

## ALCOHOLISM PHARMACOTHERAPY

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Alcoholism remains one of the most common and significant medical problems in the United States and internationally. For example, in the United States, over 4% of the general population is alcohol dependent and another 5 to 10 million people drink hazardously at least several times per month (1). The economic and medical costs of alcoholism and alcohol abuse continue to escalate. Most recent figures put the economic costs of alcohol-related expenses at \$176 billion annually in the United States (2). This includes the economic costs of increased health care expenses, lost productivity at work, and legal expenses. Similarly, although there have been some reductions in the number of motor vehicle deaths attributed to excessive alcohol drinking, the overall number of alcohol-related annual deaths is 105,000 in the United States (3).

Current psychosocial approaches to alcohol addiction are moderately effective, with perhaps as many as half the patients receiving treatment becoming abstinent or significantly reducing episodes of binge drinking (4). In the past two decades significant progress has been made in understanding the pharmacology of alcohol and why some people become dependent. This has led to the development of several medications that have been shown in research studies to improve treatment outcomes. This chapter reviews some of the possible neurobiological mechanisms involved in alcohol reward and dependence, and how medications can affect these systems to facilitate treatment. We introduce future directions for research such as the use of combinations of medications that may have additive or synergistic effects on improving treatment, and discuss the role of psychosocial support to facilitate the effectiveness of pharmacotherapy.

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### PHARMACOLOGIC TREATMENTS FOR ALCOHOL DETOXIFICATION

The first step in the pharmacologic treatment of alcoholism is to help patients safely detoxify from alcohol. Although historically, alcohol detoxification has occurred in inpatient setting, increasingly alcohol detoxification is being conducted in ambulatory settings. Except in the case of medical or psychiatric emergencies, outcome studies generally show that successful detoxification can safely and effectively be carried out in ambulatory setting using medications such as benzodiazepines (5,6). In addition, the use of anticonvulsants has received recent interest.

#### Benzodiazepines

Benzodiazepines are  $\gamma$ -aminobutyric acid (GABA) agonists that metaanalysis of placebo-controlled double-blind studies have consistently shown to be safe and effective (7). Benzodiazepines differ widely in their pharmacologic half-life, and this has been a factor in the choice of which benzodiazepines to use for detoxification. For example, one popular approach is to use a benzodiazepine with a long half-life such as chlordiazepoxide as a loading dose and let the benzodiazepine self-taper (8). The advantage of this technique is that the dose can be administered in the physician's office, which precludes problems with patient noncompliance. A second approach is to use shorter acting benzodiazepines and titrate the dose depending on symptoms. In a recent study, oxazepam was used as needed depending on the severity of withdrawal symptoms as assessed by the Clinical Institute Withdrawal Assessment for Alcohol-revised (CIWAA-R). As needed oxazepam resulted in effective alcohol withdrawal management with a lower total amount of oxazepam over a shorter duration compared to routine dosing (9).

#### Anticonvulsants

Several anticonvulsants have been used instead of benzodiazepines for alcohol withdrawal. Anticonvulsants have the

advantage of no abuse potential and a theoretical advantage of reducing kindling, a sensitization of withdrawal symptoms that occurs after multipisodes of alcohol withdrawal. In one randomized study comparing valproate, a GABAergic agent, with phenobarbital, both medications were effective in reducing withdrawal symptoms, and there were no reliable differences between mediations with the exception of less hostility in the phenobarbital group (10). Carbamazepine has also been used as an alternative to benzodiazepines to attenuate alcohol withdrawal symptoms (11). Although its mechanism of action remains unknown, research generally shows that carbamazepine is as effective as benzodiazepines. Disadvantages of carbamazepine include a rather narrow therapeutic window, the need to monitor serum levels, and hepatotoxic effects. For patients with a history of alcohol withdrawal seizures, however, anticonvulsants such as carbamazepine may be a useful alternative to benzodiazepines (12).

## PHARMACOLOGIC TREATMENTS TO REDUCE ALCOHOL RELAPSE

### Disulfiram

The aversive agent disulfiram has been available for the treatment of alcoholism since 1949. Disulfiram works by inhibiting the liver enzyme that catalyzes the oxidation of acetaldehyde, a toxic by-product of alcohol, resulting in an aversive reaction to alcohol consumption. In this way, disulfiram is thought to deter drinking by making the negative consequences of drinking more certain, immediate, and aversive than they would be otherwise. Provided that the patient takes the disulfiram, the decision about whether or not to drink is probably shifted toward abstinence when faced with opportunities to drink based on the knowledge of the disulfiram-ethanol interaction. In randomized controlled clinical trials, however, disulfiram has not been shown to be effective in the absence of supervision of ingestion, probably due to poor compliance (13). With supervision and positive contingencies for taking disulfiram, however, the effectiveness of disulfiram appears to be enhanced (14). As an alternative to behavioral methods for enhancing compliance, pharmacologic methods such as implants have been developed. However, these efforts have been unsuccessful perhaps because these implants have not yielded adequate disulfiram blood concentration required to produce a reaction to alcohol (15,16).

### Opioid Antagonists

#### Background

The role of the alcohol-induced activation of the endogenous opioid system in the reinforcing effects of alcohol has been well established in dozens of animal models of alcohol

drinking (17–33). These studies have consistently demonstrated that alcohol enhances the release of endogenous opioids, and alcohol preference is reduced when opioid receptors are blocked.

Alcohol increases the release of opioid peptides *in vivo*, particularly in rats and humans with a genetic predisposition for excessive alcohol drinking (34,35). For example, Giannoulakis and colleagues (34) have found that in humans peripheral levels of  $\beta$ -endorphin increase in family history–positive subjects following a moderate dose of alcohol, whereas there is no increase in  $\beta$ -endorphin for social drinkers without a family history of alcoholism. Moreover, Froehlich and colleagues (36) have also demonstrated that alcohol-induced  $\beta$ -endorphin responses both prior to and following alcohol administration are significantly heritable.

Genetic preference for alcohol drinking has been shown to be associated with differences in opioid receptors and opioid peptides (37,38). Nonpreferring (NP) rats exhibit differences in the densities of  $\mu$  opioid receptors in certain brain reward regions compared to alcohol-preferring rats. Transgenic mice lacking  $\beta$ -endorphin have been shown to exhibit decreased preference for alcohol compared with wild-type mice (39).

