

Emerging Pharmacologic Treatments for Alcohol Dependence

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Increased understanding of the neurobiology of alcohol dependence has led to studies of pharmacologic agents that modify drinking behavior. Because alcoholism is a heterogeneous disease involving multiple neurotransmitter and receptor systems, it is likely that a variety of pharmacologic agents will be required to have the greatest impact on outcomes across individuals. Several medications have been approved for the management of alcohol dependence. In addition, several drugs currently used for other indications have been studied for use in alcohol dependence, and some of these drugs show promise. For example, selective serotonin reuptake inhibitors have been shown to reduce drinking in subgroups of alcoholic patients, including those with comorbid depression and those with later-onset alcohol dependence. Ondansetron, a selective 5-hydroxytryptamine₃ receptor antagonist, may attenuate the urge to drink and thus increase abstinence. The anticonvulsant agent topiramate also has significantly reduced drinking behavior in early clinical studies. Baclofen, a γ -aminobutyric acid B agonist, has been shown to decrease drinking in animal models and in 1 small, placebo-controlled trial in humans. Rimonabant, a cannabinoid CB₁ receptor antagonist, has been shown to help nicotine dependence in humans, and in animal studies, to reduce alcohol consumption; no clinical trials in alcoholism have been published. Dopamine antagonists, including clozapine and the newer atypical antipsychotics, may have value in the treatment of alcoholism but require further study. Corticotropin-releasing factor 1 receptor antagonists and neuropeptide Y₁ receptor antagonists have been shown to reduce drinking behavior in animals but have not undergone clinical trials.

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Alcohol has complex behavioral effects that can be pleasant or unpleasant, stimulating or sedating. Advances in understanding of the neurobiology of addiction have led to efforts to test a variety of pharmacologic agents that target different brain neurotransmitters and their receptors (Table 1). Because of the heterogeneous nature of alcoholism, it is likely that targeting a combination of these sites may have the greatest impact on treatment outcomes.¹

Traditionally, dopaminergic systems have been the focus of attention in addictive disorders, and, indeed, dopaminergic pathways in the brain contribute to the stimulant effects of alcohol, which can be pleasurable.² Repeated ingestion of excessive quantities of alcohol may sensitize dopaminergic pathways³ and produce dysregulation in dopaminergic response.⁴

However, the effects of alcohol extend beyond dopamine, with long-term exposure to alcohol causing

neuroadaptation in multiple neurotransmitter systems.⁴ Understanding these changes should lead to a clearer picture of the pathophysiology of alcoholism and, ultimately, to the development of improved and, possibly, targeted pharmacotherapies. Examples of these changes include down-regulation of inhibitory neuronal γ -aminobutyric acid (GABA) receptors,⁵ up-regulation of excitatory glutamate receptors,⁶ alterations in GABA⁷ and glutamate⁸ receptor structure, alterations in opioid function,⁹ increased activity of corticotropin-releasing factor (CRF),¹⁰ and increased central norepinephrine activity,¹¹ all of which most likely contribute to what has been referred to as the acute and protracted withdrawal syndromes that follow the cessation of alcohol use. The protracted withdrawal syndrome has not been well defined clinically but most likely persists for months after withdrawal from alcohol and may include increased stress reactivity, irritability, dysphoric mood, anxiety, reduced hedonic response, and sleep dysregulation. These neuroadaptations may also produce enhanced craving for alcohol, which increases the probability of drinking.¹² Finally, some persons with psychiatric disorders become alcohol dependent as they self-medicate with alcohol to reduce psychiatric symptoms and distress. Therefore, drugs effective in the treatment of the underlying psychiatric disorder may also be effective in reducing the impetus for alcohol ingestion.¹³

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Table 1. Potential Therapeutic Agents in Alcohol Dependence^a

