

New pharmacotherapies for alcohol dependence

Robert Graham, Alex D Wodak and Greg Whelan

ALCOHOL ACCOUNTED for an estimated 3668 deaths and 95 917 hospital separations in Australia in the 1996–97 financial year.¹ Alcohol-related deaths in Australia declined from 460 per million population in 1990 to 369 per million in 1997.² The net economic cost of alcohol to the economy in 1992 was estimated to be \$4.5 billion (this estimate includes increased healthcare expenditure and costs to industry from impaired productivity, increased accidents and absenteeism).³

Prevention and treatment of alcohol-related problems has been improving in recent decades. In the 1980s, brief interventions⁴ were developed for problem drinkers who reject abstinence or are unsuitable for this treatment goal. Brief interventions involve a combination of techniques, including motivational interviewing, feedback to patients of likely adverse consequences of current drinking, self-monitoring of drinking, developing a contract for future drinking, providing strategies to cut down drinking, and regular follow-up. Most clinicians try to discourage patients with life-threatening complications from alcohol from pursuing brief interventions.

Recently, more effective pharmacological treatments have been developed for alcohol dependence. The aetiology, natural history, compliance with and response to treatment of alcohol dependence are similar to those for other common, chronic, relapsing–remitting conditions readily accepted by the medical profession as worthy of treatment.⁵ Treatment of alcohol dependence has been shown to sub-

ABSTRACT

- Two pharmacotherapies recently introduced in Australia, acamprosate and naltrexone, provide a major advance in the treatment of severe alcohol dependence, a common condition leading to a considerable burden of illness and major costs to the community.
- Acamprosate and naltrexone reduce alcohol intake, and increase the likelihood and prolong the duration of abstinence (Level I evidence).
- Compared with naltrexone, the benefits of acamprosate have been confirmed in a larger number of studies involving larger numbers of patients with longer durations of follow-up. Unlike naltrexone, acamprosate appears to achieve a sustained benefit.
- There is no known interaction effect between alcohol and acamprosate or naltrexone.
- Both drugs are well tolerated, although naltrexone blocks the action of opioid analgesics.
- Adjunctive psychosocial treatment with close follow-up is required for acamprosate and recommended for naltrexone.
- As yet, no studies have reported a reduction in mortality following the use of any pharmacotherapy for alcohol dependence.

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1: Profiles of acamprosate and naltrexone

Acamprosate

Action: Chronic exposure to alcohol causes a decrease in the inhibitory γ -aminobutyric acid (GABA)-ergic system and a corresponding increase in activity of the excitatory glutamate system in the central nervous system.⁷ Acamprosate, which has a similar structure to GABA, enhances GABA transmission by increasing the number of sites for GABA uptake. Acamprosate also interferes with the action of glutamate at various sites, such as *N*-methyl-*D*-aspartate (NMDA) receptors, and has also been shown to affect calcium channels, which increase in number as alcohol dependence develops.⁸

Dose: Acamprosate comes as 333 mg tablets, with the recommended daily dose for adults weighing over 60 kg being six tablets (1998 mg) orally in three divided doses, with meals. Adults weighing under 60 kg should take four tablets (1332mg) per day. Usual practice is to start at half these doses and increase by one tablet a week.

Metabolism: Only 10% of acamprosate is absorbed, of which 90% is excreted unchanged into urine.

Adverse effects: Acamprosate is well tolerated, and its predominantly gastrointestinal adverse effects (commonly diarrhoea) usually resolve spontaneously. Side effects are minimised by gradual dose increases. Other low-grade side effects, including mild abdominal pain, are reported by some patients. Rash or isolated pruritus, paraesthesiae, decreased libido and confusion have all been reported at low frequencies.

Drug interactions: Tetracyclines may be inactivated by the calcium component in acamprosate during concurrent administration.

Contraindications: Acamprosate is contraindicated in patients with known hypersensitivity to the drug, renal insufficiency or cirrhosis with severe hepatic decompensation. The safety of acamprosate in pregnancy or lactation has not been established.

Naltrexone

Action: Naltrexone, a potent opioid-receptor antagonist, blocks the effects of endogenous opioids, which increase after alcohol consumption.⁹

Dose: Naltrexone is administered orally at 25 mg for 1–2 days, and then increased to the standard dose of 50 mg daily.

