DRUG & ALCOHOL FINDINGS

Interesting times in the pharmacotherapy of alcohol dependence

by **Hugh Myrick, Kathleen Brady & Robert Malcolm**

An expert guide through all that's new in drug-based treatment of alcoholism.

About this document

Send comments to Findings

Dr Myrick is at the Department of Psychiatry, Medical University of South Carolina, fax 00 1 843 792 1724, e-mail myrickh@musc.edu.

Neuroscientific underpinnings and pharmacotherapeutic treatments of substance use disorders are rapidly developing areas of study. In particular, there have been exciting new developments in our understanding of the involvement of the opiate and serotonin neurotransmitter systems involved in alcohol withdrawal and dependence, and in subtypes of individuals with alcoholism. This article reviews these new developments, focusing on the post-withdrawal phase of treatment.[1]

Opiate antagonists

Half a century after disulfiram, the opiate antagonist (drugs which block and reverse the effects of opiates) naltrexone became the second drug the US Food and Drug Administration has approved for treating alcoholism.

Studies of naltrexone and its fellow antagonist naloxone had suggested that this class of drugs reduces alcohol consumption in 'alcohol dependent' animals.[2] More recently, three out of four placebo-controlled clinical trials of the treatment of of alcohol dependence with naltrexone have demonstrated a reduced relapse rate, fewer drinking days, longer periods of continuous abstinence, and less craving for alcohol compared to placebo.[3 4 5 6]

One of the studies found compliance critical; differences between naltrexone and placebo were seen only in subjects who took 90% or more of their medication.[5] In all the trials, an intense 'dose' of high-quality psychosocial therapy was administered prior to and throughout the course of medication. Side effects were modest but included nausea, vomiting, abdominal discomfort, daytime sleepiness, and nasal congestion.

Across these studies the efficacy of naltrexone versus placebo is modest but consistent. The studies cited above were 12-week trials; recent work indicates that taking naltrexone for up to six months can produce continued gains in drinking outcomes.[7]

The fact that compliance appears critical has prompted investigation of longer acting forms of naltrexone which need to be administered less often.[5] Preliminary work with an injectable, sustained-release form is promising.[8] In one small study, compared to placebo subjects receiving this medication had significantly fewer heavy drinking days while the injections were active and during the follow-up period. Side effects were comparable to oral naltrexone. Concentrations of naltrexone and its active metabolite in the blood appeared to be maintained at clinically effective levels for several weeks. A larger clinical trial is underway.

Nalmefene is an opiate antagonist with some potential advantages over naltrexone. It is absorbed better when swallowed and dose-related liver toxicity has not been reported. In addition, nalmefene is active not only at the same neuronal receptor sites as heroin/morphine, but has antagonist effects at other opioid receptors. In a recent placebo-controlled trial, 20 and 80mg doses of nalmefene were both more effective than placebo.[9] Relapse to heavy drinking during the 12 weeks of treatment was over twice as likely for the placebo group. No study has yet directly compared nalmefene and naltrexone. A large multi-centre placebo-controlled trial of nalmefene is in progress.

Acamprosate

Acamprosate probably counters alcohol's impact on a neurotransmitter system in the brain (the glutamate system) which excites neural activity and is implicated particularly in the symptoms of alcohol withdrawal.[10]

It has about an 18-hour half-life and blood levels build up to a steady state over five days. The fact that it is not broken down by the liver but is primarily excreted unchanged by the kidneys means that patients with liver disease can take it without difficulty, though it is not recommended in cases of impaired kidney function. Acamprosate does not affect the action of opiate-type drugs or the body's own opiate-like substances, making it suitable for alcohol-dependent patients on opiate maintenance therapies. Poor absorption[11] means acamprosate is generally given in high doses, about 2gm per day. Clinical trials have generally adjusted dose to body weight.