Opioid antagonists
Serotonin (5-HT) receptor agonists/antagonists (5-HT _{1A} and 5-HT _{1B} agonists, 5-HT ₂ and 5-HT ₃ antagonists, mixed 5-HT _{1A} agonist/5-HT _{2A} antagonist)
γ-Aminobutyric acid receptor agonists
Dopamine receptor antagonists
Glutamate receptor agonists/antagonists
Cannabinoid receptor antagonists
Corticotropin-releasing factor receptor agonists/antagonists
Neuropeptide Y receptor antagonists

^aAdapted with permission from Litten et al.¹

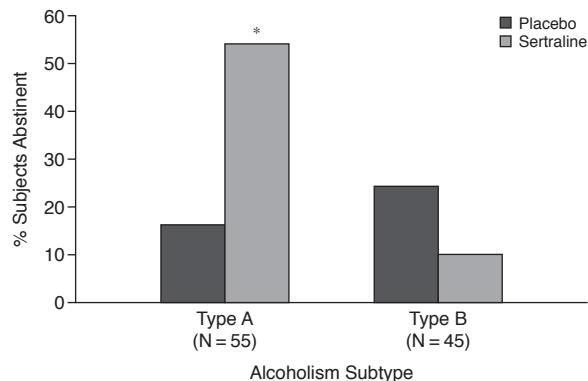
SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Alcohol dependence is common among persons with psychiatric disorders such as depression, schizophrenia, anxiety, and antisocial personality disorders.¹⁴ Because of the high comorbidity of psychiatric disorders and alcohol dependence, agents such as selective serotonin reuptake inhibitors (SSRIs) used to treat depression and anxiety also have been studied for alcohol dependence. The effects of serotonin on alcohol are complex because of the presence of multiple subtypes of serotonin receptors¹⁵ and potential 5-hydroxytryptamine (5-HT), or serotonin, abnormalities that vary across individuals.¹⁶ Several SSRIs have been studied in the treatment of alcohol-dependent individuals. Efficacy results have ranged from no response to modest responses.^{16–18} The variability in outcomes appears to reflect the different patient subpopulations studied.¹

For example, in a study of sertraline,¹⁶ 55 subjects with less severe, later-onset, or type A alcoholism responded more favorably to 14 weeks of treatment than did 45 subjects with type B alcoholism, which is characterized by a family history of alcoholism and more severe dependence, earlier onset of disease, and the presence of more comorbid psychopathology than type A alcoholism.¹⁹ Patients were randomly assigned to receive sertraline or placebo, and all patients received 12-step facilitation therapy. Approximately half of the patients had clinical depression. Type A drinkers treated with sertraline had fewer drinking days compared with type A patients treated with placebo. This difference between the active-medication and placebo groups was not seen among type B individuals. Significantly more type A drinkers also achieved complete abstinence with sertraline compared with placebo, but this finding did not hold true for type B drinkers (Figure 1).¹⁶ The authors reexamined these findings for gender differences and found that significant increase in weeks to relapse to heavy drinking and reductions in percentage of days drinking and heavy drinking days were found only in type A men.²⁰

Kranzler et al.²¹ also found that type B patients had poorer drinking-related outcomes with the SSRI fluoxetine compared with placebo. Furthermore, using the

Figure 1. Percentage of Type A (lower risk/severity) and Type B (higher risk/severity) Patients Who Were Completely Abstinent Throughout 14 Weeks of Treatment, With Respect to Medication Status^a



^aReprinted with permission from Pettinati et al.¹⁶

* $p = .004$.

type I versus type II typology originally proposed by Cloninger,²² Chick et al.²³ found that alcoholic subjects with type I profiles (similar to type A described above) had less relapse to heavy drinking taking the SSRI fluvoxamine than did those with type II profiles (similar to type B described above). This finding is of interest because it parallels the Pettinati et al.²⁰ and Kranzler et al.²¹ findings that those with early-onset, more severe alcoholism (type II or type B) may show a poor outcome with SSRIs, whereas those with later-onset, less severe (type A or type I) alcoholism may have preferential benefit from SSRIs.

In a study of 101 alcohol-dependent patients, Kranzler et al.¹⁷ found no difference in relapse frequency or severity between fluoxetine- and placebo-treated alcohol-dependent subjects. Among patients who had major depression, fluoxetine reduced depressive symptoms to a greater extent than did placebo. The authors, however, did not recommend fluoxetine as an adjunct for the prevention of relapse and questioned its utility in the treatment of nondepressed alcoholics.