Metabolism: Naltrexone undergoes extensive first-pass metabolism in the liver to β -naltrexol. Although a much weaker antagonist than naltrexone, the half-life of β -naltrexol is longer, and plasma concentrations of the metabolite are always higher than those of the parent drug. The mean elimination half-life values for naltrexone and β -naltrexol are four hours and 13 hours, respectively.

Adverse effects: Naltrexone is generally well tolerated. A number of studies indicate that non-specific and systemic symptoms, including headache, back-pain, flu-like symptoms, nausea and anorexia, have been more commonly reported by patients receiving naltrexone than those receiving placebo. However, there are also reports that side effects are no more common in patients taking naltrexone than in those taking placebo.

Drug interactions: Naltrexone blocks the action of opioid analgesics, which can be problematic in clinical practice.

Contraindications: Naltrexone is contraindicated in patients receiving long-term opioid therapy for chronic pain or heroin dependence.

2: NHMRC level-of-evidence codes

Evidence for the statements made in this article is graded according to the National Health and Medical Research Council system¹⁴ for assessing the level of evidence.

- E1 Level I: Evidence obtained from a systematic review of all relevant randomised controlled trials.
- E2 Level II: Evidence obtained from at least one properly designed randomised controlled trial.
- E3₁ Level III-1: Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- E3₂ Level III-2: Evidence obtained from comparative studies with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a parallel control group.
- E3₃ Level III-3: Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- E4 Level IV: Evidence obtained from case-series, either post-test, or pre-test and post-test.

stantially reduce healthcare costs in the period after compared with the period before treatment.⁶

Pharmacology

The main drugs used to treat alcohol dependence are acamprosate and naltrexone. Their profiles are shown in Box 1.

Efficacy

This review is restricted to major studies providing the highest-quality evidence. Studies were preferred if they were larger, had a longer study duration and were more recent. Studies or reviews with a more rigorous design were preferred. Only one study directly compared acamprosate and naltrexone.¹⁰

Acamprosate

There have been 16 randomised controlled trials (RCTs) comparing acamprosate and placebo, two systematic reviews of acamprosate only (by the same principal author),^{11,12} and one cost-effectiveness study of acamprosate compared with placebo¹³ (E1) (for an explanation of level-of-evidence codes, see Box 2). The efficacy of acamprosate has been evaluated in a large number of well-designed studies involving large numbers of participants with six to 12 months of treatment or follow-up. These reports have drawn very consistent conclusions. Fourteen showed a statistically significant beneficial effect for acamprosate on several measures of alcohol consumption, including time to first drink, total abstinence rate and duration of cumulative abstinence (the proportion of drinking days per unit time). Many studies have also found a satisfactory retention in treatment and reduction in laboratory indices of alcohol consumption (γ -glutamyltransferase, carbohydrate-deficient transferrin). However, one randomised controlled trial of acamprosate versus placebo showed only a modest treatment effect and poor compliance.¹⁵ Unlike the other studies, patients in this study began treatment an average of 25 days after the last

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St Vincent's Hospital, Sydney, NSW.

Robert Graham, MB BS, Alcohol and Drug Registrar;

Alex D Wodak, FRACP, Director, Alcohol and Drug Service.

Department of Drug and Alcohol Studies, St Vincent's Hospital, Melbourne, VIC.

Greg Whelan, FRACP, Director.

Reprints will not be available from the authors. Correspondence:

Dr Alex D Wodak, St Vincent's Hospital, 366a Victoria Street, Darlinghurst, NSW 2010. awodak@stvincents.com.au

drink; 32% had relapsed before starting drug therapy. The cost-effectiveness study estimated that treatment with acamprosate resulted in net savings of 528 euros (equivalent to approximately A\$880) per patient over 24 months compared with no pharmaceutical treatment.¹³

Naltrexone

There have been 11 randomised controlled studies comparing naltrexone with placebo, one meta-analysis¹⁶ and one systematic review¹⁷ of the use of opioid antagonists for alcohol dependence (E1). Naltrexone has been assessed in fewer studies overall, with smaller numbers of participants, and only one study¹⁸ extended beyond three months' duration. Naltrexone has been shown to have a statistically significant beneficial effect on several measures of alcohol consumption, including time to first drink, time to first episode of heavy drinking, duration of cumulative abstinence and number of standard drinks consumed. The Cochrane review¹⁷ also noted that such benefits were lost six months after completion of treatment.