Animal studies have consistently shown that acamprosate decreases alcohol consumption and that the effect is greater with greater

Golden Bullets

Essential practice points from this article

- Opiate, serotonin and glutamate neurotransmitter systems are involved in alcohol withdrawal and dependence; drugs affecting these systems are being tried as a way to treat alcohol dependence.
- The opiate antagonist naltrexone modestly but consistently reduces drinking in alcohol patients, as long as they take the pills. To improve compliance, long-acting forms are under investigation.
- Acamprosate affects the glutamate system. It improves treatment completion and abstinence rates, is acceptable to patients, and can be used in cases of liver impairment.
- Most trials find drugs which target the serotonergic system no better overall than placebo, though they may be useful for certain types of alcoholics.
- Buspirone may be effective in highly anxious alcoholics, serotonin reuptake inhibitors such as fluoxetine in patients with major depression or in certain types of alcoholics.
- Combinations of drugs with different actions could hold promise but have rarely been studied.

Alcohol typologies

	Type 1	Type 2	Type A	Type B
Age of onset	**Late**	**Early**	**Late**	**Early**
Gender split	**Equal**	**Men dominate**	**Equal**	**Men dominate**
Sociopathy	**Low**	**High**	**Low**	**High**
Polydrug use	**No**	**Yes**	**No**	**Yes**
Severity of dependence	**Low**	**High**	**Low**	**High**

Two similar ways of classifying alcohol dependent patients have been used to match them to different treatments. Serotonin reuptake inhibitors were expected to be more effective for type 2 and type B but that's not always how it worked out.

doses.[12 13 14] In France, since 1989 the drug has been available on prescription for the treatment of alcohol dependence. A recent review summarised 16 controlled clinical trials involving over 4500 alcohol-dependent outpatients.[15] In 14 of the trials, groups treated with acamprosate had higher rates of treatment completion, longer times to first drink, and higher abstinence rates compared to placebo. The studies generally showed a favourable effect (if one of variable size) on most primary outcome measures. Compliance measures indicated that the medications were well tolerated and that the dosing schedules were acceptable to patients.

In the United States a 21-site, six-month, double-blind, placebo-controlled trial of acamprosate in alcohol dependent outpatients has recently been completed. Preliminary results presented look promising.[16]

Serotonergic agents

Studies on animals and on people outside the context of alcohol treatment have shown that the brain's serotonergic neurotransmitter system is involved in alcohol consumption as well as in mood disorders and impulse regulation. Acute administration of alcohol causes serotonin (also known as 5-HT) to be released, while chronic administration decreases serotonin levels in a part of the rat brain involved in motivation and reward.[17 18] 'Alcohol-preferring' strains of rodents show serotonin deficits in several brain regions.[19 20] Animal studies have also consistently demonstrated reduced alcohol intake after administering a variety of serotonergic agents, including the medications sertraline and citalopram. These belong to a class of drugs – the serotonin reuptake inhibitors – which increase the availability of serotonin at neural junctions in the brain.[21 22]

Unfortunately, clinical trials using drugs which target the serotonergic system have not consistently confirmed that the system has a role in the treatment of alcoholism. Most trials in the 1990s on alcohol-dependent or alcohol-abusing individuals found serotonergic medications no better overall than placebo,[23 24 25 26 27] though they may be useful for certain types of alcoholics.[28 29 30 31] These findings and specific agents and studies are discussed below.

Ritanserin and buspirone

Ritanserin, which counters the effect of serotonin, was found to decrease drinking in a small trial involving alcohol-dependent individuals who knew what they were taking,[32] but not in two later placebo-controlled trials involving patients without substantial psychiatric comorbidity.[23 32]

Buspirone, a drug approved for treating generalised anxiety disorder, has some excitatory effects at a particular type of neural serotonin receptor. It has demonstrated mixed effects on alcohol consumption in alcohol-dependent subjects. Two placebo-controlled, double-blind trials found that it reduced consumption more than placebo in patients with high levels of anxiety.[33 34] In two other placebo-controlled studies, one of which did not specifically recruit anxious subjects and another which did, buspirone did not affect consumption.[25 35] Matching different drugs to drinkers with different psychiatric profiles may be a strategy particularly applicable to serotonergic agents.

