

Chapter 7 Pharmacotherapies for alcohol dependence

Overview of Pharmacotherapies

Three medications: acamprosate, naltrexone and disulfiram have been approved for use as part of a comprehensive treatment plan for alcohol dependence.

Acamprosate and naltrexone have been shown to improve treatment outcomes when combined with a psychosocial intervention (e.g. Mann et al. 2004; Bauza et al. 2004). For patients who are motivated to take the medication, both are potential tools for reducing 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 (e.g. Laaksonen et al. 2008).

Pharmacotherapy should be considered for all alcohol-dependent patients following management of withdrawal. They are best used in association with psychosocial supports as part of an after-care treatment plan.

Overview of Pharmacotherapies: Reviews and meta-analyses

An extensive overview of the clinical data on pharmacotherapy for alcohol dependence was published by Mann et al. (2004). This review concentrates on naltrexone, acamprosate and disulfiram but also mentions SSRIs, tricyclic antidepressants, benzodiazepines and all other drugs for which data were available at the time, with results of all the published clinical trials. Acamprosate produced the most beneficial effects in maintaining abstinence, having been evaluated in 16 controlled clinical trials with 4500 patients. Naltrexone appeared to have different effects and proved to be useful in reducing craving (i.e. in reducing relapses rather than maintaining abstinence). The conclusions reached were that pharmacotherapy should be considered for all alcohol-dependent patients, and be used in association with psychosocial support.

A systematic review and analysis of 33 studies was carried out by Bouza et al (2004). The number of patients involved was 4000 with DSM-III or DSM-IV criteria for dependence (all had undergone detoxification). Thirteen trials compared acamprosate with placebo; 19 compared naltrexone with placebo, and 1 compared acamprosate with naltrexone. The main findings were that acamprosate was associated with a significant improvement in abstinence rate and days of cumulative abstinence, and that short-term administration of naltrexone reduced the relapse rate significantly but was not associated with significant improvement in the abstinence rate. The side-effects of naltrexone were more numerous, but it was tolerated acceptably without compromising adherence to treatment. The overall conclusions were that acamprosate appeared to be better in achieving abstinence, whereas naltrexone seemed to be better directed at treatments where controlled drinking is the goal.

This thesis is discussed and elaborated on in a recent meta-analysis of unreported data (Rosner et al. 2008). The authors say that their primary objective was to complete the efficacy profiles for acamprosate and naltrexone and compare them with each other. Another (unstated) goal perhaps was to diminish publication bias, when negative trial results are less likely to be reported. Unreported results of registered clinical trials were requested from study investigators; they were restricted to randomised placebo-controlled trials of either acamprosate or naltrexone or both. Intention-to-treat analysis was carried out for all dichotomous variables. There were 21 trials of acamprosate, and 20 with naltrexone. Confounding and defining factors were that some patients were abstinent and a subgroup were not; some were outpatients and others not, recruitment procedures differed, and different types of psychosocial interventions were utilised. Conclusions reached were that there are specific therapeutic advantages in each drug, as they have different mechanisms of action: acamprosate is more effective in aiding abstinence and naltrexone in reducing of craving.

Overview of Pharmacotherapies: Randomised controlled trials

Efficacy of naltrexone and acamprosate were compared in a multi-centre, randomised double-blind, placebo controlled trial conducted in Australia (Morley et al. 2006). Results from 94 subjects who completed the study (of 169) showed that there were no differences between groups on outcome measure of drinking, craving or biochemical markers. Intention-to-treat analysis also showed similar results. A secondary survival analysis, on subjects with low baseline levels of dependence, did, however, demonstrate the efficacy of naltrexone in increasing the number of days to relapse relative to acamprosate. A further analysis comparing naltrexone to acamprosate in reducing craving showed that naltrexone had a greater effect on drinking when level of craving was high (Richardson et al. 2008).

The COMBINE study conducted in the USA (Anton et al. 2006) was designed to evaluate the efficacy of pharmacotherapy, behavioural therapy and their combinations for treatment of alcohol dependence and to evaluate placebo effect on overall outcome. This large RCT involved 1383 patients with the diagnosis of alcohol dependence, recently abstinent from alcohol. The treatments included naltrexone and acamprosate (alone or together), placebo (single or double), each with or without a combined behavioural intervention (CBI). The CBI integrated cognitive behavioural therapy, motivational interviewing and 12-step facilitation and was delivered by trained behavioural health specialists in up to 20 sessions of 50 min duration. All the above groups received medical management. The treatment was of 16 weeks duration. It was found that at the end of the treatment period, participants in all nine different treatments and combined interventions showed reductions in drinking, including the placebo group. Patients who received naltrexone alone, naltrexone with CBI or CBI and placebo had higher percent of days abstinent (80.6, 79.2 and 77.1 respectively) when compared to placebo group (i.e. medical management only). Naltrexone significantly increased the time to the first heavy drinking day (Hazard Risk, 0.72; 97.5% confidence interval, CI, 0.53-0.98; $p = 0.02$). Patients receiving acamprosate either alone or in combination with CBI and/or naltrexone had not significantly reduce their drinking when compared to placebo group. At one year follow up the between group differences maintained a similar trend but were no longer significant. The results of this clinical trial are in contradiction with many previously conducted studies investigating the efficacy of acamprosate in treatment of alcohol dependence.

The study found no beneficial effect of combining pharmacotherapy and behavioural interventions on improvements in outcome. It has been suggested that the variability between treatment providers may be more important than the variability between treatments (Bergmark 2008; Buhringer and Pfeiffer-Gerschel 2008).

