reduce consumption. People who are more sensitive to the sedative and aversive effects of alcohol

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TABLE 1. CRITERIA FOR ALCOHOL DEPENDENCE.*

- The diagnosis of alcohol dependence requires at least three of the following conditions during a 12-month period:
- Tolerance — that is, the need for increased amounts of alcohol in order to achieve intoxication or another desired effect, or a markedly diminished effect with use of the same amount of alcohol
 - Characteristic withdrawal symptoms, or the ingestion of alcohol to relieve or avoid withdrawal
 - Ingestion of alcohol in larger amounts or over a longer period than intended
 - Persistent desire or one or more unsuccessful attempts to reduce or to control alcohol ingestion
 - Expenditure of much time in activities necessary to get and drink alcohol, or to recover from its effects
 - Abandonment of important social, occupational, or recreational activities because of alcohol ingestion
 - Continued alcohol ingestion despite the knowledge of having a persistent or recurrent social, psychological, or physical problem that is caused or exacerbated by it

*Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition.²

TABLE 2. NEUROBEHAVIORAL EFFECTS OF ALCOHOL ASSOCIATED WITH ALCOHOL DEPENDENCE.

BEHAVIORAL PROPERTY OF ALCOHOL	EFFECT ON PROMOTING OR INHIBITING ALCOHOL USE
Stimulation, induction of pleasure, positive reinforcement	Promotes initial ingestion, maintains alcohol use
Sedation	May promote or inhibit alcohol ingestion
Aversion	Protects against alcohol ingestion
Tolerance	Promotes ingestion; larger amounts required for effect
Withdrawal	Promotes ingestion to diminish unpleasant symptoms
Craving	Promotes ingestion
Self-medication (anxiolytic, tension-reducing effect)	Promotes ingestion to alleviate psychological distress

appear less likely to drink heavily and to develop alcohol dependence.¹³ Drugs that reduce the acute and chronic symptoms of alcohol withdrawal may treat dependence by reducing the need for alcohol-dependent patients to ingest alcohol to avoid this state.¹⁴ Long-term exposure to alcohol causes adaptive changes in several neurotransmitter systems, including down-regulation of inhibitory neuronal γ -aminobutyric acid receptors,¹⁵ up-regulation of excitatory glutamate receptors,¹⁶ and increased central norepinephrine activity.¹⁷ Discontinuation of alcohol ingestion leaves this excitatory state unopposed, resulting in the nervous system hyperactivity and dysfunction that characterize alcohol withdrawal.

People who drink alcohol over long periods and

excessively also have craving, defined as the conscious desire or urge to drink alcohol. Intense craving leads to a preoccupation with alcohol and increases the probability of drinking.¹⁸ Craving can occur in several circumstances: before alcohol ingestion, during alcohol ingestion, during acute withdrawal, and during exposure to the sight or smell of alcohol long after drinking has stopped. Craving has been linked to dopaminergic, serotonergic, and opioid systems that mediate positive reinforcement and to γ -aminobutyric acid, glutamatergic, and noradrenergic systems that mediate withdrawal.¹⁴ Reductions in craving are associated with longer abstinence.^{19,20}

Finally, it is proposed that some persons with psychiatric disorders become dependent on alcohol as a result of self-medication with alcohol to reduce psychiatric symptoms and distress.²¹ Alcohol dependence is common among patients with schizophrenia, panic disorder, and depression.²² Drugs that effectively treat the underlying psychiatric disorder may reduce the impetus for alcohol ingestion.

DRUG TREATMENT FOR ALCOHOL DEPENDENCE

Most studies of drug treatment for alcoholism compare differences in drinking outcomes between treatment with the drug and with placebo in recently abstinent patients who are also receiving psychosocial therapy. Typical outcomes include increases in abstinence, expressed as the proportion of patients remaining abstinent or the length of time to the loss of abstinence (relapse), and reductions in the quantity or frequency of drinking, expressed as the number of drinking days or the number of drinks per drinking day. Although abstinence is the more stringent outcome and is preferred, reductions in consumption can nevertheless reduce alcohol-related morbidity. The drugs discussed below have been evaluated in double-blind, placebo-controlled clinical trials (Table 3).

