

Chapter 7. Pharmacotherapies for alcohol dependence

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This chapter provides a description of empirically supported pharmacological approaches for preventing relapse in alcohol dependence.

Three medications – naltrexone, acamprosate and disulfiram – are licensed in Australia for the treatment of alcohol dependence. Prescribers are referred to the MIMS Annual for detailed information about naltrexone, acamprosate and disulfiram (listed and marketed respectively as ReVia®, Campral® and Antabuse®).

Pharmacotherapy should be considered for all alcohol-dependent patients following detoxification. They are best used in association with psychosocial supports as part of an after-care treatment plan. For some, medication is associated with a critical period of sobriety, during which the patient can learn to maintain abstinence or reduced alcohol consumption. Specifically:

- **Naltrexone** and **acamprosate** have been shown to improve treatment outcomes when combined with psychosocial intervention. For patients who are motivated to take the medication, both are potential tools for reducing alcohol use and the core symptoms of alcohol dependence.
- The evidence for **disulfiram** is weaker, but the drug remains an option for relapse prevention in certain circumstances, and can be effective as part of a comprehensive treatment approach.

Despite evidence of their efficacy in reducing alcohol relapse following detoxification, these medications remain under-used in Australia.

Recommendation	Strength of recommendation	Level of evidence
7.1 Pharmacotherapy should be considered for all alcohol-dependent patients, in association with psychosocial supports.	A	Ia

Naltrexone

Naltrexone is an orally active opioid receptor antagonist. By blocking μ -opioid receptors, naltrexone reduces levels of dopamine (the major reward neurotransmitter in the brain) in response to alcohol use, reducing the rewarding effects of alcohol. Naltrexone reduces the rate of relapse to heavy drinking and increases the number of abstinence days in alcohol dependent patients. Meta-analyses suggest that compared to placebo, naltrexone reduced the relative risk ratio for relapse to heavy alcohol use by 36 per cent; the number needed to treat is seven, suggesting a moderate effect size for maintaining abstinence.

However, naltrexone has been shown to reduce the rewarding effects of alcohol, reduce craving and decrease the amount and frequency of drinking when relapse occurred. It has been shown to be more effective in reducing rate and severity of relapse rather than in maintaining abstinence. While most controlled studies of naltrexone treatment have been in conjunction with intensive psychosocial services (such as counselling), it has nevertheless also been effective in physician-led treatment with regular monitoring.

Naltrexone is licensed in Australia as an oral tablet preparation. No long-acting naltrexone products are currently licensed in Australia. A long-acting (monthly) depot intramuscular injection of naltrexone has been developed and is licensed in the United States. This agent looks promising and avoids problems of poor adherence, however it is not yet available for use in Australia.

Suitability for naltrexone

While little evidence is available to directly inform decisions about what patient populations are most suited to naltrexone treatment, some evidence and clinical expertise suggests:

- Success can be achieved with patients who are alcohol dependent and are medically stable
- Naltrexone may be more effective for preventing relapse to heavy or problem drinking and reducing high levels alcohol consumption than for maintaining abstinence from alcohol.
- Patients currently using opioids or who require opiate-based pain relief are not suitable candidates for naltrexone use.
- Naltrexone is contraindicated for people with acute hepatitis or severe liver failure, or with a history of sensitivity to naltrexone. It can be prescribed to patients with moderate elevation of liver function tests (up to approximately five times the normal values).
- No well-controlled studies of the safety of naltrexone during pregnancy or lactation have been done.
- The safety of using naltrexone for patients younger than 18 years old has not been established.
- Some reports show that patients with significant depression or more severe alcohol dependence respond less well to naltrexone treatment. Regular monitoring for depression is recommended.

Recommendation	Strength of recommendation	Level of evidence
7.2 Naltrexone is recommended as relapse prevention for alcohol-dependent patients.	A	1a

Interaction with other drugs

Naltrexone induces precipitated opiate withdrawal in patients who are currently opiate dependent. It is contraindicated in patients with current or recent use of opioid medication (such as codeine, morphine, oxycodone, methadone).

Naltrexone is a long-acting drug and will block the effects of opioids when they are used after commencement of naltrexone treatment. Naltrexone should be discontinued 48 to 72 hours before any situation where opioid analgesia may be needed (such as in patients undergoing elective surgery).

Naltrexone does not appear to alter the absorption or metabolism of alcohol; however, some patients have reported nausea after drinking alcohol while taking naltrexone.

The interaction of naltrexone and most other medications has not been tested. However, caution should be exercised when combining naltrexone with other drugs known to have hepatotoxicity. For example, it is not recommended to combine naltrexone and disulfiram.