A randomised open-label trial conducted in Finland compared the effectiveness of disulfiram, acamprosate and naltrexone in 243 treatment-seeking alcohol dependent patients over two and a half years (Laaksonen et al. 2008). In the first 12 weeks of the trial patients received supervised naltrexone, acamprosate or disulfiram (50, 1998, or 200 mg, respectively, per day) plus a brief manual-based cognitive-behavioural intervention. By the end of this period, 25% had dropped out. The second phase took place over weeks 13-52, during which patients were instructed to take the medication in connection with craving or when a relapse was imminent (a targeted medication phase). Intake during the targeted medication phase was relatively low, with 87% taking medication once a week. At the end of the second phase period, 52% of the original sample had dropped out, with no significant differences between medication groups, thereby diluting the power of the study. During the first 12 weeks disulfiram was better than naltrexone and acamprosate in reducing time to first incidence of heavy drinking in reducing the number of heavy drinking days ($p < 0.001$), increasing time to the first drink ($p < 0.0002$) and increasing the number of abstinent days ($p < 0.0001$). During the second phase there were no significant differences in most of the above measures between groups, but abstinence days were significantly more frequent in the disulfiram group than in the naltrexone group ($p = 0.0005$) and in the acamprosate group ($p = 0.0097$). The average alcohol consumption in all groups remained significantly lower than at the baseline. Over the entire 52-week period disulfiram was significantly better than naltrexone or acamprosate in increasing the time to first drink ($p = 0.001$). Supervised disulfiram appeared superior to naltrexone and acamprosate, especially during the continuous medication period.

Summary

There is evidence of effectiveness for all three types of pharmacotherapies in reducing alcohol consumption in patients with alcohol dependence. Evidence is stronger for naltrexone and acamprosate, but disulfiram remains an option for some patients. The majority of effectiveness trials of the pharmacotherapies involved some type of psychosocial interventions, or structured medical management. There is evidence of an additive effect of psychosocial interventions such as cognitive behavioural therapy (CBT), and naltrexone (see below).

Recommendation	Strength of recommendation	Level of evidence
7.1 Pharmacotherapy should be considered for all alcohol-dependent patients, in association with psychosocial supports.	A	1a

Naltrexone (NTX)

Naltrexone is an opioid receptor antagonist. By blocking mu- opioid receptors, naltrexone reduces levels of dopamine (the major reward neurotransmitter in the brain) and reduces alcohol intake (Gonzales and Weiss 1998).

Effectiveness of naltrexone: Meta-analyses and reviews

The most recent (and only) meta-analysis comes in the Cochrane review of 2004 (Srisurapanont and Jarusuraisin 2005). Articles selected for review were from the period 1966-2001. There were 2 trials of nalmefene and all the others (n = 27) were of naltrexone; the total number of participants was 3048. The authors' findings were (i) that several lines of high-quality evidence supported the short-term treatment with naltrexone for preventing relapse- the relative risk ratio (RR) for decreasing short-term relapse was 36%, with the number needed to treat (NNT) at 7, compared to placebo; (ii) that alcohol-dependent patients using naltrexone were more likely to accept the treatment program; and (iii) apart from its small benefits on time to first drink and craving, no available evidence supported a meaningful benefit after 12 weeks of treatment (Srisurapanont and Jarusuraisin 2005). There was no evidence to support the use of nalmefene in clinical practice for alcohol dependence.

Roozen et al. (2006) conducted a systematic review of the effectiveness of naltrexone in the maintenance both of opioid and alcohol dependence, summarising the evidence existing up until March 2004. We only discuss the alcohol studies here. The aims were to study the effects of naltrexone compared to placebo in the maintenance treatment of dependence; and to study whether combining naltrexone with psychological treatment was more effective than naltrexone alone. Seventeen alcohol studies were identified as fitting the Cochrane quality criteria. Conclusions from the analyses were that there is: (i) strong evidence that naltrexone is superior to placebo regarding medium term relapse rates; (ii) strong evidence that there is no difference in terms of continuous abstinence; (iii) strong evidence in favour of naltrexone reducing percentage of drinking days; (iv) conflicting evidence regarding time to first relapse; and (v) strong evidence that there is no difference in time to first drink; (v) CBT increases effectiveness of naltrexone. In a number of individual studies treatment compliance was significantly correlated with positive outcomes. Six studies were included that reported follow-up or long-term results. Conclusions drawn from the pooled effects of these studies were that there is moderate evidence in favour of the use naltrexone concerning relapse rate, and there was no difference in the long-term effects of naltrexone on percentage of drinking days and time to relapse in when compared to placebo.

Almost all studies provided some form of psychosocial treatment. Although it was not detailed in many cases, cognitive behaviour therapy including relapse prevention and coping skills were used in most. It is recommended in the review above that naltrexone should be delivered in combination with psychological interventions (Srisurapanont and Jarusuraisin 2005). Conclusions drawn from the analysis by Roozen et al. (2006) were that there was evidence that the combination with CBT increases the effectiveness of naltrexone treatment, as discussed above.

Effectiveness of naltrexone: Randomised controlled trials

Anton et al. (2005) conducted a USA-based randomised controlled trial with 4 arms (naltrexone or placebo combined with either CBT or with Motivational Enhancement Therapy, MET) among 160 outpatient alcohol dependent patients. The authors conclude that the CBT- naltrexone group did better than the others on a variety of outcome measures. Naltrexone increased the time to first relapse. They also state that although MET is easier to deliver, the combination of MET and naltrexone was less effective than CBT in this case. They also note that the positive CBT- naltrexone

outcomes emerged over time; it is possible that the skills acquired and augmented by CBT in conjunction with the pharmacological assistance provided by naltrexone have a complementary effect in mutually reinforcing the active ingredients of each.