Nonspecific and specific opioid antagonists have been found to reduce alcohol self-administration in rodents and monkeys (19,22,25,31,40–43). Preclinical studies have also evaluated the efficacy of antagonists specific for the  $\mu$  and  $\delta$  opioid receptors in reducing alcohol drinking. The  $\mu$  opioid receptor antagonist  $\beta$ -funaltrexamine (B-FNA) and the  $\delta$  opioid receptor antagonists naltrindole (NTI) and naltriben (NTB) have all been shown to reduce alcohol drinking (17, 18,41). Recent evidence also suggests a role for the  $\delta$  opioid receptors in mediating the aversive effects of alcohol as indicated by an increase in conditioned taste aversion in alcohol preferring (P) rats in the presence of the  $\delta$  opioid receptor antagonist NTI (44).

Taken together, these preclinical studies in animals and humans support the model that alcohol drinking is reinforcing at least in part because of its effects on enhancing the release of endogenous opioids. The use of opioid antagonists as an effective agent in the treatment of alcoholism is strongly predicted by these preclinical studies.

### Pharmacokinetics, Pharmacodynamics, and Safety

Naltrexone, an opioid antagonist, was originally developed for use in the prevention of relapse in detoxified opiate addicts. Naltrexone has a half-life of approximately 4 hours, and 6- $\beta$ -naltrexol, its major metabolite, has a half-life of 12 hours. Rapidly absorbed, naltrexone reaches peak plasma levels between 60 and 90 minutes. Naltrexone undergoes first-pass hepatic metabolism, and there is some evidence of dose-related hepatotoxicity at doses four to five times higher than the currently recommended 50-mg daily dos-

age. In alcohol-dependent patients, adverse events reported by at least 2% of those participating in an open-label safety study were nausea (10%), headache (8%), dizziness (4%), nervousness (4%), fatigue (4%), insomnia (3%), vomiting (3%), anxiety (2%), and somnolence (2%) (45). In addition to these new-onset adverse events, naltrexone is contraindicated for patients who are currently opioid dependent, are in acute opioid withdrawal, or require opioid analgesics for management of pain, and those with acute hepatitis or liver failure. Special considerations are involved in the management of medical emergencies requiring pain management because naltrexone is an opioid antagonist. Although there has been little formal research on drug–drug interactions, with the exception of opiate-containing medications, subjects on naltrexone who were on concurrent treatment with antidepressant therapy did not experience any increase in adverse events relative to those not on antidepressant therapy in the aforementioned safety trial.

### Efficacy

Naltrexone is currently approved for use in the treatment of alcoholism in the United States, Canada, and many European and Asian countries. The efficacy of naltrexone has been tested in several double-blind placebo controlled trials (Table 101.1).

In general, these studies have been 12 weeks in duration, with one study (52) reporting on a 6-month follow-up pe-

riod. Samples have been composed primarily of male subjects (ranging from 71% to 100%) without other complicating psychiatric or substance abuse problems, although there have been smaller studies in specialized populations, including those who use cocaine and alcohol (53) and older alcoholics (50). The behavioral interventions provided in conjunction with naltrexone include day-hospital treatment, cognitive behavioral therapy, and supportive therapy. These studies have tested the efficacy of a 50-mg daily dose against placebo; although several studies in progress are evaluating the utility of higher doses (e.g., up to 100 mg daily). The majority of studies, which have found naltrexone to be superior to placebo in treatment outcomes, have initiated treatment in subjects following a period of abstinence ranging from 5 to 7 days (46–48,51). Other ongoing studies are testing whether an opioid antagonist can be effectively used in a treatment sample to help subjects reduce and possibly initiate a period of abstinence or effectively control binge drinking.

The most consistent finding in the studies of alcohol-dependent subjects is that naltrexone decreases the risk of drinking at hazardous levels and the percentage of drinking days. In three studies, this finding was observed in the overall sample (46,48,51), and an additional investigation found that naltrexone significantly reduced hazardous drinking in a secondary analysis of subjects who were good treatment compliers (47). In contrast, no evidence of efficacy was found in a recent randomized study (54) comparing pla-

**TABLE 101.1. DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF OPIOID ANTAGONISTS FOR THE TREATMENT OF ALCOHOL DEPENDENCE**

Published Study	No. of Subjects	Therapy	Medication Dose	Duration (Weeks)	Results			
					Craving	TTFD <sup>a</sup>	Relapse <sup>b</sup>	PDD <sup>c</sup>
Volpicelli et al., 1992 (48)	70	Intensive multimodal	Naltrexone 50 mg/day	12	+	0	+	+
Volpicelli et al., 1997 (47)	97	Relapse prevention	Naltrexone 50 mg/day	12	0	0	+	+
O'Malley et al., 1992 (48)	97	Coping skills or supportive	Naltrexone 50 mg/day	12	+/0	0	+	+
Mason et al., 1994 (49)	21	CBT	Nalmefene 40 mg/day	12	0	0	+	+
Mason et al., 1994 (49)	105	CBT	Nalmefene 20 or 80 mg/day	12	0	0	+	0
Oslin et al., 1997 (50)	44		Naltrexone 50 mg/day	12	NR	0	+/0	0
Anton et al., 1999 (51)	131	CBT	Naltrexone 50 mg/day	12	+/0	0	+	+

Plus sign means a significant difference in favor of the medication group.

Minus sign means a significant difference in favor of the placebo group.

A plus/minus sign is a trend in favor of the medication group or a significant difference in a subsample.

<sup>a</sup>Time to first drink or total abstinence.

<sup>b</sup>Relapse refers to time to first episode of hazardous drinking (survival analysis)

<sup>c</sup>Percent drinking days: cumulative days abstinent or percent days abstinent.

CBT, cognitive behavioral treatment; NR, result not reported.

Adapted from Garbutt et al., JAMA Vol. 281, 14:1318–1325.

cebo, naltrexone 50 mg daily, and nefazodone. In this investigation, naltrexone therapy was associated with a higher incidence of adverse effects, poorer medication compliance, and greater attrition than placebo, leading the authors to suggest that adverse events may limit the effectiveness of naltrexone.