Concurrent administration of naltrexone with antidepressants appears to be safe.

Recommendation	Strength of recommendation	Level of evidence
7.3 Naltrexone is not suitable for people who are opioid dependent or who have pain disorders needing opioid analgesia.	S	–

Starting treatment

It is not known whether patients with a diagnosis of alcohol dependence achieve better outcomes if abstinent before taking naltrexone. However, some period of abstinence (at least three days) was the requirement of most clinical trials investigating the effectiveness of naltrexone. Recommending such a period of abstinence (three to seven days after the patient's last drink) will allow resolution of major acute withdrawal symptoms before starting treatment.

A medical history should be taken (see Chapter 2) and should include assessment for signs of chronic liver disease and hepatic failure. The assessment of hepatic insufficiency is done through clinical examination and liver function tests.

Once assessment is complete, discuss treatment goals and plan with the patient. Provide patient education about how the medication works, the side effects and realistic expectations about cravings. Arrange for a follow-up visit within one week, as early dropout is common.

Recommendation	Strength of recommendation	Level of evidence
7.4 Naltrexone should be started as soon as possible after completion of withdrawal (usually 3 to 7 days after last drink).	A	Ib

Dosage

Naltrexone is formulated in tablets of 50 mg; the recommended dose is 50 mg (one tablet per day, orally) with meals. It may be preferable to start with half a tablet (25 mg per day) for several days, and increase to 50 mg after any adverse effects have subsided.

Adverse effects and their management

Naltrexone is usually well tolerated. Common adverse effects include nausea, headache, dizziness, fatigue, nervousness, insomnia, vomiting, and anxiety in about 10 per cent of patients. These generally subside with time (usually days). Depression and dysphoria have also been reported as side effects of naltrexone.

The following strategies are recommended:

- educate the patient about expected side effects and duration
- establish a routine for timing doses – should ideally be taken in the morning with food or split between morning and evening
- introduce medication gradually (25 mg for one to two days)
- consider dose reduction (half tablets at 25 mg per day), slow titration, and stopping the medication for three to four days before reintroducing it at a lower dose
- distinguish between prolonged alcohol withdrawal symptoms and side effects of naltrexone by beginning treatment once the major features of alcohol withdrawal have subsided (generally three to 5 days after drinking cessation).

Treatment duration

The most appropriate duration of treatment continuation in alcohol-dependent patients is not yet known.

The usual treatment period is at least 3 to 6 months, but the decision on treatment duration should be made on a case-by-case basis between the patient and doctor, based on side effects, history of relapse, social and family circumstances, and other factors known to affect the patient.

Recommendation	Strength of recommendation	Level of evidence
7.5 Naltrexone is usually taken for at least 3 to 6 months.	D	IV

Clinical considerations during treatment

Treatment should continue even if the patient lapses; psychosocial relapse prevention techniques should be used to deal with the lapse or relapse (see Chapter 6).

It is also important to monitor and attend to the patient's physical and mental health.

Ending naltrexone therapy

No evidence of a withdrawal syndrome or development of dependence following use of naltrexone exists. Psychosocial relapse prevention should continue beyond the end of pharmacotherapy.

Acamprosate

Acamprosate is thought to reduce drinking by modulating the brain GABA and glutamate function, which is implicated in withdrawal symptoms. The drug only reaches desired levels in the brain after 1 to 2 weeks.

Meta-analyses of randomised controlled trials indicate that acamprosate is effective in maintaining abstinence from alcohol following withdrawal in dependent drinkers; the relative risk ratio is 1.3 to 1.5 in the first 6 months, and the number needed to treat is 7.5 over placebo.

Suitability for acamprosate

Little evidence exists to directly inform decisions about what patient populations are most suited to acamprosate treatment. However, some evidence and clinical expertise suggests that:

- acamprosate may be effective for patients who are alcohol dependent and are medically stable; as well as for those willing to comply with the dosing regimen
- acamprosate may be most effective for patients with an abstinence goal, rather than preventing excessive drinking in non-abstinent patients
- acamprosate is contraindicated in patients with a known hypersensitivity to the drug, renal insufficiency or severe hepatic failure
- the safety of acamprosate in pregnancy or lactation has not been established, so it should not be administered to women who are pregnant or breastfeeding.

Recommendation	Strength of recommendation	Level of evidence
7.6 Acamprosate is recommended as relapse prevention for alcohol-dependent patients.	A	Ia

Interaction with other drugs

Acamprosate does not interact with alcohol.

