

# Long-term drug treatment of patients with alcohol dependence

## SUMMARY

Drug therapy for alcohol dependence should only be used in conjunction with a comprehensive treatment plan.

Naltrexone and acamprosate have well established efficacy and are first-line treatments.

Naltrexone is recommended for patients aiming to cut down their alcohol intake who do not have severe liver disease or an ongoing need for opioids.

Acamprosate is recommended for those who have achieved and wish to maintain abstinence.

Disulfiram is no longer considered first-line treatment due to difficulties with compliance and toxicity.

Although baclofen and topiramate have evidence of benefit, they are not registered for alcohol dependence and should only be considered in specialist practice.

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## Key words

acamprosate, alcohol dependence, baclofen, disulfiram, naltrexone, topiramate

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## Introduction

Alcohol dependence is typically a chronic, relapsing condition in which there is evidence of significant change in the motivation and control systems in the brain.<sup>1</sup> Increasingly drug therapy is focused not just on the treatment of the acute withdrawal syndrome, but on modifying these other dysregulated brain systems. It should be used in conjunction with a comprehensive treatment plan that includes appropriate psychological and rehabilitation strategies, with the aim of reducing alcohol craving, compulsive use and impaired control. There is evidence that pharmacotherapy for alcohol dependence is underused.<sup>2</sup>

Alcohol use disorders can range from mild to severe. Pharmacotherapy is generally used for people with more severe disease. In Australia, there are three drugs currently approved – oral naltrexone, acamprosate and disulfiram. Only naltrexone and acamprosate are subsidised on the Pharmaceutical Benefits Scheme (PBS). Two others, baclofen and topiramate, are now used in specialist practice but are not approved for alcohol dependence.

## Naltrexone

Naltrexone is a mu opioid receptor antagonist. It has high receptor affinity that reduces the reinforcing euphoric reward of alcohol. Naltrexone is listed on the PBS as an authority item for alcohol dependent individuals as part of a comprehensive treatment plan with a goal of abstinence. It is also recommended for patients seeking to reduce heavy drinking.<sup>3</sup>

Naltrexone reduces relapse rates after abstinence<sup>4</sup> and also helps reduce heavy drinking in people who continue drinking during treatment.<sup>5</sup> It may be given in combination with acamprosate but there is conflicting evidence for the benefit of this combination over monotherapy. It has a slightly larger effect size than acamprosate, but has more adverse effects including headache, nausea, lethargy and dysphoria. These effects are usually transient and rarely lead to cessation of therapy.

Naltrexone is an opioid antagonist so it should not be used in patients receiving long-term opioid therapy. If opioids are needed in an acute situation, naltrexone should be stopped. Naltrexone is contraindicated in acute hepatitis or liver failure, and liver function should be monitored **monthly** during therapy. Treatment is not advised in people who have alanine aminotransferase concentrations greater than 3-5 times the normal limit.

Naltrexone comes in different forms, but not all are approved in Australia. The usual dose is 50 mg a day orally, starting 4-7 days after the last drink. Naltrexone can also be used in people who are still drinking as it may help them to cut down. Patients are often started on a half tablet (25 mg) daily for the first 3-5 days to minimise adverse effects. There are no specific ill effects from alcohol consumption during treatment and patients do not need to be advised to stop therapy if they relapse.

## Acamprosate

Acamprosate is a structural analogue of gamma-aminobutyric acid (GABA). It is thought to work by

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The word 'monthly' was removed.

affecting calcium channels and modifying transmission along GABA and glutamine pathways in the brain.<sup>6</sup> This may result in decreased positive reinforcement of alcohol intake and withdrawal cravings.

Acamprosate should be considered first-line treatment for patients with alcohol dependence seeking to maintain abstinence. Five meta-analyses concluded that abstinence was significantly higher with acamprosate.<sup>6</sup> In addition, some evidence suggests that it protects neurons from damage and death caused by the effects of alcohol withdrawal-associated neurotoxicity.<sup>7</sup>

Acamprosate is generally well tolerated. The most common adverse event is transient diarrhoea. It has no abuse potential and does not interact with alcohol or drugs commonly prescribed in people with alcoholism such as antidepressants, anxiolytics, disulfiram, naltrexone and neuroleptics. It can be given to patients with liver dysfunction.

The recommended dose is two 333 mg tablets, three times a day for people over 60 kg. Guidelines recommend acamprosate is started 5–7 days after the patient's last drink, but it can be safely started during withdrawal.<sup>3</sup> Its three-times-daily dosing regimen may contribute to its reduced adherence.

### Disulfiram

Disulfiram is a deterrent drug that does not directly influence motivation to drink. It inhibits aldehyde dehydrogenase and prevents the metabolism of alcohol's primary metabolite, acetaldehyde. Drinking alcohol within two weeks of taking disulfiram results in the accumulation of acetaldehyde in the blood. This causes unpleasant effects such as sweating, headache, dyspnoea, flushing, sympathetic overactivity, palpitations, nausea and vomiting. Seizures, coma and death can occur. Patients should be educated about avoiding unintended sources of alcohol.