Although the optimal duration of therapy with naltrexone is unknown, efficacy data are available for 12 weeks. A 6-month follow-up study (55) found that subjects who had originally been treated with naltrexone for 12 weeks were less likely to experience a day of heavy drinking during the follow-up period or to meet criteria for a diagnosis of alcohol dependence than subjects treated with placebo during that time period. However, there was evidence that the effects of naltrexone appeared to decline over time, raising the question of whether longer-term therapy may be needed. In this regard, initial evidence supporting the potential value of longer-term naltrexone therapy for some patients has been reported at scientific conferences.

Nalmefene, a newer opioid antagonist that is structurally similar to naltrexone, has also been reported to reduce the risk of relapse to heavy drinking. In a 3-month double-blind pilot study, there was initial evidence of reduced risk of heavy drinking among subjects treated with 40-mg doses of nalmefene compared to 10-mg or 0-mg doses (49). In a larger double-blind study (56) in which patients were randomized to placebo, 20 mg daily or 80 mg daily, lower relapse rates were observed for patients treated with nalmefene (combined across the 20-mg and 80-mg doses).

Since the initial published reports of naltrexone for use in alcoholism, several smaller studies have been conducted evaluating its potential in special populations of alcoholics. For example, the use of naltrexone in treating individuals with comorbid alcohol and cocaine use disorders have included one open-label study using 150 mg of naltrexone per day (57) that showed a positive effect for naltrexone, and one double-blind, placebo-controlled study using 50 mg of naltrexone per day in 64 subjects, which was negative (53). Pending additional research with larger samples at higher doses, naltrexone treatment does not appear indicated for the management of individuals with concurrent cocaine and alcohol use disorders. A small study in older alcohol-dependent men suggests that it may be efficacious (50), and in an open-label trial it was found to be helpful for adolescents (58).

The finding of reduced risk of relapse following a lapse has led to considerable interest and research into possible mechanisms underlying this effect. In the clinical trials, alcohol-dependent subjects retrospectively reported feeling less "high" (59) and lower levels of craving and incentive to continue drinking (60). Fixed alcohol dose administration studies in non-alcohol-dependent subjects suggest that naltrexone may attenuate some of the positive mood altering effects (e.g., stimulation), but not the aversive effects of alcohol (e.g., cognitive impairment, sedation) (61,62). High

rates of nausea have been noted in alcohol administration studies in non-alcohol-dependent subjects maintained on naltrexone, suggesting that naltrexone may make alcohol more aversive in some subjects, particularly at higher doses of alcohol and naltrexone (63). These fixed alcohol dose administration studies involve rapid consumption of large amounts of alcohol. Interestingly, nausea in interaction with alcohol has not been a common complaint in the clinical trials. This suggests that these alcohol-dependent individuals either may be less vulnerable to nausea or may limit their alcohol intake (both the rate of consumption and the amount consumed) to levels that do not cause nausea in interaction with naltrexone. Direct evidence that naltrexone treatment is associated with reduced speed of drinking and the number of drinks consumed has been obtained using ad libitum drinking paradigms (64). Evidence that naltrexone reduces craving or urge to drink is also accruing from this body of research (63,64).

### Summary

The evidence suggests that naltrexone 50 mg daily is efficacious in reducing the risk of heavy drinking and in increasing the percentage of days abstinent. Although the hypothesized effect of naltrexone on reduction of craving has been somewhat elusive in the clinical trials, laboratory studies provide support for this hypothesis. Additional studies are under way to test the optimal duration of therapy and the efficacy of alternative doses. Although the side-effect profile of naltrexone is acceptable, efforts to minimize adverse events should be investigated given that these events are associated with reduced compliance with therapy, and compliance has been linked to treatment outcome (65).

## Acamprosate

### Background

Ethanol has also been shown to alter levels of, and have high affinity for receptors of, two other neurotransmitters, glutamate and GABA. *In vitro* studies indicate that ethanol inhibits function of the glutamatergic *N*-methyl-D-aspartate (NMDA) receptor by inhibiting ion flux through this ionotropic receptor. Both *in vitro* and preclinical *in vivo* studies have also demonstrated that ethanol modulates NMDA-mediated release of other neurotransmitters such as acetylcholine, dopamine, and norepinephrine. Microinjections of glutamate antagonists into the nucleus accumbens of rats not dependent on alcohol has been shown to significantly decrease self-administration of alcohol. In preclinical studies, chronic alcohol administration results in an up-regulation of NMDA receptors, and NMDA antagonists given during withdrawal from alcohol have been shown to suppress withdrawal seizures. Clinical studies indicate that increased cerebrospinal fluid (CSF) levels of glutamate during

ethanol withdrawal may be associated with the development of seizures, and that repeated withdrawals increases the risk of seizures. Similarly, ethanol has also been shown to modulate the GABA system particularly GABA<sub>A</sub> receptor function. Chronic administration of ethanol results in decreases in the messenger RNA (mRNA) and protein for the  $\alpha$  subunit of the GABA<sub>A</sub> receptor. GABA levels are also found to be reduced in the brain and CSF of recently detoxified alcoholics. Moreover, drugs that modulate GABA<sub>A</sub> receptor function such as benzodiazepines, barbiturates, and anticonvulsants have been shown to suppress the symptoms of ethanol withdrawal. Given the above evidence, there has been increased interest in examining the effects of agents that alter glutamate and GABA function on alcohol drinking.

Acamprosate (calcium acetyl-homotaurine), a homotaurine derivative is a structural analogue of GABA and an upper homologue of taurine. It displays high binding capacity with GABA receptors, and it also shows functional activity in direct and indirect tests of GABA activity (66). Studies suggest it also inhibits NMDA receptors and reduces glutamate concentrations, particularly in the nucleus accumbens (67,68). A number of preclinical studies have shown that acamprosate produces dose-dependent decreases in alcohol consumption, with complete suppression of drinking seen at a dose of 400 mg/kg. It has also been shown that acamprosate diminishes reinstatement of alcohol drinking in the alcohol-dependent rat.