Another randomised controlled trial of naltrexone was conducted with 153 early problem drinkers, of whom 130 (86%) completed the 8-week program (Kranzler et al. 2004). This study compared naltrexone with placebo on a daily or targeted basis. 'Targeted' treatment was defined as encouraging patients to take at least 2 and a maximum of 5 tablets per week in anticipation of high-risk situations. All patients received additional brief skills training. Both the targeted and daily basis groups reduced their drinking days (14% fewer days) when compared to placebo. Patients receiving targeted naltrexone showed an initial decline in heavy drinking, followed by an increase when the number of tablets they had been given became fewer, while the daily naltrexone group continued their decline in heavy drinking all through the trial. Daily diaries were kept by all patients to record drinks and medications taken. Conclusions reached by the authors were that targeted naltrexone – providing adequate numbers of tablets are available – and combined with at least some skills training, is effective in reducing heavy drinking, at least in highly-educated and compliant patients. A substudy of this one examined the effects of daily interpersonal events on heavy drinkers (Armeli et al. 2006), and found that participants had at least one drink more on days that were characterised by higher levels of either positive or negative interpersonal events, especially events that were celebratory in nature.

Tidey et al. (2008) randomised 180 non-treatment-seeking heavy drinkers 63% of whom were alcohol-dependent, to daily naltrexone or placebo for 3 weeks. Naltrexone was effective in reducing the percentage of drinking days in all participants and also decreased the percentage of heavy drinking days in those with the D4 dopamine receptor (DRD4) gene polymorphism (DRD4-L genotype). The mu-opiate receptor (OPRM1) gene polymorphism did not operate in any of the naltrexone effects. No counselling interventions were reported; however, participants received regular prompted messages on handheld computers reminding them to complete their daily diaries of alcohol consumption, mood and urge to drink, activity, location and setting for drinking and this may have helped to reinforce their treatment.

Effectiveness of naltrexone: Summary

Effectiveness of naltrexone in reducing the rate of relapse to heavy drinking and increasing the number of abstinence days in alcohol dependent patients has been supported by a number of meta-analyses and reviews. Meta-analyses suggest that compared to placebo, naltrexone reduces the relative risk ratio (RR) for relapse to heavy alcohol use by 36%, with the number needed to treat (NNT) at 7, suggesting a moderate effect size for maintaining abstinence (Streeton and Whelan 2001; Krantzler and Van Kirk 2001; Srisurapanont and Jarusuraisin 2005; Roozen et al. 2006).

Naltrexone reduces the rate of relapse to heavy drinking and increases the number of abstinence days in alcohol dependent patients. Naltrexone decreases excessive drinking by reducing the reward associated with drinking alcohol. It reduces craving induced by environmental stimuli and decreases the amount and frequency of drinking when relapse occurs. It is, therefore, more effective in reducing rate and severity of relapses rather than in maintaining abstinence (Mann et al. 2004; Srisurapanont and Jarusuraisin 2005; Rosner et al. 2008).

Naltrexone is usually not prescribed without a support of some type of psychological counselling (Srisurapanont and Jarusuraisin 2005; Donovan et al. 2008). It appears to work best when supported by psychosocial interventions, particularly those aimed at relapse prevention (Roozen et al. 2006). 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, as has been shown in COMBINE study (Anton et al. 2006).

Suitability for naltrexone

There is still little evidence to directly inform decisions about what patient populations are more suitable for naltrexone. The following points should be taken into account (O'Malley 1998, Anton 2008):

- 1) Patients who are moderately to severely alcohol dependent and are medically stable are suitable for naltrexone. For example, a person who drinks on more than 50% of days, consumes more than five drinks a day, and has some alcohol-related problems (Anton 2008);
- 2) Naltrexone may be more effective for preventing relapse to heavy or problem drinking than for maintaining abstinence from alcohol (Rosner et al. 2008);
- 3) Patients currently using opioids or who require opiate-based pain relief are not suitable (Anton 2008). Due to its antagonist properties at the mu-opioid receptor, naltrexone will precipitate acute opioid withdrawal in patients currently using opioids. For the same reason, being on naltrexone will render opioid analgesia ineffective.
- 4) While hepatotoxicity has not emerged as a wide-spread problem (Croop et al 1997), naltrexone is contraindicated for people with acute hepatitis or severe liver failure. It is also contraindicated in patients with a history of sensitivity to naltrexone.
- 5) There are no well controlled studies of the safety of naltrexone during pregnancy or lactation.
- 6) There are some reports that patients with significant depression or more severe alcohol dependence respond less well to naltrexone treatment. Regular monitoring for depression is recommended (Latt et al 2002; Morley et al. 2006).

Recommendation	Strength of recommendation	Level of evidence
7.2 Naltrexone is recommended as relapse prevention for alcohol-dependent patients.	A	1a
7.3 Naltrexone is not suitable for people who are opioid dependent or who have pain disorders needing opioid analgesia.	S	

Interaction with other drugs

Naltrexone is a mu-opioid receptor antagonist and induces precipitated opiate withdrawal in patients who are currently opiate dependent. It is contraindicated in patients with current or recent use of opioid medication (e.g. 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 48-72 hours prior to any situation where opioid analgesia may be required (e.g. 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 (e.g. disulfiram).

Concurrent administration with antidepressants appears to be safe (Croop et al 1997).