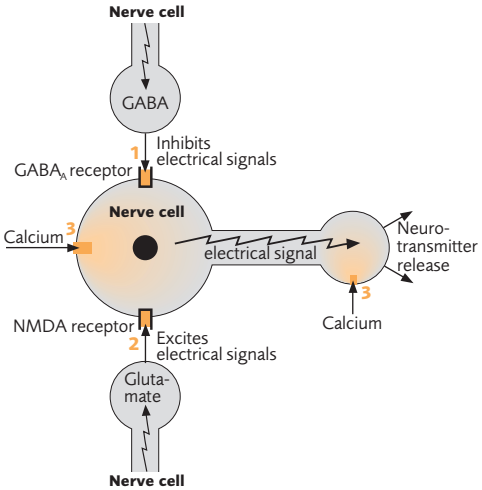
Serotonin reuptake inhibitors

In the United States serotonin reuptake inhibitors such as fluoxetine are now the most commonly prescribed drugs for mood and anxiety disorders. Early studies, particularly with non-dependent heavy drinkers, indicated that they also held promise for alcohol use disorders.[24 27 36] Unfortunately, several placebo-controlled, double-blind studies of alcohol-dependent subjects without psychiatric comorbidity failed to show that fluoxetine reduced drinking.[26 37]

However, the effectiveness of these drugs in common psychiatric disorders raises particular interest in matching their use to subtypes of patients. Disturbance of the serotonin system is thought to be involved in conditions such as depression, anxiety, eating disorders and compulsive and/or impulse regulation disorders. Presumably by helping to correct this disturbance, serotonin reuptake inhibitors are effective in conditions including depression, panic, social phobia, and post-traumatic stress.[38 39 40] A potential for treating alcohol dependence and abuse is suggested by their strong associations with several emotional and anxiety disorders.[41] Also, alcoholics often exhibit traits such as impulsivity thought to be linked to serotonin dysfunction.

Inconsistent findings on the effectiveness of serotonin agents in alcohol dependence may themselves be related to inconsistencies in the populations under study. Despite disappointing results overall, there may yet prove to be a role for these agents in the treatment of alcoholics with the hallmarks of serotonin abnormalities. For instance, one double-blind, placebo-controlled study of alcohol-dependent patients suffering from major depression recorded significantly greater improvements in depressive symptoms and larger decreases in alcohol consumption in the fluoxetine group.[30]

These thoughts raise the issue of how to categorise alcohol-dependent individuals in order to match them to the best treatment. Several approaches have been tried. Babor and colleagues' two-factor typology[42] (types A and B) has been shown to predict treatment outcomes[43 44] ◤ *Alcohol typologies*. Characteristics associated with serotonin dysfunction (depression, anxiety, aggression, and personality disorder) are clustered in type B. As such, serotonin reuptake inhibitors can be expected to be more effective for type B than for type A. The same can be



■ Marks where alcohol exerts effects on the brain's nerve cells. Modifying these effects may be how drugs help in treatment.

1 Increases the effects of the neurotransmitter gamma-aminobutyric acid (GABA) which inhibits electrical signaling through the nerve cell.

2 Further decreases electrical activity by inhibiting the excitatory neurotransmitter, glutamate.

3 Alters the flow of calcium through channels at the cell body and terminal, where calcium is necessary for neurotransmitter release.

LINKS Nuggets 7.2 6.4 5.2 5.1 • *Disulfiram treatment of alcoholism*, issue 6

expected of type 2 versus type 1 in a roughly equivalent typology.[45]

Several studies have explored this possibility. One 12-week, placebo-controlled trial which divided patients into type 1 and type 2 found citalopram no more effective for one type than the other.[28] Another reanalysed data from a negative placebo-controlled trial of fluoxetine by dividing the alcohol-dependent subjects according to Babor's typology.[29] Contrary to expectations, it found that on fluoxetine type B alcoholics drank *more* during treatment than on placebo. Similarly, a 12-week, placebo-controlled trial of sertraline in alcohol dependent individuals found that the drug reduced drinking in type A subjects but had no effect on type B.[30]

In conclusion, there may be a role for serotonin-specific agents in treating alcohol dependence, and subtyping by psychiatric disorder and other characteristics shows promise, but much work remains to be done.