### **Pharmacodynamics, Pharmacokinetics, and Safety**

Acamprosate has low bioavailability (10%), is not metabolized by the liver, and is primarily excreted through the kidney, with an excretion half-life of 18 hours (69,70). Acamprosate has an excellent safety profile. The most common adverse effect distinguishing acamprosate from placebo is diarrhea; other reported side effects that may be associated with acamprosate are rash and changes in libido. Drug interaction studies indicate that acamprosate does not interact with a variety of medications prescribed to individuals with alcohol dependence (e.g., antidepressants, anxiolytics, disulfiram, hypnotics, or neuroleptics) (69).

### **Efficacy**

Acamprosate is approved for use as a treatment for alcohol dependence in most European countries and in many Latin American countries as well as in Australia, South Africa, and Hong Kong. The efficacy of acamprosate has been evaluated in over ten published placebo-controlled trials ranging from 3 to 12 months, with follow-up periods ranging from

0 to 12 months following the discontinuation of therapy (Table 101.2).

The treatment period generally began following completion of inpatient detoxification. With respect to dose, earlier studies typically adjusted the dose of acamprosate for body weight, whereas more recent studies have used a fixed dose of 1,998 mg/day, with two 333-mg tablets given three times per day (six tablets per day). The nature of the concurrent behavioral interventions was not specified and typically was that used by a particular site. The primary outcome measures included retention in treatment and measures of abstinence, such as rate of abstinence preceding study visits, continuous abstinence (i.e., completing the study without having a drink), or a measure of cumulative abstinence duration (e.g., total number of days abstinent or percentage of days abstinent during treatment the study). Information about the actual quantity of alcohol consumed on a nonabstinent day was rarely reported.

Summarizing across the studies in Table 101.2, the majority of studies find an advantage of acamprosate over placebo on measures of total abstinence, time to first drink, and/or cumulative abstinence duration (71–74,77–81). For example, in an early 12-week trial, Lhuentre et al. (71) found that abstinence rates for patients treated with acamprosate were nearly double (61%) that of patients treated with placebo (32%). Paille et al. (74) demonstrated that the effects of acamprosate on measures of abstinence were dose dependent. Specifically, point prevalence measures of abstinence at 6 months were 18.6% in the placebo group, 27.7% in the 1.3-g/day condition, and 34.7% in the 2-g/day condition. Similar dose effects were found on retention in treatment. In a study of 272 severely dependent alcoholics who had been abstinent 14 to 28 days prior to acamprosate treatment, 43% of the acamprosate-treated patients were continuously abstinent compared to 21% of those who received placebo over the course of 48 weeks (75). Although overall abstinence rates were lower in a different sample of severely dependent alcoholics with only 5 days of abstinence pretreatment (76), differences in abstinence rates were found favoring acamprosate over placebo during the 360-day treatment period. The advantage of acamprosate over placebo continued once acamprosate was discontinued after 6 and 12 months of active treatment.

At this time, there is no information available about the optimal duration of treatment with acamprosate. Although the duration of treatment has varied across studies (e.g., 3 to 12 months), there are no studies that have examined the effect of treatment periods of different lengths or the value of continued acamprosate in treatment responders. Given that differences between acamprosate and placebo appear to emerge after 2 to 3 months of treatment and generally persist after treatment is discontinued, studies addressing the potential value of short- versus long-term treatment are warranted to guide clinical practice.

Whether results comparable to those obtained in Euro-

**TABLE 101.2. DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF ACAMPROSATE FOR THE TREATMENT OF ALCOHOL DEPENDENCE**

Published Study	No. of Subjects	Duration (Weeks)	Results			
			Craving	TTFD <sup>a</sup>	Relapse <sup>b</sup>	PDD <sup>c</sup>
Lhuintre et al., 1990 (71)	569	12	NR <sup>d</sup>	NR <sup>d</sup>	NR <sup>d</sup>	NR <sup>d</sup>
Pelc et al., 1992 (72)	102	24	0	+	NR	+
Ladewig et al., 1993 (73)	61	24	NR	0/+	NR	+
Paille et al., 1995 (74)	538	52	0/+	+	NR	+
Sass et al., 1996 (75)	272	48	NR	+	NR	+
Whitworth et al., 1996 (76)	448	52	NR	+	NR	+
Roussaux et al., 1996 (77)	127	52	0	0	NR	NR
Geerlings et al., 1997 (78)	262	24	NR	+	NR	+
Barrias et al., 1997 (79)	302	52	NR	+	NR	+
Pelc et al., 1997 (80)	188	12	+	+	NR	+
Poldrugo, 1997 (81)	246	26	0	+	NR	+

Plus sign means a significant difference in favor of the medication group.

Minus sign means a significant difference in favor of the placebo group.

A plus/minus sign is a trend in favor of the medication group or a significant difference in a subsample.

<sup>a</sup>Time to first drink or total abstinence.

<sup>b</sup>Relapse refers to time to first episode of hazardous drinking (survival analysis).

<sup>c</sup>Percent drinking days: cumulative days abstinent or percent days abstinent.

<sup>d</sup>The primary outcome for this study was gamma-glutamyl transpeptidase (GGT) and was significantly lower in acamprosate compared to placebo.

NR, result not reported.

Adapted from Garbutt et al., *JAMA* Vol. 281, 14:1318–1325.

pean studies will be obtained in the United States is of great interest. A 21-site, 6-month, double-blind, placebo-controlled trial has recently been conducted to determine safety and efficacy of acamprosate in 601 U.S. alcohol-dependent patients (82). This study tested the efficacy of a 2-g daily dose against placebo and includes an exploratory 3-g dose, given the absence of rate-limiting side effects. In contrast to European studies in which patients were randomized into study treatments following inpatient detoxification, the U.S. study allowed for randomization at as early as 2 days of abstinence. The results of this study are not published as of this time.

### Summary

The evidence suggests that acamprosate can have a positive effect on measures of abstinence from alcohol following inpatient detoxification. These effects appear to be dose dependent, favoring the higher doses of acamprosate that have been tested. Although it is hypothesized that the efficacy of

the acamprosate is due to its effects on conditioned withdrawal and withdrawal-related craving (83–85), ratings on analogue scales of craving have not distinguished acamprosate and placebo-treated patients in the clinical trials to date. In addition, the potential effect of acamprosate on alcohol reward and drinking following a lapse in abstinence is not understood at this time, because the majority of studies collected information on abstinence only, and there are no laboratory studies examining the interactions of acamprosate and alcohol. The results of the U.S. trial, however, may provide additional information because daily reports of drinking quantity were obtained.