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 3 days) was the requirement of most clinical trials investigating the effectiveness of naltrexone. The patient's ability to achieve abstinence in this period is a good indication of their motivation to adhere to a course of naltrexone. It has been suggested that such abstinence is the most judicious approach (Anton 2008).

Naltrexone dosing is recommended to begin 3-7 days after the patient's last drink and after resolution of acute withdrawal symptoms. In most randomised controlled studies (e.g. reviewed by Srisurapanont and Jarusuraisin 2005) investigating effectiveness of naltrexone, treatment was initiated within one week of completing managed withdrawal.

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 50mg, with the recommended dose being 50mg (1 tablet/day orally) with meals. It may be preferable to commence with ½ tablet (25mg/day) for several days, and increase to 50mg after any adverse effects have subsided.

There has been only one study comparing several doses of naltrexone (O'Malley et al 2008). This was a placebo-controlled dose-range study, investigating the effect of oral naltrexone (25mg, 50mg and 100mg) on alcohol consumption in hazardous drinkers (not seeking treatment), combined with open-label transdermal nicotine patch for enhancing smoking cessation. The lowest dose (25mg) was more effective in reducing levels of drinking. The authors conclude that given its efficacy, favourable side-effect profile and a lower cost when compared to higher doses, the 25-mg dose should be considered for future studies of combination therapy.

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 percent of patients. These generally subside with time (usually days) (e.g. Srisurapanont and Jarusuraisin 2005).

Based on clinical practice, the following strategies may help reduce the impact of potential side effects on treatment outcome:

- 1) Patient education about expected side effects and duration
- 2) Timing of doses: establish a routine; ideally taken in the morning with food or splitting the dosage between the morning and evening
- 3) Gradual introduction of medication (25mg for 1-2 days)
- 4) Dose reduction (half tablets at 25mg/day), slow titration, and stopping the medication for three to four days before reintroducing it at a lower dose
- 5) Distinguishing between prolonged alcohol withdrawal symptoms and side effects of naltrexone by beginning treatment once the major features of alcohol withdrawal have subsided (generally 3-5 days after drinking cessation) may be important.

Treatment duration

The most appropriate duration of treatment continuation in an alcohol-dependent patient is not yet known. The usual treatment period used in majority of randomised controlled studies (e.g. Srisurapanont and Jarusuraisin 2005) as well as in clinical practice is 3-6 months and in some cases up to 12 months.

However, the decision on the 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.

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 6a: *Psychosocial interventions*)

Monitoring and attending to physical and mental health is important. Depression and dysphoria have been reported as side effects of naltrexone (Farren and O'Malley 1999; Mendelson et al 1978)

Ending naltrexone therapy

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

Acamprosate

Acamprosate is thought to reduce drinking by modulating the brain GABA (gamma-aminobutyric acid) and glutamate function which is implicated in withdrawal symptoms. The drug only reaches desired levels in the brain after one to two weeks (Wright and Myrick 2006; Mann et al. 2008).

Effectiveness of Acamprosate: Reviews and Meta-analyses

A meta-analysis by Mann et al. (2004) examined results of 17 randomised clinical trials investigating efficacy of acamprosate in the maintenance of abstinence in alcohol dependent patients. A total of 4087 patients were included, of whom 53% received the intervention medication. Findings showed that continuous abstinence rates at 6 months were significantly higher in the acamprosate-treated patients than in placebo group (36.1 and 23.4% respectively, with the relative risk ratio of 1.47 (95% CI, 1.29–1.69; $p < 0.001$). At 12 months, the pooled difference in success rates between acamprosate and placebo was 13.3%, with number needed to treat (NNT) at 7.5. The conclusions of this study were that acamprosate had a significant beneficial effect in enhancing abstinence in detoxified alcohol-dependent individuals.

Another study evaluated the results of 3 double-blind, placebo-controlled trials carried out in Belgium and France, France alone, and Germany (Kranzler and Gage 2008). Acamprosate was delivered in doses of either 1332mg or 1998mg per day. In one study of 48 weeks (in Germany), the doses were assigned according to body weight (as recommended) and in the other two (13- and 52-week studies) they were randomly assigned. All patients received counselling. Drinking outcomes were measured by blood tests (GGT and MCV), breath, blood or urine alcohol concentrations, and by reports from patients and family members. Results showed that 54% of patients receiving acamprosate completed the trials versus 39% of control group patients. Intention-to-treat analysis was used; patients with missing data or unknown status were assumed to relapse to non-abstinence. The intervention group reported significantly higher percentage of days abstinent than placebo patients in all 3 studies ($p < 0.01$). Differences ranged from 18% in the 52-week study ($p = 0.001$) to 38% in the 13-week study ($p < 0.001$). Overall, the rate of complete abstinence was significantly higher with acamprosate than placebo ($p < 0.05$). Acamprosate significantly increased percent days abstinent and time to first drink compared to placebo patients ($p < 0.01$). Conclusions were that acamprosate is an effective medication and was also the first to demonstrate efficacy in maintaining complete abstinence, when combined with psychosocial support.