Aversive Drugs

Alcohol metabolism is a two-stage process. Ethanol is converted to acetaldehyde by alcohol dehydrogenase, and acetaldehyde is then converted to acetate by aldehyde dehydrogenase (Fig. 1). For most people ingesting alcohol, acetaldehyde is metabolized rapidly and efficiently, so that it does not accumulate. When it does accumulate, it causes tachycardia, flushing, diaphoresis, dyspnea, nausea, and vomiting. Inhibition of aldehyde dehydrogenase by disulfiram, an irreversible inhibitor, or calcium carbimide, a shorter-acting, reversible inhibitor, causes the accumulation of sufficient acetaldehyde to cause symptoms. The possibility of having these unpleasant symptoms provides a deterrent to alcohol ingestion.

Although disulfiram has been reported to be an effective treatment for alcohol dependence in case

TABLE 3. DRUGS WITH SOME EVIDENCE OF EFFICACY IN PATIENTS WITH ALCOHOL DEPENDENCE.*

DRUG	CLASS	PROPOSED MECHANISM OF ACTION IN ALCOHOL DEPENDENCE	NEUROTRANSMITTER SYSTEM AFFECTED
Approved†			
Acamprosate	NMDA and GABA _A receptor modulator	Reduces unpleasant effects of alcohol abstinence, reduces craving	Glutamate, GABA
Calcium carbimide	Aversive agent	Increases aversive effects of alcohol by increasing acetaldehyde	Unknown
Disulfiram	Aversive agent	Increases aversive effects of alcohol by increasing acetaldehyde	Dopamine (?)
Naltrexone	Opioid antagonist	Reduces pleasurable, stimulating effects of alcohol, reduces craving	Opioid
Tiaprside	Dopamine antagonist	Reduces pleasurable, stimulating effects of alcohol, reduces anxiety	Dopamine
Experimental			
Bromocriptine	Dopamine agonist	Reduces unpleasant effects of abstinence	Dopamine
Bupirone	Anxiolytic	Reduces anxiety in anxious alcohol-dependent patients	Serotonin
Carbamazepine	Mood stabilizer, anti-convulsant	Reduces unpleasant effects of alcohol withdrawal and abstinence	Unknown
γ -Hydroxybutyric acid	Sedative	Reduces unpleasant effects of alcohol withdrawal and abstinence	GABA
Nalmefene	Opioid antagonist	Reduces pleasurable, stimulating effects of alcohol, reduces craving	Opioid
SSRIs	Antidepressant	Reduce depression and anxiety associated with alcohol dependence in depressed patients	Serotonin
Tricyclic antidepressants	Antidepressant	Reduce depression and anxiety associated with alcohol dependence in depressed patients	Serotonin, norepinephrine

*NMDA denotes *N*-methyl-D-aspartate, GABA γ -aminobutyric acid, and SSRIs selective serotonin-reuptake inhibitors.

†These drugs have been approved by regulatory agencies in the United States, Canada, or Europe for the treatment of alcohol dependence.

reports and open-label studies, placebo-controlled clinical trials have been inconclusive.^{23,24} In the most rigorous and best-controlled double-blind treatment study, in which 605 alcohol-dependent men were treated with 250 mg of disulfiram daily, 1 mg of disulfiram daily (a pharmacologically ineffective dose), or no drug for a year, there were no differences in rates of abstinence or the length of time to a first drink among the three groups.²⁵ Only men receiving 250 mg of disulfiram who ingested alcohol and became ill subsequently drank less alcohol than those in the other two groups. The authors concluded that disulfiram neither improves the rate of continuous abstinence nor delays the resumption of drinking, but that it may reduce drinking after relapse.

In spite of its lack of efficacy as compared with placebo, some physicians and patients believe that disulfiram is an effective psychological deterrent to drinking. The usual dose of disulfiram is 250 mg per day, although doses of 125 mg to 1000 mg are sometimes given, depending on side effects and response. Some patients take disulfiram only when they are at high risk for relapse; others take it con-

tinuously. Administration of disulfiram under direct observation reportedly increases its effectiveness.²⁶

Patients taking disulfiram must be aware of the danger of consuming alcohol in beverages, foods, over-the-counter medications, or mouthwashes. Disulfiram inhibits the metabolism of several medications, notably anticoagulant drugs, phenytoin, and isoniazid, thereby exaggerating their actions and toxic effects. It should be given cautiously to patients with liver disease and is contraindicated in pregnant women and patients with ischemic heart disease. Disulfiram can cause hepatitis, and liver-function tests should therefore be performed regularly during treatment.