Cornelius et al.¹⁸ found that in comparison with placebo, fluoxetine relieved depressive symptoms and reduced total alcohol consumption in 51 patients recruited from an inpatient service approximately 1 week following detoxification and meeting criteria for major depressive disorder and alcohol dependence. In this 12-week study, total alcohol consumption and the number of heavy drinking days were 3 times lower in the fluoxetine group ($n = 25$) compared with the placebo group ($n = 26$). Cumulative number of drinking days and number of drinks per drinking day were twice as high in the placebo group, and number of weeks abstinent until first heavy drinking was higher in the fluoxetine group. In addition, symptoms

of depression were significantly reduced with fluoxetine in comparison with placebo.¹⁸ It is important to note that patients in this study were more depressed and suicidal (39% attempted suicide in their current depressive episodes) than are most depressed alcoholics in the general population. A subset of these subjects was able to be followed up after 1 year, and there was some evidence that subjects who had initially received fluoxetine continued to show benefit in mood and drinking behavior.²⁴ The fluoxetine subjects also were more likely to have received an SSRI in the intervening 9 months compared with subjects originally assigned to placebo.

Overall, there is some evidence to suggest that SSRIs have value in alcoholic patients with persistent depression, but the effects in alcohol consumption are inconsistent. Whether SSRIs may be beneficial for subtypes of primary alcoholism is of considerable interest, but additional clinical trials are needed.

ONDANSETRON: A SELECTIVE 5-HT₃ RECEPTOR ANTAGONIST

Selective 5-HT₃ receptor blockade attenuates dopamine release²⁵ and reduces alcohol consumption in animal models.^{26,27} Ondansetron, a selective 5-HT₃ receptor antagonist, is commonly used to prevent nausea and vomiting caused by cancer chemotherapy, radiation therapy, anesthesia, and surgery. It has also been studied in the treatment of persons with alcohol dependence. Johnson et al.²⁸ conducted a double-blind, randomized, placebo-controlled, 11-week clinical trial of ondansetron in the treatment of 271 patients with alcoholism. The investigators compared the results for a group with early-onset alcoholism (onset at 25 years of age or before and believed to have a genetic predisposition) with the results for a group with late-onset alcoholism (onset after 25 years of age). All patients also received cognitive-behavioral therapy. Among patients with early-onset alcoholism, ondansetron in a dose of 1, 4, or 16 µg/kg twice a day significantly reduced the average number of drinks per day and drinks per drinking day compared with placebo. In this group, ondansetron in a 4 µg/kg b.i.d. dose appeared to work best across all drinking outcomes assessed (percentage of days abstinent and total days abstinent in addition to the 2 measures already mentioned). Ondansetron-treated patients with late-onset alcoholism did not have significant reductions in alcohol consumption or improvements in abstinence compared with those who received the placebo.

Johnson et al.²⁸ concluded that differences between the types of alcoholism may reflect differences in functioning of the serotonin receptors and account for the variability of response to ondansetron. As a potential emerging therapy, ondansetron and other 5-HT₃ antagonists are of interest and require further clinical trials to understand the scope and strength of their potential efficacy.