Effectiveness of Acamprosate: Randomised controlled trials

One pragmatic trial of acamprosate was undertaken over 149 general practices in France with 422 alcohol dependent patients (Kiritze-Topor et al. 2004). Patients were randomised to receive acamprosate with standard care (which in France includes a rehabilitation program, often with some type of psychosocial therapy) or standard care alone. The purpose of the trial was to test its efficacy in routine practice. The principal outcome measure was change from baseline on the Alcohol-Related Problems Questionnaire (ARPQ), a questionnaire that measures the influence of alcohol consumption on patients' lives with respect to health, work, financial, family and relationship and legal/judicial problems. Secondary outcome measures were abstinence (measured by proportion of days abstinent during the trial), and the success of the treatment from the physician's point of view. Results from the 12

month follow-up showed a level of significance in favour of acamprosate, with a relative risk ratio (RR) of 1.26. The number needed to treat was 7.14; i.e. 7 patients need to be treated to save one additional patient from alcohol-related problems. Half of all patients reported no alcohol-related problems during the study period. Study completion rate was high at 82.5%; intention-to-treat analysis was used. Conclusions of the study were that acamprosate is successful in reducing alcohol-related problems, and also that the treatment can be practically carried out in routine general practice with alcohol-dependent patients.

Psychosocial treatment was the subject of two trials where it was tested with alcohol-dependent patients and compared with acamprosate. A study conducted in Netherland compared acamprosate alone with acamprosate plus minimal motivational enhancement, and acamprosate plus brief cognitive behavioural therapy (de Wildt et al. 2002). Another similar study in Sweden compared two types of intervention: minimal psychosocial intervention and extended psychosocial intervention; both arms contained treatment with acamprosate (Hammarberg et al. 2004).

The de Wildt et al. (2002) study was conducted with 248 alcohol-dependent outpatients from 14 addiction treatment centres in the Netherlands; the study period was 28 weeks. Minimal intervention (group 2) was 3 sessions of 20 minutes each in weeks 2, 3, and 4. Extended intervention (group 3) was 5 standard and 2 elective weekly 60-minute sessions of CBT in weeks 2-8. In contrast, 'no intervention' (group 1) patients were seen by the physician 6 times in 28 weeks. All patients were prescribed acamprosate for 28 weeks. At the end of the treatment period 114 patients (47%) remained in the study. Outcome measures were number of abstinent days, time to first relapse and number of drinks per drinking day. The results showed that adding a psychosocial intervention did not enhance drinking outcomes or medication compliance. Total number of abstinent days was 108.5 for group 1, 119.1 for group 2, and 108.1 for group 3; rates of continuous abstinence were 13%, 21% and 10% respectively; time to first relapse was 53.4, 65.5 and 55.4 days respectively. Intention-to-treat analysis was used. No statistical differences were found between the treatment groups; the authors suggest that this may partly have been explained by the 'no intervention' group spending the same amount of time in consultations as the 'minimal intervention' group. Although the protocol was strictly adhered to, sources of potential bias were addressed in the randomisation of patients to treatment arms, and the sample size was powerful enough to detect differences in outcomes, it remains unknown why the interventions did not produce a larger effect than expected. It concludes that this trial could not demonstrate an effect for brief psychosocial treatments and either a much more intensive treatment is needed or that acamprosate with medical management is adequate to produce decreases in drinking.

The study by Hammarberg et al. (2004) compared two intensities of psychosocial interventions (extensive and minimal) with 70 alcohol dependent patients, all being treated with acamprosate. Results showed that the extended intervention was not more effective in prolonging time to first drink, with reducing either the number of drinking days or of heavy drinking days than the minimal intervention. There were no differences between groups in compliance to medication during the trial, or in AST, GGT or CDT levels in blood tests conducted after 24 weeks. There was a slight reduction in ALT levels in the minimal intervention group. The authors suggest that the extended intervention may not have been intensive enough to produce a dose-response effect, or conversely (similar to the above study) medication with minimal intervention is sufficient to reduce drinking levels.

Patient motivation was found to have a significant effect on the outcome in a study conducted in the USA which tested the dose-dependent effectiveness of acamprosate in alcohol-dependent patients in a double-blind placebo-controlled trial (Mason et al. 2006). There were 3 arms to the trial; 3 placebo tablets (nil dose); 2 tablets of acamprosate and one placebo (2g); or 3 tablets of acamprosate (3g); all given twice daily. All patients received brief counselling and self-help materials at 8 study visits, for 24 weeks. The primary outcome measure was alcohol-free days, measured by the timeline follow-back method. Results show no statistically significant difference in alcohol-free days across all arms, although a slight trend was noticed (54% for nil dose, 56% for 2g, and 61% for 3g. However, by examining results from a subgroup whose goal at baseline was to be completely abstinent, it was found acamprosate had a significant linear dose effect, with 3g superior to 2g ($p=0.01$) and 2g superior to nil dose ($p=0.04$), using both intention-to-treat analysis and actual completers' results.

Reid et al. (2005) conducted a small randomised trial ($n = 40$) to evaluate the effectiveness of compliance therapy in increasing adherence to treatment with acamprosate in patients with alcohol dependence. Patients received acamprosate, with or without compliance therapy for 4 months ($n = 20$ in each group). All subjects received routine medical care (seven medical reviews each of 15 minutes duration over 4 months). Compliance therapy consisted of four to six individual sessions (60 minute duration) and included motivational interviewing and cognitive behaviour therapy techniques with the focus on exploration of beliefs about medication side effects, the benefits of treatment ambivalence and relapse prevention. Intention-to-treat analyses of data showed no differences between the two groups in the number of days taking acamprosate, days to first drink, days to first relapse. However, it was found that participation in three or more sessions of compliance therapy was associated with better adherence to acamprosate and better overall treatment outcomes.