Calcium carbimide (Temposil, Lederle, Markham, Ont., Canada), previously available in Canada and Australia, was withdrawn from the market by its manufacturer. It has not been studied as extensively as disulfiram. Like disulfiram, it also has been no more effective than placebo in clinical trials. In a four-month, randomized, double-blind, crossover study of calcium carbimide and placebo in 128 alcohol-dependent patients, those who completed the study

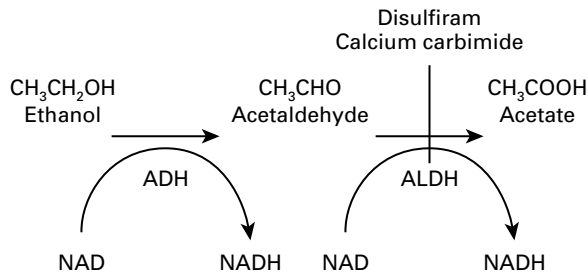


Figure 1. The Site of Action of Disulfiram and Calcium Carbimide in the Metabolism of Ethanol.

ADH denotes alcohol dehydrogenase, ALDH aldehyde dehydrogenase, NAD nicotinamide adenine dinucleotide, and NADH reduced NAD.

had lower alcohol consumption and increased rates of abstinence during both the placebo and calcium carbimide treatment periods.²⁷ The authors concluded that calcium carbimide acted as a psychological deterrent to drinking, because even while patients were receiving placebo, the possibility that they might be taking the active drug reduced alcohol ingestion. However, the lack of a group that received no medication makes these conclusions speculative. Calcium carbimide has few side effects, but it has been associated with leukocytosis and hypothyroidism.

Opioid Antagonists

The observation that μ -opioid (morphine-like) agonists increased alcohol consumption and that μ -opioid antagonists reduced alcohol consumption in animals^{28,29} led to clinical trials of naltrexone in patients with alcohol dependence. It has been proposed that naltrexone reduces drinking and increases abstinence by reducing the positively reinforcing, pleasurable effects of alcohol and by reducing the craving for alcohol. Naltrexone and other μ -opioid antagonists block the alcohol-induced release of dopamine in the nucleus accumbens.^{30,31} Social drinkers report less positive and more sedative and unpleasant effects of alcohol when taking naltrexone.³² Patients with alcoholism who drink during treatment with naltrexone report experiencing less alcohol "high" and are less likely to progress to heavy drinking.³³ Naltrexone also reduces the craving for alcohol in both alcoholic patients³⁴ and social drinkers.³⁵

Several double-blind, placebo-controlled trials have found that naltrexone is efficacious when combined with psychosocial treatments for alcohol dependence. In a 12-week, placebo-controlled, randomized clinical trial of 50 mg of naltrexone daily in 70 alcohol-dependent men receiving outpatient psychotherapy, the patients receiving naltrexone had significantly fewer drinking days than those given placebo (4 percent vs. 14 percent of study days), and fewer later re-

sumed heavy drinking, defined as consuming five or more drinks in a day (23 percent vs. 54 percent of the men).³⁶ In a double-blind study of 97 alcohol-dependent men and women given 50 mg of naltrexone or placebo per day and assigned either to therapy targeted to increasing individual coping skills and relapse prevention or to supportive therapy for 12 weeks, alcohol consumption was lower and the abstinence rate was higher among the naltrexone-treated patients.³⁷ Fewer than half the patients in the naltrexone group resumed heavy drinking, as compared with more than 80 percent of those in the placebo group. Naltrexone was most effective for patients who reported strong cravings at study entry.³⁸ An interaction between medication and psychotherapy was found, in that naltrexone increased abstinence among patients assigned to receive supportive psychotherapy but not among those assigned to psychotherapy designed primarily to increase coping skills. However, for patients taking naltrexone who drank, those who received coping-skills training were less likely to drink heavily than those who received supportive therapy.