The meta-analysis concluded that in the seven existing studies of naltrexone versus placebo, involving 804 patients, naltrexone produced a modest benefit: a reduction in relapse rates of 14% and an improvement in abstinence rates of 10%. All seven studies were of three months' duration. The incidence of at least one adverse event or discontinuation of treatment because of adverse events was comparable. However, nausea, somnolence, abdominal pain, anorexia and vomiting were significantly more common in patients treated with naltrexone. The systematic review concluded that the short-term benefits of naltrexone included an increase in total abstinence, and a reduction in the percentage of drinking days and the number of standard drinks of alcohol consumed. However, six months after the completion of treatment, the benefits of treatment were generally lost. Overall, the observed effects have been modest, and there is no evidence that these benefits extend beyond the duration of treatment.

Intention-to-treat analyses of two recent studies comparing naltrexone and placebo resulted in largely unimpressive findings.^{18,19} However, in one of these studies,¹⁹ the overall completion rate was much lower than other studies. In a recent study of older, predominantly male, patients, 12-step facilitation counselling was used in conjunction with naltrexone,¹⁸ whereas other studies tended to use coping-skills therapy or relapse-prevention training. Two recent Australian studies showed a reduction in relapse rate for naltrexone compared with placebo;^{20,21} one of these was conducted in a standard clinical setting without extensive psychosocial intervention.²¹

Acamprosate and naltrexone

In the only direct comparison of both drugs, there was no difference between treatments in time to first drink¹⁰ (E2). However, patients treated with naltrexone had a significant benefit in several measures of alcohol consumption compared with the acamprosate group. At the end of the first year, 41% receiving naltrexone and 17% receiving acamprosate had not relapsed, defined as having five or more drinks

in a day. However, in this study patients and the doctors were aware of the treatment received.

A meta-analysis for both drugs found that both drugs exerted significant, but modest, effects on drinking outcomes, with sizeable variability in results between studies²² (E1). More recent and more rigorous studies of naltrexone have found less favourable outcomes than earlier research. One systematic review concluded that both drugs achieved similar results, but naltrexone was not as well tolerated.²³ Another systematic review of a similar selection of the literature concluded that both drugs reduced the frequency and severity of drinking over most of the aforementioned end-points.²⁴ A multi-centre, placebo-controlled trial of naltrexone and acamprosate, alone or in combination, is in progress and may resolve some of these differences.²⁵

Specific indications

Formulating guidelines for pharmacotherapy of alcohol dependence is difficult because of the paucity of data from direct comparison of acamprosate and naltrexone. However, acamprosate should probably be considered the first-line treatment for patients with moderate to severe alcohol dependence, because of the larger body of supporting evidence and the benefits extending after treatment. Naltrexone is indicated for alcohol-dependent patients in whom acamprosate has not proved effective or has not been well tolerated, or for individuals whose lifestyle or past history indicates that compliance with taking medication is poor. The use of naltrexone for managing heroin dependence is controversial. However, there may be a place for prescribing naltrexone to alcohol-dependent patients who are also dependent on heroin.

Discussion

Defining clear guidelines for use of the two main pharmacotherapies (acamprosate and naltrexone) is difficult in the present state of knowledge. This difficulty stems from the fact that the various studies have examined the use of these drugs over varying groups of outcome measures and study durations. Studies of acamprosate have generally used absolute-abstinence-based measures as the primary outcomes, while naltrexone studies have also measured more relative "harm-reduction" measures, such as relapse to heavy drinking or total amount of alcohol consumed. Acamprosate appears to have a prolonged action for up to a year after therapy has ceased, but compliance with a medication requiring thrice-daily administration is often difficult. On the other hand, naltrexone has well documented efficacy, at least in the initial three months of treatment, and is easier to take on a once-daily basis. Consideration of the outcomes desired by the patient, compliance history, other drug therapy and medical conditions may all influence the choice made by the prescriber.