Combination pharmacotherapy

Combination pharmacotherapies are effective in the treatment of several common psychiatric disorders. Animal studies suggest that the same may be true of alcohol disorders. For instance, one study of 'alcohol-dependent' rodents found that two agents acting together on different parts of the serotonin system had a greater effect than either alone.[46] Many drugs known to reduce drinking in alcohol-dependent individuals act by distinctly different mechanisms (eg, naltrexone and acamprosate), making it likely that they can act together in an additive or even synergistic fashion. There are no specific toxic interactions between these agents, suggesting that they can safely be administered together.

Very few clinical studies have explored this potential. One pilot study did investigate the opioid antagonist naltrexone in combination with sertraline, a serotonin reuptake inhibitor. It documented a trend toward longer retention in treatment and more days abstinent.[47] In another pilot, patients who had not responded to the opioid antagonist nalmefene had sertraline added to their treatment. Compared to the pre-treatment period or to nalmefene alone, the combination was associated with significant decreases in alcohol consumption.[48]

Two double-blind, placebo-controlled trials have investigated the combination of acamprosate and disulfiram. One found a statistically significant advantage in cumulative abstinence in patients receiving both compared to those receiving either alone,[49] but another similar comparison found no added benefit from the combination.[50] Recently, the US National Institute on Alcoholism and Alcohol Abuse has initiated a large multi-site trial comparing acamprosate, naltrexone, and a combination of the two, which should provide valuable information.

Exciting developments

Several avenues could profitably be explored in the pharmacotherapeutic treatment of alcohol disorders. Growing knowledge about the part played in these disorders by opioid and excitatory neurotransmitter systems in the brain has led to successful exploration of agents (naltrexone, nalmefene, acamprosate) which exert therapeutic effects through these same systems. Matching serotonergic agents to subtypes of alcohol-dependent patients also shows promise. Finally, combination pharmacotherapies have theoretical and preclinical support but are under-investigated in clinical populations. In all, this is an extremely exciting and hopeful time.

1 Treatments for alcohol withdrawal were included in the original version of this review.

2 Myers R. *et al*. "Antagonism by naltrexone of voluntary alcohol selection in the chronically drinking macaque monkey." *Alcohol*: 1986, 3, p. 383–388.

3 Volpicelli J.R. *et al*. "Naltrexone in the treatment of alcohol dependence." *Arch. Gen. Psych.*: 1992, 49(11), p. 876–880.

4 O'Malley S.S. *et al*. "Naltrexone and coping skills therapy for alcohol dependence. A controlled study." *Arch. Gen. Psych.*: 1992, 49(11), p. 881–887.

5 Volpicelli J. *et al*. "Naltrexone and alcohol dependence: role of subject compliance." *Arch. Gen. Psych.*: 1997, 54, p. 737–742.

6 Anton R.F. *et al*. "Naltrexone and cognitive behavioral therapy for the treatment of outpatient alcoholics: results of a placebo-controlled trial." *Am. J. Psych.*: 1999, 156(11), p. 1758–1764.

7 O'Malley S. *et al*. "Naltrexone: effect of therapy and treatment duration." In: *American Psychiatric Association 2000 Annual Meeting Syllabus*: May 2000, Chicago, p. 58.

8 Kranzler H.R. *et al*. "Sustained-release naltrexone for alcoholism treatment: a preliminary study." *Alcoholism: Clinical and Experimental Research*: 1998, 22(5), p. 1074–1079.

9 Mason B. *et al*. "A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence." *Arch. Gen. Psych.*: 1999, 56, p. 719–724.

10 Littleton J. "Acamprosate in alcohol dependence: how does it work? *Addiction*: 1995, 90, p. 1179–1188.

11 Wilde M.I. *et al*. "Acamprosate. A review of its pharmacology and clinical potential in the management of alcohol dependence after detoxification." *Drugs*: 1997, 53(6), p. 1038–1053.