### Serotonergic Medications

#### Background

The use of medications that affect the serotonin (5-HT) system was initially anticipated by clinical observations regarding similarities between alcoholism and mood, anxiety, impulse control, and antisocial personality disorders. Given

the presumed relationship between these various disorders and a dysfunction in the serotonin system, this clinical observation led to speculation that alcohol dependence was also related to some serotonin dysfunction. Several lines of preclinical research in animals and social drinkers support the notion that alcohol drinking compensates for some deficiency in serotonergic activity. Most of these have consistently shown certain precursors to reducing alcohol drinking. More specifically, studies conducted in animals selectively bred for high alcohol drinking (HAD) or low alcohol drinking (LAD) behavior indicate that tissue content of serotonin and its metabolite 5-hydroxyindoleacetic acid are substantially lower in certain brain regions of the alcohol-preferring (P) animals compared with NP and in the HAD compared with the LAD rats (86). Smith and Weiss (87) have recently shown that ethanol-naive P rats have higher basal levels 5-HT release compared with NP rats, whereas chronic alcohol treated P rats had decreased extracellular levels of 5-HT in comparison to NP rats. However, although acute administration of alcohol results in increased levels of serotonin in the brain and periphery of alcohol-naive animals, this release is not altered by a genetic predisposition toward high alcohol drinking (88).

The evidence on densities of serotonin receptors in rats with a genetic predisposition to alcohol drinking is controversial. Alcohol-preferring (P) rats have higher 5-HT<sub>1A</sub> binding and lower 5-HT<sub>1B</sub> and 5-HT<sub>2</sub> binding in several brain regions when compared with NP rats (89). In contrast, the replicate HAD and LAD lines do not display the same differences in receptor densities, and in the alcohol-drinking fawn-hooded rats the densities of 5-HT<sub>1A</sub> receptors were lower and those of the 5-HT<sub>2</sub> receptors higher compared to that of LAD Wistar rats (see ref. 90 for review). Preclinical studies indicate that 5-HT<sub>1A</sub> agonists and serotonin reuptake inhibitors reduce ethanol intake in P and HAD rats as well as in unselected rat lines (86,91). In contrast, the role of the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor systems in alcohol drinking behavior is controversial (see ref. 90 for review). Although some studies indicate that ethanol drinking is reduced by both 5-HT<sub>2</sub> receptor agonists and antagonists, other investigators report no effects with antagonists of 5-HT<sub>2</sub> receptors. Similarly, the role of the 5-HT<sub>3</sub> receptor system in mediating ethanol drinking is also controversial, with reductions in drinking seen in paradigms using continuous access to alcohol, but little efficacy being observed in paradigms using limited access to alcohol. In contrast, studies using serotonin uptake inhibitors such as fluoxetine reported robust decreases in alcohol drinking in the P rats (86,92).

### **Pharmacodynamics, Pharmacokinetics, and Safety**

There are currently five Food and Drug Administration (FDA) approved selective serotonin reuptake inhibitors

(SSRIs) available today: fluoxetine (Prozac), fluvoxamine (Luvox), paroxetine (Paxil), sertraline (Zoloft), and citalopram (Celexa). SSRIs have in common the ability to block the reuptake of serotonin, and this functionally enhances serotonergic activity. Fluoxetine is characterized by a long plasma half-life with a range of 1 to 4 days and its active metabolite norfluoxetine has a half-life of up to 2 weeks. In contrast, the half-life of the other SSRIs varies between 21 hours for paroxetine and 36 hours for citalopram (93). The long half-life for fluoxetine offers some pharmacokinetic advantage for patients who are less compliant with taking their medications, and fluoxetine has less of a discontinuation syndrome compared to the shorter duration SSRIs paroxetine and sertraline (94). SSRIs are inhibitors of cytochrome P-450 isoenzymes, with paroxetine an especially strong inhibitor of the P-450-2D6 isoenzyme, whereas fluvoxamine is an especially potent inhibitor of P-450-1A2. Thus there are important drug-drug interactions when SSRIs are combined with medications that are metabolized by the P-450 system. Despite their common mechanism of action, there are important pharmacokinetic and pharmacodynamic differences. Despite their name, SSRIs are not completely selective in affecting just serotonin reuptake. For example, sertraline and to a lesser extent fluoxetine are relatively potent dopamine reuptake inhibitors, and the various SSRIs can also block the reuptake of norepinephrine (95). In addition, the SSRIs also antagonize muscarinic and histaminic receptors leading to anticholinergic and sedative side effects. Of the most disturbing side effects to SSRIs, initial nausea and sexual dysfunction are the most common.

### **Efficacy**

None of the SSRIs is currently approved for the treatment of alcoholism. The results of several placebo-controlled double-blind studies using SSRIs for the treatment of alcohol dependence have led to conflicting results. In an Italian study with 81 subjects randomized to placebo, fluvoxamine, or citalopram, both of the SSRI groups showed a higher incidence of continuous abstinence compared to the placebo group (96). Similarly, in a Finnish study of 62 randomized subjects, citalopram was more effective than placebo in alcohol drinking outcomes (97). These studies are not consistent with two American trials. For example, in a 12-week trial using fluoxetine in a general sample of alcohol-dependent subjects, there were no overall differences between the medication and placebo groups (98). At doses of up to 60 mg per day in a group of 101 subjects who also received weekly sessions of relapse prevention therapy, fluoxetine did not reduce any measure of alcohol drinking.