Other studies of naltrexone found no evidence of efficacy. In a randomized trial, 108 patients with alcohol dependence and cocaine and opiate abuse received both psychosocial therapy and either placebo or 50 or 100 mg of naltrexone daily; naltrexone did not alter drinking.³⁹ Similarly, in a randomized, double-blind trial in the United Kingdom, there were no differences in drinking-related outcomes among 175 patients with alcoholism who were assigned to minimal psychosocial treatment and received either 50 mg of naltrexone per day or placebo for 12 weeks.⁴⁰ In a randomized, double-blind, placebo-controlled trial of 50 mg of naltrexone per day or placebo in 64 patients with combined alcohol and cocaine dependence, naltrexone was no more beneficial than placebo.⁴¹

There are several possible reasons for the positive effects of naltrexone on drinking outcomes found in some studies and the lack of effect in others. One of the negative studies of naltrexone⁴¹ was probably too small to detect differences between the drug and placebo groups for a drug with a moderate effect. In two of the negative studies,^{39,41} the patients abused multiple substances, which may have limited the efficacy of naltrexone. Another important variable is compliance with medication. In the negative study in the United Kingdom, naltrexone significantly decreased the total number of drinks consumed and the number of drinks per day, as compared with placebo, but only among patients who took at least 80 percent of the prescribed medication.⁴⁰ The importance of compliance is supported by a U.S. study comparing naltrexone with placebo in 97 patients with alcoholism who also received weekly counseling. Those who were more compliant with naltrex-

one therapy were significantly less likely to report episodes of heavy drinking than those assigned to placebo (14 percent vs. 52 percent) and had fewer drinking days (2.8 percent vs. 11 percent), whereas the results among the noncompliant patients did not differ from those in the placebo group.⁴²

For the first 90 days of abstinence, when the risk of relapse is greatest, the recommended dose of naltrexone is 50 mg once daily, but doses of 25 to 100 mg daily are sometimes used. The most common side effects are nausea (10 percent), headache (7 percent), anxiety (2 percent), and sedation (2 percent).⁴³ The ingestion of naltrexone results in insensitivity to opioid drugs for 72 hours; if an opiate analgesic drug is required in an emergency, administration of a higher dose of opiates can overcome this insensitivity, but respiratory monitoring is mandatory. Although doses of 300 mg of naltrexone daily have been associated with hepatotoxic effects, such effects are rare at daily doses of 50 mg.⁴⁴ Indeed, serum aminotransferase concentrations are often lower in patients given naltrexone than those given placebo, presumably because of their decreased alcohol ingestion.³⁸ Nevertheless, patients with liver disease should be given naltrexone cautiously, and their liver function should be monitored periodically throughout treatment.⁴⁵

Nalmefene, a μ - and κ -opioid antagonist, which is approved by the FDA for the reversal of opioid intoxication and overdose, is chemically similar to naltrexone but less hepatotoxic.⁴⁶ In a 12-week clinical study of 21 patients with alcohol dependence who were given daily doses of 10 mg of nalmefene, 40 mg of nalmefene, or placebo, the higher-dose nalmefene group was more abstinent than the other two groups.⁴⁷

Acamprosate

Acamprosate is thought to have agonist activity at γ -aminobutyric acid receptors⁴⁸ and inhibitory activity at *N*-methyl-D-aspartate receptors.^{49,50} Acamprosate normalizes the glutamatergic excitation that occurs in alcohol withdrawal and early abstinence.^{51,52} This effect may reduce craving and distress and may thus decrease the need to consume alcohol.⁵³

The observation that acamprosate reduced alcohol consumption in animals^{54,55} led to studies in humans with alcoholism. In all but one of several European multicenter clinical trials, approximately twice as many patients given acamprosate as patients given placebo remained abstinent from alcohol during treatment periods of three months to one year.⁵⁶⁻⁶²

Three studies are representative of the several studies of acamprosate. In a clinical study of 85 recently abstinent patients with alcoholism who were receiving psychosocial therapy and were treated with 2000 mg of acamprosate daily or placebo for 12 weeks, 60 percent of the patients receiving acamprosate remained abstinent, as compared with 22 percent of

those receiving placebo.⁵⁷ In a 48-week study of 272 alcohol-dependent patients, 43 percent of the acamprosate group remained abstinent, as compared with 21 percent of the placebo group.⁶⁰ The one negative study of acamprosate was a 24-week multicenter study of mildly alcohol-dependent patients in the United Kingdom, in which 20 percent of both the acamprosate and placebo groups remained abstinent⁶³; the lack of effectiveness of acamprosate could have been due to the mildness of the patients' alcohol dependence, however.

Acamprosate is not metabolized but is eliminated by renal excretion. It should therefore be given cautiously to patients with renal impairment. Its main side effects are diarrhea (10 percent) and headache (20 percent). The usual dose of acamprosate is 2 to 3 g per day in divided doses. Acamprosate is not yet available in the United States.