TOPIRAMATE: A GABAERGIC/GLUTAMATERGIC AGENT

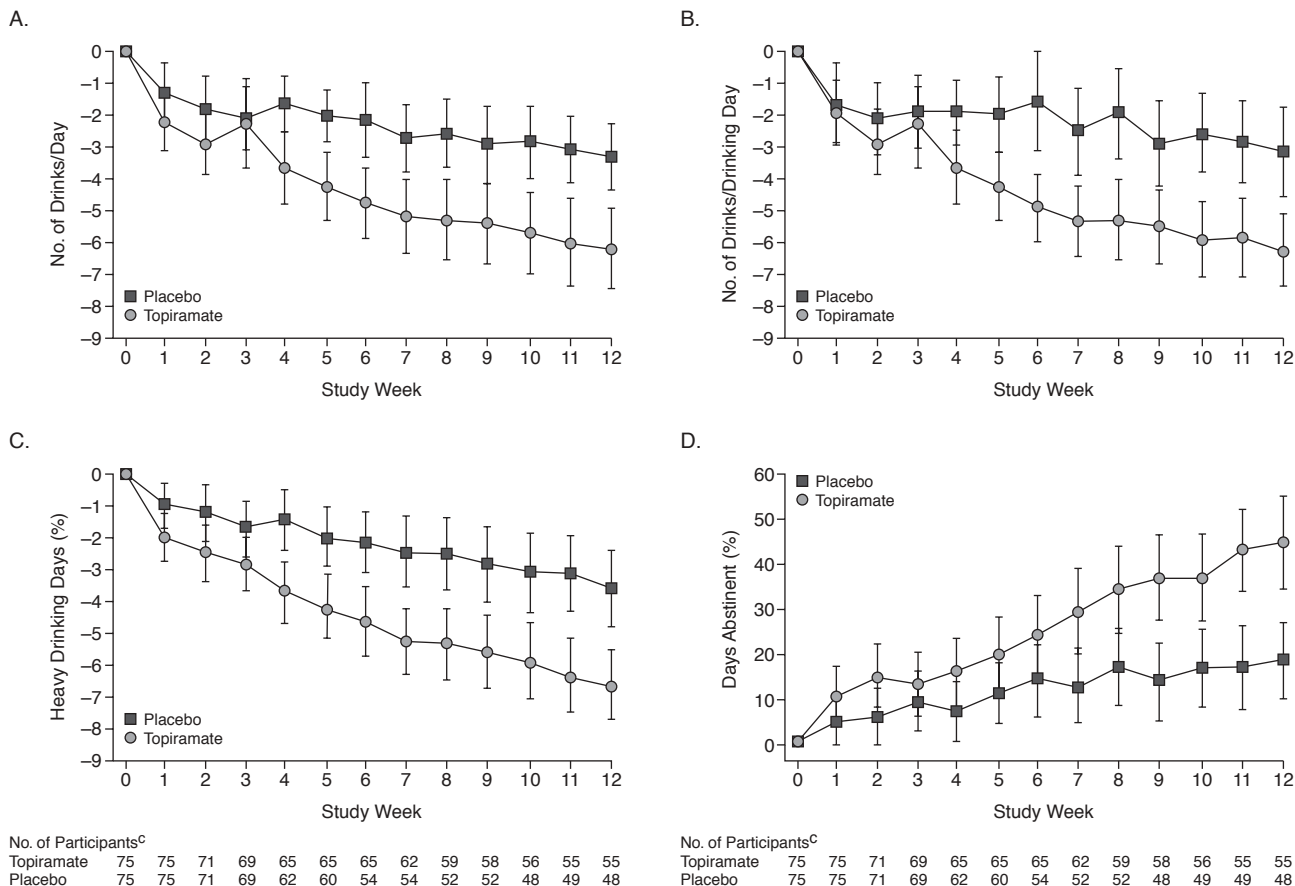
Topiramate is an anticonvulsant approved for use in preventing migraine headaches. Johnson et al.²⁹ postulated that topiramate may be effective in treating alcohol dependence because it may decrease dopamine activity in the brain after alcohol intake, in part because of the ability of the drug to enhance GABA-mediated inhibition through nonbenzodiazepine receptors³⁰ and its antagonism of the excitatory effects of glutamate activity at the α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and kainate glutamate receptors.³¹ Thus, topiramate may also help in the management of alcohol dependence by countering the changes that occur at these receptors with chronic alcohol use.²⁹