There is a high rate of non-adherence with this drug which can be improved when disulfiram administration is directly observed by a friend, relative or pharmacist. The maintenance dose is 200 mg daily (maximum 300 mg). Due to the risk of significant toxicity and limited evidence of effectiveness some clinical practice guidelines do not recommend disulfiram for routine use.<sup>8</sup> Informed consent discussion should be documented.

### Baclofen

Baclofen is a stereoselective GABA receptor agonist. It has been used since the 1920s to control spasticity.<sup>9</sup> Much of alcohol's acute effects on the central nervous system are mediated by its stimulation of the GABA system, which is neuroinhibitory.<sup>10</sup>

In animals, baclofen reduces alcohol's reinforcing, rewarding, stimulating and motivational properties.<sup>11,12</sup> It has been shown to reduce the risk of relapse in high-risk drinkers<sup>13–16</sup> and seems most suited to patients who have more chronic and severe disease and a history of regular high-dose drinking, including those with advanced liver disease.<sup>14</sup> It is primarily aimed at drinkers seeking to maintain abstinence but is not approved for this indication in Australia.

Baclofen is highly toxic in overdose and should be used with caution in patients with a history of overdose or other substance use as well as those with a history of psychotic illness or renal insufficiency.<sup>17</sup> Patients at risk of suicide were often excluded from trials.

The baclofen dose needs careful titration over weeks, beginning with 5 mg three times a day. The optimum dose generally ranges between 30 mg and 75 mg. Adverse effects include sedation and impairment of ability to drive or use machinery. These are exacerbated by concurrent alcohol. Baclofen may also cause nausea, visual disturbance and urinary disturbance. Abrupt cessation may result in seizures or confusion.

### Topiramate

Topiramate, a sulfamate-substituted monosaccharide related to fructose, is an antiepileptic with neuroprotective properties. It reduces the rewarding effects of acute alcohol use by suppressing dopamine release, and normalises dopamine activity in chronic alcohol use. This reduces cravings for alcohol and withdrawal symptoms.<sup>18</sup> Topiramate has mood stabilising properties and may be efficacious in bipolar disorder, borderline personality disorder and post-traumatic stress disorder. As alcohol use is often comorbid with psychiatric disorders, topiramate may be viewed as a way to address multiple disorders with one drug.<sup>19</sup>

The therapeutic effects of topiramate appear to be robust and there is evidence of better outcomes than with acamprosate, naltrexone or disulfiram.<sup>18</sup> However, it is not approved in Australia for alcohol dependence.

Adverse effects are generally mild to moderate but include dizziness, paraesthesia, psychomotor slowing, memory or concentration impairment and weight loss. A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has occasionally been reported. If there are sudden vision changes, eye pain or redness then topiramate should be ceased and medical review arranged.

Topiramate can be commenced before cessation of alcohol.<sup>18</sup> Dosing requires slow titration from 25 mg daily to a maximum of 150 mg twice daily.

## General points for managing alcohol dependence long term

People who have long-term alcohol dependence often have other social, psychological and physical difficulties. These should be addressed with a comprehensive treatment plan.

The usual medication treatment period is at least 3–6 months, but the decision on treatment duration should be made on a case-by-case basis. Long-term follow-up of patients after an intensive treatment program is recommended. Drug treatment needs to be combined with counselling and psychological therapies.<sup>3</sup>

Naltrexone has been used cautiously in pregnancy due to an absence of known harmful effects, but acamprosate, disulfiram, baclofen and topiramate are contraindicated. Consultation with a specialist is recommended for patients using multiple medicines or with serious medical or psychiatric conditions.

### Thiamine

Thiamine administration is important for patients withdrawing from alcohol. Treatment is subsidised on the PBS for Aboriginal and Torres Strait Islander people. There is evidence that parenteral thiamine is underused and that oral therapy is often ineffective.

Australian guidelines recommend that healthy patients with a good diet take oral thiamine 300 mg per day for 3–5 days, then 100 mg for a further 4–9 days. For chronic drinkers who have a poor diet, intramuscular or intravenous thiamine 300 mg per day for 3–5 days is recommended, followed by oral thiamine 300 mg per day for several weeks.<sup>3</sup>

## Conclusion

Alcohol dependence fits a chronic disease model. Primary care uptake of pharmacotherapeutic drugs for long-term alcohol relapse prevention remains insufficient. Naltrexone and acamprosate are first-line treatments with well established efficacy. Naltrexone is recommended for patients aiming to cut down alcohol but cannot be used in those who have severe liver disease or need opioids. Acamprosate is recommended for people who have achieved abstinence and want to maintain it.<sup>20</sup> Disulfiram is no longer considered first-line treatment due to difficulties with adherence and toxicity. Baclofen and topiramate have evidence of benefit but are not approved in Australia for this indication and should be used only after specialist consultation. ◀

*Conflict of interest: none declared*

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