Dopaminergic Drugs

Given the theoretical importance of dopamine in the neurobiology of alcohol dependence, there is interest in dopaminergic drugs as treatments for alcohol dependence. In animals, dopamine agonists and antagonists both decrease the stimulant and positively reinforcing properties of alcohol and decrease alcohol consumption. Dopamine antagonists can block the reinforcing effects of alcohol⁶⁴; agonists may alleviate a dopamine-deficiency state.⁶⁵ Tiapride, a dopamine D2-antagonist drug marketed in Europe as an atypical neuroleptic and anxiolytic drug, reduces the symptoms of alcohol withdrawal and is approved for the treatment of acute and chronic alcoholism.⁶⁶ Its efficacy in patients with alcohol dependence has been evaluated in three clinical trials. In the largest, 100 recently abstinent alcohol-dependent patients were randomly assigned to receive 300 mg of tiapride per day or placebo for three months. Although only 54 percent of subjects complied with medication for at least one month, those who did and who received tiapride were more likely to remain abstinent and had lower rates of use of health care services.⁶⁷

The dopamine agonist bromocriptine, used in the treatment of Parkinson's disease, was initially reported to reduce drinking in patients with alcoholism.⁶⁸ However, a long-acting injectable bromocriptine preparation was no more effective than placebo in preventing relapses of drinking in 366 alcohol-dependent patients.⁶⁹

Other Drugs

Several other drugs have been tested in patients with alcohol dependence, usually after they have been observed to reduce alcohol consumption in animals. Although some have reduced alcohol consumption in humans, none have been approved for the treatment of alcohol dependence.

Mood Stabilizers

Lithium reduces alcohol consumption in animals and blocks alcohol intoxication in social drinkers.⁷⁰ In a double-blind, placebo-controlled study of 457 patients with alcoholism, lithium carbonate did not reduce drinking.⁷¹ A review concluded that lithium was ineffective in treating alcohol dependence.⁷²

The mood stabilizer and anticonvulsant drug carbamazepine has been used to treat alcohol withdrawal and has been reported to improve the treatment of alcohol dependence.⁷³ A randomized, double-blind study of 29 alcohol-dependent patients who received carbamazepine or placebo for 12 months beginning at detoxification found less drinking in those receiving carbamazepine.⁷⁴ However, the small number of patients makes the findings inconclusive.

Sedative Drugs

Although benzodiazepines and other drugs are often given to treat alcohol withdrawal, they are not given to treat alcohol dependence. Alcohol-dependent patients who receive maintenance doses of a sedative can become dependent on the sedative.⁷⁵ The γ -aminobutyric acid agonist γ -hydroxybutyric acid reduced alcohol consumption in a double-blind clinical trial conducted in Italy.⁷⁶ In this three-month outpatient study, 82 patients were randomly assigned to receive 50 mg of γ -hydroxybutyric acid per kilogram daily or placebo. Drinking was assessed on the basis of the patients' own reports and measurements of serum aminotransferase concentrations. At the end of treatment, 30.6 percent of the patients treated with γ -hydroxybutyric acid remained abstinent, as compared with 5.7 percent of the patients given placebo. Since γ -hydroxybutyric acid can be abused as a sedative, its use in maintenance therapy would be harmful in alcohol-dependent patients.

Serotonergic Drugs

Serotonin may modulate the behavioral effects of alcohol, although its effects are complex because of the presence of multiple subtypes of serotonin receptors.⁷⁷⁻⁸⁰ Selective serotonin-reuptake inhibitors, such as fluoxetine, sertraline, and citalopram, which are used clinically as antidepressant and anxiolytic drugs, increase serotonergic function and reduce alcohol consumption in animals. In trials in patients without depression who were heavy drinkers, selective serotonin-reuptake inhibitors reduced alcohol consumption by 15 to 20 percent.^{81,82} Patients who are taking one of these drugs report a decreased desire and liking for alcohol.⁸³ However, the results in patients with diagnosed alcohol dependence have been less impressive. In a three-week prospective study of fluoxetine, alcohol intake decreased only during the first week,⁸⁴ and in a double-blind study comparing fluoxetine treatment with placebo in 101 patients, in which both groups received cognitive-behavioral psy-

chotherapy, there was no difference in drinking between the groups.⁸⁵

Several serotonin-receptor agonists and antagonists that reduced alcohol consumption in animals were tested in alcohol-dependent patients. Buspirone (an anxiolytic drug that is a partial serotonin agonist at 1A and 2 receptors), ondansetron (an antagonist at serotonin-3 receptors), and ritanserin (an antagonist at serotonin-2 receptors) all reduced alcohol consumption in alcohol-drinking rats.⁸⁶⁻⁸⁸ However, placebo-controlled clinical trials of these drugs in patients with alcohol dependence have not demonstrated efficacy for any of them.⁸⁹⁻⁹¹