12 Boismare F. *et al*. A homotaurine derivative reduces the voluntary intake of ethanol by rats: are cerebral GABA receptors involved?" *Pharmacol. Biochem. Behav.*: 1984, 21(5), p. 787–789.

13 Le Magnen J. *et al*. "Lack of effects of Ca-acetyl homotaurinate on chronic and acute toxicities of ethanol in rats." *Alcohol*: 1987, 4, p. 103–108.

14 Gewiss M. *et al*. "Acamprosate and diazepam differentially modulate alcohol-induced behavioural and cortical alterations in rats following chronic inhalation of ethanol vapour." *Alcohol & Alcoholism*: 1991, 26(2), p. 129–137.

15 Mason B. *et al*. "Acamprosate for the treatment of alcohol dependence: a review of double-blind, placebo-controlled trials." *CNS Spectrum*: 2000, 5(2), p. 58–69.

16 Mason B. *et al*. "Acamprosate: new preclinical and clinical research." Presented at 23rd Annual Scientific Meeting of the Research Society on Alcoholism: 24–29 June 2000, Denver, Colo.

17 Yoshimoto K. *et al* ."Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens." *Alcohol*: 1992, 9(1), p. 17–22.

18 Carmichael F.J. *et al*. "Effects of ethanol on neurotransmitter release by rat brain cortical." *J. Pharmacol. Exp. Ther.*: 1975, 93(3), p. 824–834.

19 McBride W.J. *et al*. "Serotonin-2 receptors in the CNS of alcohol-preferring and -nonpreferring rats." *Pharmacol. Biochem. Behav.*: 1993, 46(3), p. 631–636.

20 Pandey S.C. *et al*. "Alterations in serotoninIB (5HT1B) receptor subtypes in the brain of ethanol-treated rats." *Drug and Alcohol Dependence*: 1996, 41(3), p. 219–225.

21 Naranjo C. *et al*. "Modulation of ethanol intake by serotonin uptake inhibitors." *J. of Clinical Psychiatry*: 1986, 47 (suppl), p. 6–22.

22 Higley J. *et al*. "The serotonin reuptake inhibitor sertraline reduces excessive alcohol consumption in nonhuman primates: effect of stress." *Neuropsychopharmacology*: 1998, 18(6), p. 431–443.

23 Johnson B.A. *et al*. "Ritanserin in the treatment of alcohol dependence – a multicenter clinical trial." *Psychopharmacology*: 1996, 128, p. 206–215.

24 Angelone S.M. *et al*. "Effects of fluvoxamine and citalopram in maintaining abstinence in a sample of Italian detoxified alcoholics." *Alcohol and Alcoholism*: 1998, 33(2), p. 151–156.

25 Malec T.S. *et al*. "Efficacy of buspirone in alcohol dependence: a review." *Alcoholism: Clinical and Experimental Research*: 1996, 20(5), p. 853–858.

26 Kabel D. *et al*. "A double-blind study of fluoxetine in severe alcohol dependence: adjunctive therapy during and after inpatient treatment." *Alcoholism: Clinical and Experimental Research*: 1996, 20, p. 780–784.

27 Janiri L. *et al*. "Effects of fluoxetine and antidepressant doses on short-term outcome of detoxified alcoholics." *Int. Clin. Psychopharmacol.*: 1996, 11, p. 109–117.

28 Tiihonen J. *et al*. "Citalopram in the treatment of alcoholism: a double-blind placebo-controlled study." *Pharmacopsychiatry*: 1996, 29(1), p. 27–29.

29 Kranzler H.R. *et al*. "Fluoxetine treatment seems to reduce the beneficial effects of cognitive-behavioral therapy in type B alcoholics." *Alcoholism: Clinical and Experimental Research*: 1996, 20(9), p. 1534—1541.

30 Cornelius J.R. *et al*. "Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial." *Arch. Gen. Psych.*: 1997, 54(8), p. 700–705.