In patients with alcohol dependence who also suffer from chronic pain, naltrexone will cause some not insurmountable problems. In this situation, or in acute pain, analgesia can be provided by non-opioid drugs such as non-steroidal anti-inflammatory drugs (including parenteral ketorolac). Other approaches could include local or regional anaesthesia. Attempting to overcome blockade with high doses of opioids

is dangerous and not recommended outside an intensive care unit. Opioid withdrawal may be precipitated in alcohol-dependent patients treated with naltrexone if they have also been taking heroin recently. Naltrexone has been used (with uncertain benefit) for treating heroin dependence, but to avoid the problem of precipitating heroin withdrawal naltrexone should only be introduced in patients who have abstained from opioids for seven to 10 days.

The optimal duration of acamprosate or naltrexone treatment has not been established, but six months should be considered a minimum, and 12 months a more desirable duration of treatment.

It is generally recommended that naltrexone should be avoided in patients with advanced liver disease or elevated results on liver function tests. Higher than recommended doses of naltrexone may elevate liver function test results, but these dangers may be overstated. It is not clear how severe liver damage has to be before naltrexone administration becomes dangerous. Avoiding naltrexone in patients with decompensated liver disease is prudent; naltrexone should also be used with caution in patients with less severe forms of hepatic impairment. Some authors recommend that naltrexone be avoided in patients with aspartate transaminase levels three times greater than normal, while others set the limit at five-times normal.

Few studies have included many patients with the combination of severe alcohol dependence and mental illness. It is therefore unclear what effect mental illness has on the efficacy of acamprosate or naltrexone. However, one study included patients with stable mental illness and showed that they could be treated safely.²⁰

There are no existing studies on the effectiveness and safety of the combination of acamprosate and naltrexone, but there is no theoretical reason preventing the combined use of these drugs.

Acamprosate and naltrexone have been approved under the Pharmaceutical Benefits Scheme (PBS) for use in treating alcohol dependence, provided that the patient is in a comprehensive treatment program for alcohol dependence with the goal of maintaining abstinence. Each authority prescription lasts for two months. There is no stated limit to the duration of treatment, but further extension of PBS authority requires an additional application each time. The PBS subsidy reduces the price (30 days' supply) from \$170.10 (acamprosate) or \$167.28 (naltrexone) to \$22.40 (both drugs). Product information for naltrexone states that treatment duration is up to 12 weeks. However, the length of treatment is at the discretion of the prescriber.

Other drugs

Disulfiram inhibits acetaldehyde dehydrogenase, so that alcohol consumption results in a build up of acetaldehyde, causing extremely distressing symptoms, including flushing, syncope, nausea, vomiting and diarrhoea. It is available in 200-mg tablets; the usual starting dose is 100 mg daily increasing to 300 mg maximum, with 200 mg being the usual dose. It has been available for many years for treating alcohol dependence, but is prescribed rarely as compliance is

3: Managing patients who drink hazardous or harmful quantities of alcohol

Assess alcohol consumption and alcohol-related problems in all new adult patients and reassess all adult patients at regular intervals

Assess all patients presenting with alcohol-related problems

Give feedback to patients of the nature and extent of risk of alcohol-related health, social and economic complications

Where relevant, encourage patients to identify their own precise goals of treatment (reduced consumption or abstinence) and provide menu of strategies for patient to achieve these

Goal:
Reduced consumption (controlled drinking)

Strategies:

- Drinking diary
- Use strategies to slow alcohol consumption
- Identify high risk factors
- Encourage alternative activities
- Careful follow-up
- Consider pharmacotherapy if the above are ineffective

Goal:
Abstinence

Strategies:

- Arrange detoxification
- Refer to self-help group
- Consider pharmacotherapy
- Careful follow-up

often poor. Evidence of efficacy is limited, although this may be partly due to difficulties in trial design²⁴ (E1).

Nalmefene has similar properties and a proposed similar mechanism of action to naltrexone²⁶ (E2). It is not currently used to treat alcohol dependence other than in research settings.