Johnson et al.²⁹ tested their ideas in a randomized, double-blind, 12-week controlled study in which the investigators compared escalating doses of topiramate (up to 300 mg/day) with placebo in 150 alcohol-dependent subjects. From baseline to study end, topiramate significantly reduced the number of drinks per day ($p = .0006$), number of drinks per drinking day ($p = .0009$), and percentage of heavy drinking days ($p = .0003$) and increased the percentage of days abstinent ($p = .0003$) (Figure 2). Reductions in γ -glutamyl transferase level, a liver function test that is a proxy of alcohol consumption, also were significant in topiramate-treated patients. These subjects had significantly reduced drinking obsession scores ($p = .003$), automaticity of drinking ($p = .001$), and interference due to drinking ($p = .0003$) as measured by the Obsessive Compulsive Drinking Scale. Craving reductions were significantly related to reduced self-reported drinking. Johnson et al.³² reported more recently that in this same group of patients, topiramate improved the odds of well-being ($p = .01$), the reported rate of abstinence and not seeking alcohol ($p = .001$), and overall life satisfaction ($p = .01$) and reduced the consequences of harmful drinking ($p = .01$) compared with the results obtained with placebo. Several phase 3 clinical trials of topiramate for alcohol dependence are ongoing.

OTHER GABAERGIC AGENTS

Baclofen is a selective GABA_B agonist approved for use in relieving muscle spasm, spasticity, cramping, and tightness.¹ It is postulated that activation of GABA_B receptors modulates dopamine transmission in the mesolimbic system.^{1,33} Baclofen has been shown to suppress alcohol withdrawal symptoms³⁴ and voluntary alcohol intake in rats.³⁵ In a 2002 double-blind, randomized, placebo-controlled study of alcohol-dependent individuals, Addolorato et al.³⁶ found that a significantly higher number of baclofen-treated patients (14 of 20, 70.0%) achieved and maintained abstinence over 30 days com-

Figure 2. Change in Self-Reported Drinking Outcomes From Baseline (week 0) for Topiramate Versus Placebo by Study Week^{a,b}



^aReprinted with permission from Johnson et al.²⁹
^bValues are means (95% confidence intervals).
^cNumbers of participants are those with available data at each time point.

pared with placebo-treated subjects (4 of 19, 21.1%; $p < .005$). Drinking was almost completely eliminated in the first week (mean daily drinks fell from approximately 18 drinks to fewer than 0.5 drinks). Moreover, the objective craving score was consistently lower in baclofen-treated patients than in the placebo group. No patients discontinued treatment with baclofen because of side effects. Additional single-center trials of baclofen for alcohol dependence are ongoing. It is of interest that baclofen has been reported to reduce cocaine use in cocaine dependence,³⁷ suggesting that it could have value in more than 1 addictive disorder.

DOPAMINE ANTAGONISTS

Pharmacologic blockade of mesolimbic dopaminergic neurotransmission with dopamine D₁ or D₂ receptor antagonists blocks the reinforcing effects of alcohol and affects drug intake.^{15,38} Various dopamine antagonists have been studied. Ecopipam, a selective D₁ antagonist, has re-

duced both the appetite and consumption responses for ethanol in rat models without diminishing the reward from water under thirst conditions.³⁸ Flupenthixol is a neuroleptic agent with mixed D₁ and D₂ receptor antagonist properties as well as 5-HT_{2A} antagonist activity.³⁹ For the most part, flupenthixol has not been effective in alcoholism, as exemplified by the superiority of placebo over flupenthixol in maintaining abstinence in alcohol-dependent subjects.⁴⁰ Some investigators believe that optimal results with this drug may be found in patients with comorbid substance abuse and psychiatric disorders.³⁹

Haloperidol has been reported to reduce craving for alcohol in a small clinical trial⁴¹ but has not been tested in a larger population. In 1 study,⁴² olanzapine has been shown to reduce cue-induced craving for alcohol and alcohol consumption in alcohol-dependent subjects who have the 7-repeat allele variant of the D₄ dopamine receptor. Finally, clozapine has been reported to reduce alcohol consumption in patients with schizophrenia.⁴³ Acute and long-term side

effects remain a concern for the use of clinically available dopamine antagonists in primary alcohol dependence.