The calcium component in acamprosate may render tetracycline inactive.

Starting treatment

Acamprosate dosing is recommended to begin three to seven days after the patient's last drink and after resolution of any acute withdrawal symptoms. Acamprosate could be safely initiated during alcohol withdrawal, but starting acamprosate at the beginning of detoxification compared to after detoxification has not been shown to improve treatment outcomes.

Medical history should be taken (see Chapter 3). Physical examination may include assessment for signs of chronic liver disease and hepatic failure. The assessment of hepatic insufficiency is done through clinical examination and liver function tests. Investigations may include liver function tests and, since 90 per cent of acamprosate is excreted through the kidney, tests of kidney function (urea and electrolytes).

Once assessment is complete, discuss treatment goals and plan with the patient. Provide patient education about how the medication works, the side effects and realistic expectations about cravings. Arrange for a follow-up visit within one week, as early dropout is common.

Recommendation	Strength of recommendation	Level of evidence
7.7 Acamprosate should be started as soon as possible after completion of withdrawal (usually 3 to 7 days after last drink).	A	Ib

Dosage

Acamprosate is formulated in oral tablets of 333 mg; the recommended dose for adults is 1998 mg with meals (6 tablets per day – 2 tablets in three doses). Adults under 60 kg should take 1332 mg/day (4 tablets per day in 3 doses: 2, 1, 1).

Adverse effects and their management

Acamprosate is usually well tolerated. Its predominantly gastrointestinal adverse effects, commonly diarrhoea, usually resolve spontaneously within days. Mild abdominal pain, rash or isolated pruritus, paraesthesiae, altered libido and confusion have been reported at low frequencies.

The clinician should educate the patient about expected side effects and duration; and should distinguish between prolonged alcohol withdrawal symptoms and side effects of acamprosate by beginning treatment once the more pronounced features of withdrawal have subsided (after first 3 to 5 days).

Treatment duration

The usual treatment period is 3 to 6 months. However, the decision on the duration of treatment should be made on a case-by-case basis between the patient and doctor, taking into account side effects, history of relapse, social and family circumstances and other individual factors.

Recommendation	Strength of recommendation	Level of evidence
7.8 Acamprosate is usually taken for at least 3 to 6 months.	D	IV

Clinical considerations during treatment

Treatment should continue even if the patient lapses; the clinician should use psychosocial relapse prevention techniques to deal with the lapse or relapse (see Chapter 6).

The clinician should regularly monitor the patient's progress and attend to any physical, mental health and social issues the patient may be facing.

As some patients will find it difficult to adhere to a medication regimen that involves taking tablets three times a day for long periods, the clinician should devise strategies to increase the likelihood of patients taking their medication (see 'Increasing medication adherence' below).

Ending acamprosate therapy

No evidence exists of a withdrawal syndrome following use of acamprosate or of developing dependence. Psychosocial relapse prevention interventions should continue beyond the end of pharmacotherapy.

Combined acamprosate and naltrexone

Given the different theoretical approaches of acamprosate and naltrexone in reducing alcohol consumption, some clinicians administer both medications concurrently. Studies have found this to be a safe and promising approach. Most evidence suggests that while combined acamprosate and naltrexone may be more effective than acamprosate alone, it is no more effective than naltrexone alone.

Disulfiram

Disulfiram primarily works by inhibiting the action of aldehyde dehydrogenase, an enzyme involved in the second step in the metabolism of alcohol, namely the conversion of acetaldehyde to acetate. This leads to accumulation of acetaldehyde following consumption of alcohol. The resulting unpleasant symptoms – flushing, dizziness, nausea and vomiting, irregular heartbeat, breathlessness and headache – are due to the toxicity of accumulated acetaldehyde.

Disulfiram acts as a deterrent to drinking because the patient expects to experience these negative consequences. Evidence indicates that disulfiram is most effective when the medication is provided to the patient under supervision.

Suitability for disulfiram

Disulfiram is an appropriate medication for patients who:

- are motivated to abstain from alcohol
- accept the need for external control of their drinking and are prepared to be supervised in their daily medication use
- have a spouse, family member or friend willing to supervise and monitor medication use
- have no medical or psychosocial contraindications.

The treating clinician should undertake a risk–benefit analysis of using disulfiram to discover any **medical or psychosocial contraindications before recommending use of this treatment**. Monitoring of cardiac and liver condition is recommended. The intensity of the disulfiram–alcohol reaction varies among patients and in rare cases may result in cardiovascular collapse, myocardial infarction, respiratory depression, convulsion and death. Accordingly, treatment is contraindicated for patients with significant cardiovascular, hepatic or pulmonary disease. Some patients most suited to disulfiram in other respects may suffer from these problems.