31 Pettinati H.M. *et al*. "Sertraline treatment for alcohol dependence: interactive effects of medication and alcoholic subtype." *Alcoholism: Clinical and Experimental Research*: 2000, 24(7), p 1041–1049.

32 Le A.D. *et al*. "Use of serotonin (5-HT) and opiate-based drugs in the pharmacotherapy of alcohol dependence: an overview of the preclinical data." *Alcohol and Alcoholism*: 1996, 31(suppl. 1), p. 27–32.

33 Tollefson G.D. *et al*. "Treatment of comorbid generalized anxiety in a recently detoxified alcoholic population with a selective serotonergic drug (buspirone)." *J. of Clinical Psychopharmacoly*: 1992, 12(1), p. 19–26.

34 Kranzler H.R. *et al*. "Buspirone treatment of anxious alcoholics. A placebo-controlled trial." *Arch. Gen. Psych.*: 1994, 51(9), p. 720–731.

35 Malcolm R. *et al*. "A placebo-controlled trial of buspirone in anxious inpatient alcoholics." *Alcoholism: Clinical and Experimental Research*: 1992, 16(6), p. 1007–1013.

36 Naranjo C.A. *et al*. "The serotonin uptake inhibitor citalopram attenuates ethanol intake." *Clin. Pharmacol. Ther.*: 1987, 41(3), p. 266–274.

37 Kranzler H.R. *et al*. "Placebo-controlled trial of fluoxetine as an adjunct to relapse prevention in alcoholics." *American J. of Psychiatry*: 1995, 152(3), p. 391–397.

38 Brady K.T. *et al*. "Comorbidity of psychiatric disorders and posttraumatic stress disorder. *J. of Clinical Psychiatry*: 2000, 61(suppl. 7), p. 22–32.

39 Stein M.B. *et al*. "Paroxetine treatment of generalized social phobia (social anxiety disorder): a randomized controlled trial." *JAMA*: 1998, 280(8), p. 708–713.

40 Lydiard R.B. "Tricyclic-resistant depression: treatment resistance or inadequate treatment?" *J. of Clinical Psychiatry*: 1985, 46(10), p. 412–417.

41 Kessler R.C. *et al*. "The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization." *Am. J. Orthopsych.*: 1996, 66(1), p. 17–31.

42 Babor T.F. *et al*. "Types of alcoholics, I. Evidence for an empirically derived typology based on indicators of vulnerability and severity." *Arch. Gen. Psych.*: 1992, 49(8), p. 599–608.

43 Kadden R.M. *et al*. "Matching alcoholics to coping skills or interactional therapies: posttreatment results." *J. of Consulting and Clinical Psychology*: 1989, 57(6), p. 698–704.

44 Litt M.D. *et al*. "Types of alcoholics, II. Application of an empirically derived typology to treatment matching." *Arch. Gen. Psych.*: 1992, 49(8), p. 609–614.

45 Cloninger C.R. *et al*. "Inheritance of alcohol abuse. Cross-fostering analysis of adopted men." *Arch. Gen. Psych.*: 1981, 38(8), p. 861–868.

46 Zhou F.C. *et al*. "Additive reduction of alcohol drinking by 5-HT1A antagonist WAY 100635 and serotonin uptake blocker fluoxetine in alcohol-preferring P rats." *Alcoholism: Clinical and Experimental Research*: 1998, 22(l), p. 266–269.

47 Farren C.K. *et al*. "Occurrence and management of depression in the context of naltrexone treatment of alcoholism." *American J. of Psychiatry*: 1999, 156(8), p. 1258–1262.

48 Williams L.D. *et al*. "Combination pharmacotherapy in nalmefene non responders." *Alcoholism: Clinical and Experimental Research*: 1997, 21(suppl.), p. 33A.

49 Besson J. *et al*. "Combined efficacy of acamprosate and disulfiram in the treatment of alcoholism: a controlled study." *Alcoholism: Clinical and Exp. Research*: 1998, 22, p. 573–579.

50 Poldrugo F. "Acamprosate treatment in a long-term community-based alcohol rehabilitation programme." *Addiction*: 1997, 92(11), p. 1537–1546.