Although the overall results of SSRIs for alcoholism treatment are generally negative, there may be subtypes of patients who benefit from treatment with SSRIs and other serotonergic medications (Table 101.3). For example, in a study of 51 alcoholics with severe comorbid major depres-

**TABLE 101.3. DOUBLE-BLIND, PLACEBO-CONTROLLED TRIALS OF SEROTONINERGIC AGENTS FOR THE TREATMENT OF ALCOHOL DEPENDENCE**

Study	No. of Subjects	Alcohol/Subtype	Medication	Duration (Weeks)	Results			
					Craving	TTFD <sup>a</sup>	Relapse <sup>b</sup>	PDD <sup>c</sup>
Janiri et al., 1996 (101)	50	AD	Fluoxetine	8	NR	NR	NR	+
Tiihonen et al., 1996 (97)	62	AD	Citalopram	12	NR	NR	NR	NR
Cornelius et al., 1997 (99)	51	MD/AD	Fluoxetine	12	NR	NR	NR	+
Kranzler et al., 1996 (102)	60	AD/type A	Fluoxetine	14	NR	NR	0	0
	35	AD/type B			NR	NR	0	-
Pettinatti et al., 2000 (103)	55	AD/type A	Sertraline	14	NR	NR	0	+
	45	AD/type B			NR	NR	0	0
Malec et al., 1996 (104)	57	AD	Buspirone	12	0	NR	NR	0
Fawcett et al., 2000 (105)	156	AD	Buspirone	24	NR	0	NR	0
Malcolm et al., 1992 (106)	67	GAD/AD	Buspirone	24	NR	0	0	0
Tollefson et al., 1992 (107)	51	GAD/AD	Buspirone		+0	NR	NR	NR
Kranzler, 1994 (108)	61	GAD/AD	Buspirone	12	NR	NR	+	+
Wiesbeck, 1999 (109)	493	AD	Ritanserin	24	0	0	0	0
Sellers et al., 1994 (110)	71	AD (mild)	Ondansetron	6	NR	NR	NR	+0
Johnson et al., 2000 (111)	161	AD/early onset	Ondansetron	11	NR	NR	NR	+
	160	AD/late onset			NR	NR	NR	0

Plus sign means a significant difference in favor of the medication group.

Minus sign means a significant difference in favor of the placebo group.

A plus/minus sign is a trend in favor of the medication group or a significant difference in a subsample.

<sup>a</sup>Time to first drink or total abstinence.

<sup>b</sup>Relapse refers to time to first episode of hazardous drinking (survival analysis).

<sup>c</sup>Percent drinking days: cumulative days abstinent or percent days abstinent.

AD, alcohol dependence; GAD, generalized anxiety disorder; MD, mood disorder; NR, result not reported.

Adapted from Garbutt et al., *JAMA* Vol. 281, 14:1318–1325.

sion, subjects randomized to fluoxetine experienced less depression and less alcohol drinking than placebo-treated subjects (99). At 1-year follow-up the results for both depression and alcohol continued to favor the fluoxetine group (100).

Given that there may be important subgroups of alcoholics who self-medicate with alcohol, Kranzler and colleagues (102) subsequently reanalyzed their data after using a *k*-cluster technique to identify type A and type B alcoholics. Type B alcoholics are thought to reflect some underlying serotonergic dysfunction because they tend to be more impulsive, have more emotional distress, and have increased severity of alcohol dependence. Contrary to the prior predictions, type B alcoholics drank more when given fluoxetine compared to placebo subjects (102). There were no medication differences in type A alcoholics. Similarly, Pettinatti and colleagues (103) found that in a 14-week placebo-controlled trial of sertraline (200 mg per day), there was no main effect of sertraline on any alcohol drinking measure, but a significant alcoholic subtype by medication interaction. Subjects with presumed serotonergic dysfunctions

(type B) treated with sertraline tended to drink more than placebo-treated subjects, whereas the less severe type A subgroup of alcoholics showed a favorable response to sertraline in several drinking measures.

### Other Serotonergic Medications (Buspirone, Ritanserin, Ondansetron)

There are a variety of other medications that affect the serotonin system but work through different mechanisms than the reuptake inhibitors. The results are mixed and suggest that these medications may be effective only for certain subtypes of alcoholics.

#### *Buspirone*

The results of buspirone, a serotonin 1A partial agonist, on alcohol drinking are mixed and may depend on the subgroup of alcoholics studied (104–108). As Table 101.3 shows, in a general sample of alcoholics buspirone shows little evidence of clinical efficacy. In anxious alcoholics,

however, studies consistently show that buspirone reduces anxiety in subjects and may reduce alcohol drinking and, in one study, days in which alcohol was craved (107).

### Ritanserin

In a large multicentered placebo-controlled trial, 493 subjects were randomized to receive placebo or one of three doses of ritanserin, a 5-HT<sub>2</sub> receptor antagonist, with a treatment duration of 6 months. The results of the study showed no differences between the placebo group and any of the three medication groups (109).

### Ondansetron

More encouraging are the results of the 5-HT<sub>3</sub> antagonist ondansetron. A 6-week placebo-controlled study of 71 patients, found that 0.5 mg/d but not 4 mg/d of ondansetron reduced alcohol intake, although this effect was at the level of a trend ( $p = .06$ ) (110). Johnson and colleagues (111) found that among early-onset alcoholics (onset prior to age 25), 4 µg/kg reduced the intensity of drinking compared to placebo. Among subjects receiving ondansetron, the percent of days abstinent was about 70% compared to 50% for those subjects treated with placebo (111). There were no differences between the medication and placebo groups for late-onset alcoholics.

### Summary

Although there are suggestions that serotonergic mechanisms are involved in excessive drinking, the results of using serotonergic medications for alcoholism treatment are inconsistent. An understanding of which patients may be helped by which serotonergic medications is complicated by the heterogeneous nature of alcohol-dependent patients and the subtle pharmacokinetic and pharmacodynamic differences among serotonergic medications. The finding that some subtypes of alcoholics may do worse while taking serotonergic medications is of considerable clinical interest, because many alcoholic-dependent patients may be taking a serotonergic medication to treat a comorbid psychopathology. Given the widespread use of SSRIs and other serotonergic medications, it is likely that there are more alcoholics patients taking serotonergic medications than those taking all the medications specifically approved for the treatment of alcohol dependence combined. Rather than improve their drinking status, use of these medications may be interfering with alcohol recovery in some patients.