The enzyme that metabolizes dopamine into norepinephrine and epinephrine is inhibited by disulfiram, which may result in exacerbation of psychosis. Nonetheless, a trial in a psychotic population did not reveal significant problems.

Disulfiram treatment is best suited to people with social supports, such as family, who will help **supervise medication adherence**. Supervision has a marked effect on adherence and greatly improves the effectiveness of this intervention.

A written ‘disulfiram agreement’ should be considered between a carer and patient (see Appendix 7). While a spouse or partner can be an obvious choice to supervise medication adherence, it is important to stress that the spouse cannot be expected to control their partner’s drinking. However, a disulfiram agreement is an important part of effective disulfiram treatment. The agreement should include an outline of the likely effects of drinking and products that may need to be avoided (such as some mouthwashes), recognition that the patient will allow the medication to be supervised, that the carer will be the supervisor and that the supervisory role includes contacting the health professional if medication compliance becomes a problem.

Recommendation	Strength of recommendation	Level of evidence
7.9 Disulfiram is recommended in closely supervised alcohol-dependent patients motivated for abstinence and with no contraindication	A	Ib

Interaction with other drugs

The basis of disulfiram’s therapeutic effect is that it interacts with the metabolism of alcohol.

It increases the blood concentration of benzodiazepines, caffeine, phenytoin, tetrahydrocannabinol, isoniazid, barbiturates, anticoagulants, tricyclic agents and paraldehyde.

Disulfiram should not be given concomitantly with paraldehyde because paraldehyde is metabolized to acetaldehyde in the liver.

Starting treatment

Treatment should begin after detoxification, approximately 3 to 7 days after drinking cessation.

The clinician should take the patient's medical history (see Chapter 3), and discuss the effects of the drug when alcohol is taken. This is an important part of the therapeutic strategy, as the patient's anticipation of its effects will greatly enhance the drug's effectiveness as a deterrent against drinking.

Discuss motivation, supervision, and the role of a treatment contract with the patient.

Disulfiram should be seen as an aid that does not detract from the patient's own responsibility in maintaining abstinence.

Dosage

Disulfiram is formulated in tablets of 200 mg; the recommended dose is 200 to 400 mg (1 to 2 tablets per day orally). Some patients can continue to drink on 200 to 400 mg without significant adverse effects, and the dose should be increased. The maintenance dose should generally not exceed 600 mg a day. In many patients, two or three doses per week may be sufficient, and this approach may be more practical and easier to schedule with supervision.

Adverse effects and their management

Some of the common adverse effects of disulfiram include drowsiness, nausea, headache and fatigue. Some patients may report taste disturbance (metallic or garlic-like). Rarely, jaundice, hepatitis (sometimes fatal), peripheral neuropathy, psychosis, confusion, optic neuritis, blood dyscrasias and rash may occur.

Clinicians should educate patients about expected side effects and duration; and should distinguish between prolonged alcohol withdrawal symptoms and side effects of disulfiram by beginning treatment once the more pronounced features of withdrawal have subsided (after the first 3 to 5 days). Patients should be advised to stop taking disulfiram at once and tell their doctor if they notice yellowing of the whites of their eyes, dark urine or pale bowel motions.

Even very small amounts of alcohol may cause unpleasant effects. Clinicians should advise patients to avoid using alcohol in cooking and choose skin and oral hygiene products (such as perfumes, body lotions, mouth washes) that do not contain alcohol. Some medicines contain alcohol and should also be avoided. However, the strength of the alcohol–disulfiram interaction varies between individuals. Some patients react to very small amounts of alcohol, others have little reaction when consuming large quantities of alcohol.

Treatment duration

Disulfiram is likely to be a useful treatment for the first 3 to 6 months of treatment. Longer-term studies are not available, however there are anecdotal reports of long-term (years) of successful disulfiram treatment in some patients. The decision on treatment duration should be made on a case-by-case basis between the patient and doctor, based on side effects, history of relapse, social and family circumstances and other individual factors.

Clinical considerations during treatment

Treatment should be suspended if the patient lapses; psychosocial relapse prevention techniques should be used to deal with the lapse or relapse (see Chapter 6). Disulfiram may be recommenced after 48 hours abstinence.