PATIENTS WITH PSYCHIATRIC DISORDERS

Alcohol dependence is associated with major depression, anxiety disorders, and schizophrenia.^{22,92,93} The relation of alcohol consumption to these illnesses is complex; it may precede the psychiatric illness or be precipitated by it. By reducing symptoms of the psychiatric illness, drug therapy may reduce the impetus for patients to medicate themselves with alcohol.²¹

In patients with both alcohol dependence and major depression, antidepressant drugs combined with psychosocial treatments improve depression and, to a lesser extent, alcohol dependence. In a double-blind, placebo-controlled trial of the tricyclic antidepressant drug desipramine in 71 recently abstinent patients with alcoholism, with or without secondary depression, desipramine improved depression.⁹⁴ Although there were no significant differences in the rate of abstinence between the treatment groups, the depressed patients who were treated with desipramine had fewer heavy-drinking days (8 percent, vs. 40 percent in the placebo group). In a double-blind, placebo-controlled trial of imipramine and weekly psychotherapy designed to prevent relapses in 69 patients with alcoholism and primary major depression or dysthymia, imipramine improved mood slightly but did not decrease drinking.⁹⁵ In a 12-week randomized, double-blind, placebo-controlled study of fluoxetine in 51 patients with major depression and alcohol dependence, fluoxetine improved depression and reduced the total number of drinks consumed during the trial by 50 percent, as compared with placebo.⁹⁶

Two studies examined the anxiolytic drug buspirone in the treatment of patients with anxiety and alcoholism, with different outcomes. In a 12-week study of 60 mg of buspirone or placebo daily in 61 patients with anxiety and alcoholism who were receiving behavioral therapy, those given buspirone remained in treatment longer and drank less than those receiving placebo (mean, 4 vs. 10 drinking days).⁹⁷ However, in a double-blind study of 67 patients with anxiety and alcoholism, buspirone was not more effective than placebo.⁹⁸

RECOMMENDATIONS

Drug therapy should be considered for all patients in whom alcohol dependence is diagnosed who do not have medical contraindications to the use of the drug and who are willing to take it. Of the several drugs studied for the treatment of alcohol dependence, the evidence of efficacy is strongest for naltrexone and acamprosate. Naltrexone is currently available in the United States; acamprosate and tiapride are currently available in Europe but not in the United States.

Although disulfiram is approved for treatment of alcohol dependence in the United States and calcium carbimide was approved in Canada, there is little evidence to support the use of these aversive drugs. Still, some patients and clinicians believe that aversive drugs provide an effective psychological deterrent to drinking.

Alcohol-dependent patients with psychiatric disorders, such as depression and anxiety disorders, should be treated with drugs that are effective for the psychiatric condition. The selection of a specific drug should depend on the patient's clinical state and the pharmacokinetics of the drug. For suicidal patients, selective serotonin-reuptake inhibitors are preferred over tricyclic antidepressant drugs because of their relative lack of toxicity. Because chronic, heavy alcohol use can induce higher concentrations of hepatic metabolic enzymes, higher-than-usual doses of antidepressant drugs may be required to achieve therapeutic plasma concentrations.⁹⁹

Although therapy with two or more drugs with different mechanisms of action, given together or in sequence, may yield additive or synergistic benefits in patients with alcohol dependence, there is no evidence that multiple-drug therapy improves the effectiveness of treatment. Drug therapy for alcohol-dependent patients should be combined with psychosocial therapy to provide emotional support, to address the psychological and social problems associated with alcohol dependence, and to increase compliance with drug therapy. Finally, clinicians and patients should recognize that alcohol dependence is tenacious. Current drug therapies do not eliminate alcohol dependence but, rather, help to reduce drinking and achieve longer periods of abstinence for some patients.

CONCLUSIONS

In patients with alcohol dependence, drug therapy can improve the outcomes of treatment and thereby reduce morbidity and mortality and improve the quality of life. Questions remain about the optimal drug dosage, the duration of treatment, concomitant psychosocial therapy, the cost effectiveness of drug therapy, and the types of patients who will benefit most from a specific drug.

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