The COMBINE study (Anton et al. 2006), described above, found that acamprosate was not more effective in reducing drinking than placebo (with medical management) either alone or in combination with psychological intervention or with naltrexone or both. It should be noted, however, that in this study percent days abstinent at the end of the 16-week treatment period was similar in placebo, acamprosate and naltrexone groups (mean, placebo acamprosate 77.6 vs acamprosate 78.4; placebo naltrexone 77.2 vs naltrexone 78.8). The assessment of interactions between treatment combinations showed that naltrexone, but not acamprosate, was significantly more effective than placebo in reducing the number of percent days abstinent, although the actual difference was small (mean, placebo naltrexone without CBI 75.1 vs naltrexone without CBI 80.6).

There was a significant "placebo effect" in the COMBINE study resulting from pill taking and meetings with a medical professional. The latter may have contributed by repeated advice to attend Alcoholics Anonymous and instilling sense of optimism about a medication effect (Weiss et al. 2008).

Effectiveness of acamprosate: Summary

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 (Mann et al. 2004). Acamprosate increases the number of days of continuous abstinence as well as the percent of days abstinent and time to first drink (Kranzler and Gage 2008).

Acamprosate is more likely to be effective in patients motivated to stay abstinent at the start of treatment (Mason et al. 2006).

While there is no sufficient evidence to suggest that acamprosate is more effective when used together with psychosocial interventions, the current approach is to use acamprosate as part of a more comprehensive treatment plan that may include psychosocial interventions.

Suitability for acamprosate

There is still little evidence to inform decisions about what patient groups are most suitable for acamprosate.

Verheul et al. (2005) pooled the results of 7 European trials with the aim of identifying if there was a particular subgroup of patients who responded better to acamprosate. They analysed the results of 1485 patients with alcohol dependence using the outcome measures of cumulative abstinence duration, continuous abstinence, and time to first relapse. The overall results concluded that acamprosate can be considered potentially effective for all patients with alcohol dependence, as despite the large sample size and sufficient statistical power to detect any variations, no differences were detected for any of the variables (craving, anxiety, study, and treatment) entered into the analysis. It is posited by the authors, however, that evidence from 2 other studies suggests that naltrexone or disulfiram combined with acamprosate would improve its effectiveness.

Based on available evidence, acamprosate is a suitable treatment option for patients with alcohol dependence (usually, moderate to severe), who are medically stable and are willing to comply with the dosing regimen may benefit for acamprosate (Reid et al. 2005).

Acamprosate may be more effective for patients with an abstinence goal rather than preventing excessive drinking in non-abstinent patients (Mason et al. 2006; Rosner et al. 2008).

Acamprosate is contraindicated in patients with a known hypersensitivity to the drug, renal insufficiency or severe hepatic failure (Childs Pugh classification C) (MIMS 2008).

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 (MIMS 2008).

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. Tetracyclines may be rendered inactive by the calcium component in acamprosate.

Starting treatment

Acamprosate dosing is recommended to begin 3-7 days after the patient's last drink, and after resolution of any acute withdrawal symptoms. Acamprosate can be safely initiated during alcohol withdrawal (Gual and Leheret 2001) and its potential neuroprotective effect may be useful early in withdrawal (Koob et al. 2002).

Starting acamprosate at the beginning of detoxification versus after completion of detoxification has not been shown to improve treatment outcomes (Kampman et al. 2009).

However, pre-treatment with acamprosate 8 days prior to withdrawal management has been shown to improve sleep during withdrawal and in a post-withdrawal period (Staner et al. 2006).

Medical history should be taken, as per Chapter 3: *Screening and assessment*. Physical examination may include assessment for signs of chronic liver disease and hepatic failure. Investigations may include tests of kidney function (urea and electrolytes), since 90 percent of acamprosate is excreted through the kidney, and liver function tests.

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 tablets of 333 mg, with the recommended dose for adults being 1998mg with meals (six tablets/day, orally in three doses: 2; 2; 2). Adults under 60kg should take 1332 mg/day (four tablets/day in three 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 (Wilde and Wagstaff 1997).

The following strategies are recommended:

- 1) Patient education about expected side effects and duration.
- 2) Distinguishing between prolonged alcohol withdrawal symptoms and side effects of acamprosate by beginning treatment once more pronounced features of withdrawal have subsided (after first 3-5 days).

Treatment duration

The usual treatment period is 3-6 months (Mann et al. 2004). However, the decision on the duration of treatment 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.

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; psychosocial relapse prevention techniques should be used to deal with the lapse or relapse (see Chapter 6a: *Psychosocial interventions*) (Mann et al. 2004).

Some clinicians do not prescribe acamprosate during continued drinking. This is not because of drug interactions but due to the belief that medication is of most use for patients that possess a higher motivation to change

Regular monitoring and attending to physical, mental health and social issues is necessary.

Some patients will have difficulty adhering to a medication regime that involves taking tablets three times a day for prolonged periods (Reid et al. 2005) (see also material later in this chapter on increasing medication adherence).

Ending acamprosate therapy

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

Combined Acamprosate and Naltrexone

Some clinicians administer acamprosate and naltrexone concurrently given the different theoretical approaches of the two medications in reducing alcohol consumption. Studies have found this to be a safe and promising approach. Nonetheless, most evidence suggests that while combined naltrexone and acamprosate may be more effective than acamprosate alone, the combination is no more effective than naltrexone alone (Kiefer et al. 2003; Anton et al. 2006).