### Tricyclic Antidepressants (TCAs)

The tricyclic antidepressants (e.g., imipramine, desipramine, amitriptyline) represent a rather large class of medications that have been used for several decades to successfully treat

mood and anxiety disorders. This class of medications, like the SSRIs, blocks the reuptake of serotonin but are far less specific in their actions. They also block the reuptake of norepinephrine and dopamine, and antagonize muscarinic and histaminic receptors to varying degrees. The effect of TCAs on antagonizing muscarinic receptors and histaminic receptors give TCAs substantial anticholinergic and sedative effects. These anticholinergic effects include dry mouth, constipation, and tachycardia. The antihistamine effects include drowsiness and sedation. The TCAs are metabolized in the liver by the cytochrome P-450-2D6. Thus TCAs can interact with medications that are also metabolized by the P-450 system. Of note, alcohol can induce liver enzyme activity and reduce plasma TCA levels.

### Efficacy

Studies using TCAs for the treatment of comorbid depression and alcohol dependence have generally shown that TCAs effectively reduce symptoms of depression but have little effect of alcohol drinking. For example, Mason and colleagues (112) tested the effectiveness of desipramine in a double-blind, placebo-controlled trial of 71 alcohol-dependent subjects with (28 subjects) or without (41 subjects) concurrent symptoms of depression (112). Overall, desipramine did not reduce alcohol drinking, but it was effective in reducing depression scores in those subjects with coexisting depression. Similarly, McGrath et al. (113) studied a group of 69 subjects with a history of depression that either predated or occurred independently of alcohol abuse. In this double-blind, placebo-controlled study, imipramine combined with relapse prevention therapy was effective in improving depression but had little effect on alcohol drinking. Among subjects who showed a good clinical response on depressive symptoms, there was evidence that imipramine was associated with greater reductions in alcohol drinking compared to placebo. In summary, the results of these small-scale studies provide suggestive evidence that there is a subgroup of patients with coexisting depression who may benefit from TCAs.

### Lithium

The use of lithium for the treatment of alcoholism was suggested on the basis of clinical observations that many patients with mood disorders, particularly bipolar disorder, report alcohol use as a way to control mood instability. Early small-scale trials of lithium in the treatment of alcoholics were encouraging (114). For example, there were some data that among patients who received therapeutic levels of lithium, there were improved treatment outcomes (115). However, in a large multicenter placebo-controlled trial with 457 male alcoholics involving both depressed and nondepressed alcoholics, there were no significant improvements in alcohol drinking outcomes overall or in the depressed subgroup

(116). Similarly, in a recent double-blind, placebo-controlled study there were no significant reductions in alcohol drinking for a general population of alcoholics (105). Based on these larger, well-designed studies, the use of lithium to treat alcoholism does not receive empirical support. Its use in controlling bipolar symptoms may still be important for those with coexisting bipolar disorder and alcoholism.

### Combination Therapy

Research on rational combinations of medications to treat alcoholism is an area that is rapidly developing. Given that the acute and chronic effects of alcohol involve a number of neurotransmitter systems, a therapeutic approach targeting more than one system may be more effective than monotherapy. In addition, medications may be combined to target distinct aspects of the process of relapse (craving, abstinence, and/or relapse following an initial lapse in abstinence) in order to help a larger number of individuals with alcohol dependence. Finally, combination therapy with efficacious agents may permit the use of lower doses of one or both medications, thereby potentially improving tolerability and compliance with treatment and maximizing treatment outcome.

A number of preclinical studies using rodent models have examined the effect of combining naltrexone and other agents thought to alter alcohol intake, including fluoxetine (117–119), a thyrotropin-releasing hormone analogue TA-0910 (120), the calcium channel blocker isradipine (121), the 5-HT<sub>3</sub> antagonist ondansetron (122), and the 5-HT<sub>1A</sub> antagonist WA-100635 (123). The majority, but not all (121), of these studies have found at least an additive effect of combining naltrexone with these agents. Whether or not similar effects will be obtained in human subjects is under investigation for the combination of naltrexone and ondansetron (124) and the SSRI sertraline, with very small preliminary reports suggesting some optimism for continuing to investigate these approaches to combination therapy (124,125).

The possibility that disulfiram can be used to augment the efficacy of acamprosate has been evaluated in secondary analyses of a double-blind, placebo-controlled study (126). In this study, 118 Swedish subjects were randomized to either acamprosate or placebo, and disulfiram use was permitted on a voluntary basis. Comparisons of subjects who took disulfiram in combination with either acamprosate ( $n = 24$ ) or placebo ( $n = 22$ ) and those who received acamprosate or placebo only indicated that combined use of acamprosate and disulfiram was associated with the highest number of continuous abstinent days compared to the other three groups. These findings are of interest; however, they must be interpreted cautiously because subjects taking disulfiram were self-selected, differed from those who did not use disulfiram on a number of measures, and had much

more frequent contact with the treatment program due to the fact that disulfiram administration was supervised.

There is considerable interest in the potential effect of combining acamprosate and naltrexone for the treatment of alcohol dependence. These agents target different neurobiological systems altered by alcohol drinking and dependence, and have been found to influence different aspects of the relapse process. Acamprosate has been shown to have its primary effect on measures of abstinence, whereas naltrexone is most noteworthy for its effect of reducing the risk of relapse following a lapse in abstinence. Finally, these two medications are eliminated through different pathways (hepatic metabolism for naltrexone and excretion for acamprosate). Preliminary data supporting the safety of this combination derived from laboratory studies of normal volunteers (56) and alcohol-dependent subjects (124). A large-scale multisite evaluation of the efficacy of these two medications alone and in combination when provided with behavioral interventions of different intensities is planned (127).

## PHARMACOLOGY AND INTERACTION WITH BEHAVIORAL INTERVENTIONS

### Psychosocial Treatment Approaches

Medications for the treatment of alcoholism are generally given in the context of psychosocial treatment. There are a variety of psychosocial approaches to alcoholism treatment and little evidence that one type of treatment is superior to others. Project MATCH (Matching Alcoholism Treatments to Client Heterogeneity) provides the clearest presentation of our state-of-the-art psychosocial treatments (4). In this large multicentered study, over 1,700 subjects were randomly assigned to motivational enhancement treatment (MET), cognitive behavioral treatment (CBT), or twelve-step facilitation (TSF). The results clearly demonstrate that subjects presenting for treatment and receiving some type of psychosocial intervention general reduce their alcohol consumption. For example, alcohol was consumed on about 75% of the days prior to starting treatment and then with treatment was consumed on less than 25% of days. These were few differences between the three psychosocial conditions and limited evidence that one type of treatment was better for a particular type of patient (4).