Recommendation	Strength of recommendation	Level of evidence
7.10 Disulfiram is usually taken for at least 3 to 6 months.	D	IV

Ending disulfiram therapy

Alcohol metabolism returns to normal between 7 and 10 days (sometimes three weeks) after stopping disulfiram, as new enzymes must be synthesised. Patients may experience adverse reaction if they drink alcohol within 7 days after stopping treatment. Psychosocial relapse prevention interventions should continue beyond the end of pharmacotherapy.

Other medications

Several new agents are emerging in the literature. These include **anticonvulsants**, such as gabapentin and topiramate; **antipsychotic medications**, such as olanzapine and aripiprazole; and baclofen, a **skeletal muscle relaxant**.

While these medications appear promising as agents in reducing alcohol relapse, the need for further controlled trials and the cost of these agents means they cannot be recommended for use as first-line treatments for alcohol dependence.

While some patients commonly seek **benzodiazepines**, no studies support their efficacy in reducing alcohol use beyond the immediate withdrawal period, and indeed there may be adverse effects of benzodiazepine dependence and interaction with alcohol.

Antidepressants are not recommended as relapse prevention agents in alcohol dependence.

Minimal evidence exists for the efficacy of **serotonergic agents** (such as selective serotonin reuptake inhibitors [SSRIs], buspirone and ondansetron) for treating the main symptoms of alcohol dependence. However, these agents may have a role in certain patients who have concomitant symptoms of anxiety or depression; evidence suggests they are effective for these symptoms in the presence of alcohol use (see Chapter 9 and Chapter 10).

Recommendation	Strength of recommendation	Level of evidence
7.11 A range of medications appear promising agents in reducing alcohol relapse (such as topiramate, gabapentin, baclofen, aripiprazole); however, need further research and are not recommended as first-line options at this stage.	B	II
7.12 Benzodiazepines and antidepressants are not recommended as relapse prevention agents in alcohol dependence.	B	II

Integration with psychosocial treatments

Treatment is significantly more successful when the patient is receiving concurrent psychosocial treatment. Referral to specialist counselling or drug and alcohol services may be appropriate (see also Chapter 6), and should include close communication between service providers. Pharmacotherapy for relapse prevention should be accompanied by close follow-up by the prescribing clinician.

Increasing medication adherence

Alcohol pharmacotherapy has been shown to be more effective than placebo among highly compliant participants. However, adherence rates of alcohol dependent patients are generally low, consistent with many chronic health conditions.

Poor medication adherence may be due to relapse to heavy drinking, adverse side effects, stigma attached to taking medication for an alcohol use disorder, no immediate reward for complying with these pharmacotherapies, and/or fears about the safety and side effects of the medication.

Adherence to pharmacotherapies may be assisted by:

- Eliciting the patient's thoughts and concerns about taking medication and using cognitive restructuring techniques to help them change unhelpful or maladaptive thoughts about taking medication.
- Providing the patient with a realistic view of the way in which the medication can help, its side effects, and any risks associated with its use.
- Using motivational interviewing techniques to help the patient to identify their personal costs and benefits of taking the medication.
- Providing the patient (and carers) with some take-home reading material about the medication.
- Tailoring the psychosocial intervention according to the patient's drinking goal: some studies show that coping skills training combined with naltrexone is better for helping patients cope with lapses and relapses, whereas supportive therapy is more effective in helping patients maintain abstinence.
- Following up patients who miss appointments.

Compliance therapy, based on these cognitive behavioural and motivational interviewing techniques, has demonstrated effectiveness in increasing medication compliance in alcohol dependent patients. Adherence may also be a problem in patients who suffer cognitive impairment from chronic drinking. Aids to enhance adherence in such instances include family supervision, medication calendars, special containers, dispensing systems, reminders and follow-up monitoring from health professionals.

Recommendation	Strength of recommendation	Level of evidence
7.13 Medication compliance can be improved with use of adherence enhancing strategies.	B	Ia

Selecting medications for individual patients

Available evidence does not enable clear recommendations as to which medication is best suited to individual patients. Deciding on choice of medication includes consideration of:

- **Available evidence:** the general conclusions from various meta-analyses suggest that acamprosate and disulfiram appear better suited to those seeking to achieve complete abstinence from alcohol, whereas naltrexone seems better directed at treatments where reduced or controlled drinking is the goal.
- **Individual patient factors:** such as side effects, prior experience with medications, treatment goals, capacity to adhere to treatment regimen, concomitant medical conditions.
- **Resource factors:** the cost of some medications (for example, topiramate, gabapentin, aripiprazole) will be prohibitive for some patients. Disulfiram treatment is best suited to people with social supports (such as family) that will help supervise medication adherence.