Combined acamprosate and naltrexone: Meta-analyses and reviews

An evidence-based risk-benefits assessment was carried out by Mason (2003) who assessed all published double-blind placebo-controlled trials of acamprosate and naltrexone. Sixteen studies of acamprosate were found, of which 15 used standardised methodology and were included; 14 studies were found of naltrexone and 3 of the two medications combined. The naltrexone trials differed more in their methodology than the others. The advantages of this were that the drug was evaluated under many conditions, from short- to long-term, and with and without accompanying psychosocial treatment. Based on this review, the conclusions were that both medications are useful in the treatment of alcohol dependence. However,

as the two drugs act in different ways and have different effects on the brain, there is a case for combining the two, and it was suggested that this may offer an advantage for some patients.

Combined acamprosate and naltrexone: Randomised controlled trials

Kiefer et al. (2003) compared naltrexone, acamprosate, and a combination of the two in a double-blind placebo-controlled study. After detoxification, 160 alcohol dependent patients were randomised to receive naltrexone, acamprosate, both, or placebo for 12 weeks. All patients attended group therapy weekly, utilising CBT and coping skills training. Full blood tests were also carried out, and breath and urine were randomly tested for alcohol. Results were that both medications were superior in achieving abstinence compared to placebo, with a tendency for a better outcome in the naltrexone group compared to acamprosate in maintenance of abstinence. There was no significant difference in time to first drink between naltrexone and acamprosate. Additional benefits were observed in combining naltrexone and acamprosate ($p = 0.002$). The combined medication group had a relapse rate of 25%. At follow-up (week 24) patients who received combined medication had rates significantly lower relapse rate than placebo, but not lower than acamprosate. Both naltrexone and acamprosate were superior to placebo. Relapse rates were 80% (placebo), 54% (acamprosate), 53% (naltrexone) and 34% (combined medication).

The results of COMBINE study (Anton 2006), discussed above, showed no advantage of adding acamprosate to naltrexone.

Disulfiram

Disulfiram primarily works by inhibiting the action of an enzyme (aldehyde dehydrogenase) involved in the second step in the metabolism of alcohol, namely the conversion of acetaldehyde to acetate. This leads to the accumulation of acetaldehyde following consumption of alcohol while on disulfiram. The resulting symptoms are unpleasant including flushing, dizziness, nausea and vomiting, irregular heart beat, breathlessness and headaches. Disulfiram acts as a deterrent to drinking because the patient expects to experience these negative consequences (Heather 1989). Evidence indicates that the maximal effect of disulfiram is achieved when the medication is provided to the patient under supervision (Chick et al. 1992; Hughes and Cook 1997; Laaksonen et al. 2008).

There is one recently reported trial of disulfiram and acamprosate (De Sousa and De Sousa 2005), which was randomised but not blinded. Better outcomes were noticed with disulfiram as the trial progressed, and it was found significantly better both at preventing relapse during the study ($p = 0.0003$), maintaining abstinence ($p = 0.0002$) and increasing days to first relapse ($p = 0.0001$).

Another trial in Finland compared disulfiram, acamprosate and naltrexone in a randomised open-label study with 243 treatment-seeking alcohol dependent patients over two and a half years (Laaksonen et al. 2008). Results show that during the first 12 weeks disulfiram was better than naltrexone and acamprosate in reducing time to first incidence of heavy drinking ($p < 0.001$). During the second phase (dosing targeted to risk situations) there were no significant differences in these measures between groups, but abstinence days were significantly more frequent in the disulfiram group ($p = 0.0005$ in the naltrexone group; $p = 0.0097$ in the acamprosate

group). Supervised disulfiram appeared superior to naltrexone and acamprosate, especially during the continuous medication period. This trial is described in more detail in Section 1.2 above.

Suitability for disulfiram

Based on the results of the recent studies discussed above and previous clinical experience, disulfiram is an appropriate medication for patients who are motivated to abstain from alcohol. It is beneficial for patients that accept a need for an external control on their drinking and are prepared to be supervised in the daily dosing of the medication (Chick et al. 1992; Hughes and Cook 1997). Since it is most effective with supervised administration, willingness of patient's spouse, family member or a friend is an important factor.

Disulfiram can cause significant toxicity if relapse occurs. It should only be prescribed to patients that display no medical or psychosocial contraindications as described below.

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

Precautions

The intensity of the disulfiram-alcohol reaction varies amongst 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. Several of the patients most suited to disulfiram in other terms may suffer from these problems. A risk-benefit analysis of the treatment should therefore be undertaken by the treating clinician. Careful monitoring of cardiac and liver condition is recommended if disulfiram treatment is started.

The enzyme that metabolizes dopamine into norepinephrine and epinephrine is inhibited by disulfiram, which may result in an exacerbation of psychosis. Nonetheless, a trial in a psychotic population did not reveal significant problems (Petrakis et al. 2006).

Interaction with Other Drugs

Disulfiram interacts with the metabolism of alcohol. It increases the blood concentration of benzodiazepines, caffeine, phenytoin, the active ingredient in marijuana, isoniazid, barbiturates, anticoagulants, tricyclic agents and paraldehyde (MIMS 2008). Disulfiram should not be given concomitantly with paraldehyde because paraldehyde is metabolized to acetaldehyde in the liver. Disulfiram should not be combined with naltrexone as both medications are potentially hepatotoxic.

Starting Treatment

Treatment should begin after detoxification, approximately 24-48 hours after drinking cessation. Medical history should be taken. It is important to discuss the effects of the drug when alcohol is taken, including potential severe, life threatening reaction. The patient's anticipation of its effects will greatly enhance the drug's effectiveness as a deterrent against drinking. 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 200mg, with the recommended dose being 200-400mg (1-2 tablets/day orally). Some patients can continue to drink on 200-400 mg without significant aversive effects, and the dose should be increased. The maintenance dosage 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.