Inspection of the various double-blind studies on the effectiveness of medications to reduce alcohol drinking generally shows that the psychosocial interventions alone have a dramatic effect in reducing alcohol drinking. For example, as shown in the project MATCH data, it is common for baseline drinking to occur on the average of 60% to 75% of days prior to starting the study and for placebo subjects to reduce drinking to less the 20% of the days (46–48, 51). The additional benefit of pharmacotherapy is thus an

adjunct to the considerable benefit of participating in a clinical trial that includes a psychosocial intervention.

### Special Issues in the Use of Psychopharmacology in the Treatment of Alcoholism

Despite the convincing clinical treatment research results, the clinical use of medications for the treatment of alcoholism lags behind the pharmacotherapy of other psychiatric disorders. With the exception of medications that treat alcohol withdrawal symptoms, the medications presented here do not provide any immediate relief of symptoms. The long-term beneficial effects have been shown in terms of reductions in slips from abstinence or relapses to heavy drinking, but to the individual patient these outcomes are difficult to attribute to the use of a medication. A successful outcome for the medication is the absence of some adverse clinical event that may or may not happen in the future. In contrast, medications used to treat other psychiatric disorders do provide relief of emotional distress even if the relief is delayed by several weeks, as is the case for antidepressants in the treatment of mood disorders. In general, there are no obvious rewarding properties of taking a medication to treat alcoholism. Coupled with the fact that the immediate effect of drinking alcohol is to feel good or reduce some unpleasant feeling, it makes it a challenge to help patients become and remain compliant with taking their prescribed medication.

Given the lack of easily experienced positive effects from taking medications for alcoholism, it is not surprising that medication compliance is an important factor in the efficacy of medications. For example, in a 12-week, double-blind, placebo-controlled trial using naltrexone in conjunction with addiction counseling, with a total sample of 98 randomized subjects, naltrexone had a modest effect in reducing alcohol relapse rates. However, among subjects who took at least 80% of their prescribed medication, the relative effectiveness of naltrexone was much improved, as 52% of placebo subjects relapsed compared to 14% of the naltrexone subjects (47).

### Compliance-Enhancement Techniques

To enhance motivation to remain in treatment and comply with taking medication, several behavioral interventions have been implemented. For example, the BRENDA approach, developed at the University of Pennsylvania (128), incorporates various behavioral strategies such as giving people feedback, developing an empathic therapeutic relation, working collaboratively with the patient to develop treatment goals, and continuing to assess treatment adherence.

A comparison of compliance rates of patients treated with the BRENDA approach to historical compliance rates at the Treatment Research Center at the University of Pennsylvania (103) suggests that BRENDA can enhance treat-

ment and medication compliance. A randomized controlled study is currently under way to directly compare the BRENDA approach to cognitive behavioral therapy and simple physician medication management.

### Integration of Behavioral and Pharmacotherapies

In a sense all pharmacotherapy studies are combined behavioral and pharmacotherapy studies. The effectiveness of medication is superimposed in a context of behavioral treatment. Thus, all the studies reported here reflect the additional benefits of an active medication group superimposed on the benefit of a behavioral treatment. The behavioral treatment intervention of subjects presenting for treatment has rather large effects as reflected on the improvement seen in the placebo groups in pharmacotherapy trials.

It remains to be determined how the behavioral interventions interact with pharmacotherapy, but there is a potential for additive or even synergistic effects of combining behavioral and pharmacologic treatments. Just as different medications may address different biochemical mechanism to improve treatment outcome, the integration of medications with psychosocial interventions can address different aspects of recovery. As discussed above, behavioral strategies can enhance medication compliance and treatment retention, thus giving the medication a better chance to be effective. Similarly, pharmacotherapy can reduce the chance of relapse to clinically significant drinking and increase the chance the patient will stay in treatment sufficiently to learn new behavioral coping skills. For example, a medication such as naltrexone can act immediately to reduce the severity of a slip and a return to hazardous drinking. When combined with cognitive and behavioral strategies to cope with triggers for relapse, the synergistic effects of the combined approach can be seen when the naltrexone is stopped, as the patient can now rely on learned skills to avoid and cope with a lapse.

### CONCLUSION

The past two decades have shown dramatic changes in the understanding of the pharmacology of alcohol. From understanding alcohol's nonspecific effects on membranes to alcohol's specific effects on neurotransmitter systems and second messengers, dramatic advances in the field have led to newer more effective treatments. Recent understanding of the pharmacology of alcohol has led to the development of new medications that improve treatment outcome and help show why some people are vulnerable to becoming addicted to alcohol. Of the new medications, the opiate antagonist naltrexone and acamprosate offer the most immediate promise. For specific populations, serotonergic medications, tricyclic antidepressants, and mood stabilizers offer

hope for treatment. The use of these medications alone or in combinations remains fertile avenues for research. Finally, special challenges are involved with the clinical use of medications for alcoholism treatment. Psychosocial treatments designed to improve motivation to remain in treatment and adhere to the medication regimen are important adjuncts to pharmacologic treatment. The use of the compliance-enhancing techniques can be safely and effectively integrated into primary care models, thus bring addiction treatment to a wide range of health care providers. Ultimately, the intensity and/or nature of the behavioral intervention may interact with the effects of medication to determine the ultimate outcome of treatment. Given dramatic reductions in the availability of intensive treatment, such as inpatient rehabilitation, and the fact that few individuals seek specialized alcoholism treatment, the availability of effective pharmacotherapies should extend the range of patients who can be successfully managed with less intensive behavioral interventions and increase the probability that individuals with alcohol dependence are identified in primary care settings and offered treatment.

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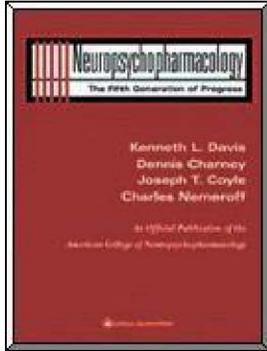
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