Dopamine D₃ receptors in the limbic region of the brain may have a role in drug dependence and addiction, including rewarding and drug-seeking behaviors.⁴⁴ Therefore, selective D₃ receptor antagonists for alcohol dependence are being studied in early-phase trials.

CANNABINOID ANTAGONISTS

The cannabinoid system is involved in a variety of physiologic functions, including appetite, obesity, anxiety, memory, motor function, emotional response, and nausea.¹

Cannabinoid CB₁ receptors have been associated with alcohol drinking as well as the development of tolerance of and dependence on alcohol.^{1,45,46}

Rimonabant, a cannabinoid CB₁ receptor antagonist, has been shown to suppress alcohol seeking and to reduce voluntary alcohol intake in rats.⁴⁷ At least 1 phase 2 clinical trial is being conducted to determine the effects of rimonabant on alcohol abuse. This agent also shows promise in the treatment of obesity and smoking.^{48,49} For example, rimonabant in combination with reduced food intake produced greater weight loss and improvements in dyslipidemia over a year's time compared with placebo.^{50,51}

CORTICOTROPIN-RELEASING FACTOR AGONISTS/ANTAGONISTS

Corticotropin-releasing factor is a small, 41–amino-acid peptide that appears to be a key mediator of the heightened sensitivity to stress that accompanies ethanol abstinence following previous use and the associated susceptibility to relapse.⁵² This system may also interact with other brain systems in the regulation of ethanol self-administration after abstinence. Pharmacologic agents that block CRF₁ receptors attenuate the anxiety-like response to stress during protracted alcohol abstinence in alcohol-dependent rats.⁵³ On the other hand, activation of CRF₂ receptors attenuates stress-induced responses.¹ Both CRF₁ and CRF₂ receptors are potential therapeutic targets, although clinical trials have not been completed to date.

NEUROPEPTIDE Y ANTAGONISTS

Neuropeptide Y (NPY) is a 36–amino-acid peptide neuromodulator involved in food intake, thermogenesis, seizure activity, neuronal development, cardiovascular homeostasis, integration of emotional behavior, and circadian rhythms.^{54,55} It may also play a role in the stress response to alcohol withdrawal. Blockage of Y₁ receptors with selective antagonists in the brains of mice and rats has been shown to reduce alcohol consumption and the motivation to self-administer alcohol.^{55,56} Low levels of NPY in central brain regions may stimulate alcohol drinking,

and high levels in other brain regions may protect against excessive alcohol consumption.⁵⁴ In addition, genetic differences in mice lead to different responses in alcohol consumption when NPY is centrally administered.⁵⁴ Human testing with agents that modify NPY activity requires further exploration.

CONCLUSIONS

In many ways, this is a momentous time in the alcoholism treatment field. Discoveries in neuroscience are identifying molecular targets that may lead to novel treatments for alcohol dependence. Both academia and the pharmaceutical industry are showing interest in developing medications for alcoholism, and it is likely that more phase 3 trials in alcoholism have occurred in the past 5 years than in the previous 50 years. It is not clear which drugs targeting which neurocircuits will emerge as the next wave of therapeutic agents. It is also not clear what role medication combinations will play or whether “tailoring” medications to individual phenotypic or genetic characteristics will emerge as clinically important. Nevertheless, what is clear is that the pharmacotherapy of alcoholism has changed dramatically since the discovery of disulfiram. Future developments, some perhaps emerging from the studies noted in this review, should lead to improvements in clinical practice and offer clinicians more therapeutic options in managing alcoholism.

Drug names: baclofen (Lioresal, Kemstro, and others), clozapine (Clozaril, FazaClo, and others), disulfiram (Antabuse), fluoxetine (Prozac and others), haloperidol (Haldol and others), olanzapine (Zyprexa), ondansetron (Zofran), sertraline (Zoloft and others), topiramate (Topamax and others).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, baclofen, clozapine, ecopipam, fluoxetine, flupenthixol, fluvoxamine, haloperidol, olanzapine, ondansetron, rimonabant, sertraline, and topiramate are not approved by the U.S. Food and Drug Administration for the treatment of alcohol dependence.

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