Ondansetron, a selective 5-HT₃-receptor antagonist, has been shown in one study to have a beneficial effect on early-onset alcohol dependence²⁷ (E2), presumably by modulating dopamine release in mesocorticolimbic dopamine pathways. There is insufficient evidence to justify its routine use at present.

Other psychoactive drugs, such as lithium and some selective serotonin-reuptake inhibitor antidepressants, have been suggested, but no positive effect on alcohol dependence has been demonstrated in addition to the documented benefits in treating depression and other psychiatric conditions²⁴ (E1).

General management

When pharmacotherapy is included in the management of alcohol dependence, doctors should ensure that patients are also followed up closely and regularly, and should draw up a comprehensive treatment plan with each patient. This should include attempts to resolve any psychosocial issues. Prescribers are required to obtain a Health Insurance Commission (HIC) authority before prescribing acamprosate. The comprehensive plan can be provided by general practitioners using, where required, Expanded Primary Care (EPC) items. Engaging allied health professionals, such as alcohol and drug counsellors, may help patient management

4: Advice for patients

- Alcohol dependence is a chronic, relapsing–remitting condition.
- Treatment is moderately effective and comparable with that for many other chronic medical conditions.
- Inducing remission is usually less difficult than preventing relapse.
- It may help to attend self-help groups such as Alcoholics Anonymous <<http://www.alcoholicsanonymous.org.au/>> or the less well established Rational Recovery <<http://www.rationalrecovery.net/>>, although these interventions are difficult to evaluate and do not appeal to all. Self-help groups are also available for family members and children <http://www.al-anon.alateen.org/alalist_world.html#link02>.
- As the risk of relapse is high, it is important to try to identify high risk factors and then to develop strategies to avoid these. Relapse should be dealt with by undergoing detoxification when required.
- It is helpful to attend follow-up with a doctor with whom you can establish a strong therapeutic relationship.
- Telephone counselling services are available 24 hours a day, seven days a week:

Alcohol and drug telephone help-lines in Australia

ACT: "Alcohol & Drug Programs" (02) 6205 4545

NSW: "Alcohol and Drug Information Service (ADIS)" 9361 8000 in Sydney, 1800 422 599 elsewhere in the State

NT: "Alcohol & other Drug Service" (08) 8922 8399; Central Australia (08) 8951 7580

QLD: "ADIS" (07) 3236 2414; 1800 177 833

SA: "ADIS" (08) 8274 3333; 1300 13 13 40

TAS: "ADIS" 1800 811 994
(from interstate call 03 9416 1818)

VIC: "Directline" (03) 9416 1818; 1800 136 385

WA: "ADIS" (08) 9442 5000; 1800 198 024

and also helps fulfil HIC requirements. A comprehensive treatment plan should be tailored to the needs of the individual patient and may need to involve combinations of modalities, including detoxification, counselling, referral to self-help groups or group therapy. The diagram in Box 3 may help guide doctors through the stages of managing patients who drink hazardous or harmful quantities of alcohol.

Box 4 provides advice for patients, as well as telephone numbers for help-lines throughout Australia.

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time capsule**The general practitioner and his reading**

TO BE EFFECTIVE, medical reading should be regular and systematic. This is not always easy. The general practitioner has an exacting life and, apart from his work, many demands are made on him. However, if he wishes to read, he will find the time to devote to it. He may read from text-books or from journals.

Members of the British Medical Association in Australia receive both *The Medical Journal of Australia* and *The British Medical Journal*. In the pages of these journals most of the newer aspects of medical science are discussed and abstracts from journals of other countries are published.

In urging medical practitioners, . . . to look to their journals for their reading matter, we would suggest that each practitioner should subscribe to at least one extra journal. He would then be in a position to help his neighbour as well as himself, and he might initiate a seminar or study circle for the exchange and discussion of journals.

From time to time the statement is made that the day of the general practitioner is done, that so much is being filched from him by the major and the minor specialist on the one hand and by the governmental octopus on the other that little will remain or even now remains for him. It will be a sorry say for medicine and for the public if this should ever happen. . . .

There will always be need for the man who takes the whole of medicine for his province, and he will always be the most honoured and honourable of its servants. The general practitioner can best preserve his status by remaining a student all his days.

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