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 6a: *Psychosocial interventions*). Disulfiram may be recommenced after 48 hours abstinence.

Supervision

Based on the outcomes of the recent studies discussed above, disulfiram treatment is best suited to individuals with social supports (e.g. family) who will help supervise medication adherence (Chick et al. 1992; Hughes and Cook 1997; Laaksonen et al. 2008). Supervision has a marked effect on adherence and may greatly improve the effectiveness of this intervention.

A spouse/partner is an obvious choice for married/de facto patients. It is important to stress that the spouse cannot be expected to control the other person's drinking. A written 'disulfiram contract' should be considered between a carer and patient. This contract should include an outline of the likely effects of drinking and products that may need to be avoided (e.g. facial products), the 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.

Treatment duration

Disulfiram is likely to be a useful treatment for the first 3-6 months of treatment. After that the benefits of continuing use are less clear and the patient should be encouraged to maintain abstinence without disulfiram.

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

Other medications

Serotonergic agents

There is minimal evidence for the efficacy of serotonergic agents (e.g. SSRIs, buspirone and ondansetron) for treating the main symptoms of alcohol dependence.

However, these agents may have a role in certain patients that have concomitant symptoms of anxiety or depression and there is evidence they are effective for these symptoms in the presence of alcohol use (see *Chapter 8: special population groups* and *Chapter 9: comorbidity*).

Other formulations and medications

There are several new agents emerging in the literature. These include anticonvulsants such as gabapentin (Furieri and Nakamura-Palacios 2007) and topiramate (Johnson et al. 2007), a gamma aminobutyric acid type B (GABA-B) receptor agonist baclofen (Addolorato et al. 2007), a N-methyl-d-aspartate (NMDA) receptor antagonist memantine (Evans et al 2007) and antipsychotic medications such as olanzapine (Guardia et al. 2004) and aripiprazole (Anton et al. 2008). Whilst some of these medications appear promising as agents in reducing alcohol relapse, the need for further controlled trials and the cost of these agents means that they cannot be recommended for use as first line treatments for alcohol dependence at this time.

A long-acting (monthly) depot intramuscular injected preparation of naltrexone has been developed and is licensed in the USA (e.g. Garbutt et al. 2005). This agent looks promising and avoids problems of poor adherence, however it is not yet available for use in Australia.

Whilst benzodiazepines are commonly sought after by some patients, there are no studies to support the use of benzodiazepines beyond the immediate withdrawal period in reducing alcohol use, and indeed there may be adverse effects of benzodiazepines dependence and interactions with alcohol.

Gabapentin

The efficacy of gabapentin (an anticonvulsant) in reducing alcohol consumption and craving has been examined by Furieri and Nakamura-Palacios (2007) in a randomized, double-blind, placebo-controlled trial performed in a Brazilian public outpatient drug treatment clinic. Subjects (n = 60) with alcohol dependence who received routine management of withdrawal with diazepam were randomised on treatment with gabapentin (300 mg twice daily) or placebo for 4 weeks. At the end of the treatment period patients receiving gabapentin had a significant reduction in both number of drinks per day and mean percentage of heavy drinking days ($p = 0.02$ for both), and an increase in the percentage of days of abstinence ($p = 0.008$), compared to the placebo group. Gabapentin was well tolerated.

Topiramate

Oral topiramate (an anticonvulsant) has also been trialled as an antagonist for alcohol's rewarding effects. It was tested against placebo with 150 alcohol-dependent treatment-seeking individuals in a double-blind randomised controlled study (Johnson et al. 2003) in the USA, and later in an identical study with 371 individuals at 17 US sites (Johnson et al. 2007). Outcome measures of the first study were, using the timeline followback method: number of drinks per day; average number of drinks per drinking day; percentage of heavy drinking days, and percentage of days abstinent. Results showed that topiramate was significantly more effective than placebo on all outcome measures. Secondary outcome measures included plasma GGT levels and self-reported craving and these also fell significantly. The dosage of topiramate was increased slowly for the first 8 weeks and so a time effect cannot be separated from a dosage effect. The authors conclude that topiramate is a safe and effective medication for alcohol dependence.

Other favourable results of this study have been reported elsewhere; namely one of improvement of quality of life and physical health associated with the use of topiramate (Johnson et al. 2008).

The later and larger trial of more sites and subjects, but using more rapid titration of dose (Johnson et al. 2007), replicated the findings of the first trial but with more rigorous statistical testing and therefore was able to conclude that the therapeutic effect of topiramate was replicable. The dropout rate, however, was found to be higher in the intervention group due to side-effects and they recommend slower titration of dose, as in the first trial. One of the drawbacks of the trial, as they report, is that no follow-up was conducted and so it is not known if the effects on reduction of drinking persisted.

Another study tested the effects of topiramate on urge to drink (Miranda et al. 2008) and found no conclusive effects on this feature, but did confirm others' findings that it reduced the frequency of drinking; it also reduced the stimulating effects of alcohol but was only significant in the 200mg group. As the authors report, the sample size was small (n = 61) and was a preliminary study only.

The scientific concepts and clinical evidence for the development of topiramate in the treatment of alcohol dependence have been reviewed by Johnson (2005).

Baclofen

The effectiveness and safety of baclofen (a muscle relaxant acting through activation of the GABA-B receptor) was assessed in a double-blind randomised controlled trial of 84 alcohol-dependent patients in Italy with liver cirrhosis (Addolorato et al. 2007). Results from this study showed that 71% of baclofen patients achieved and maintained abstinence compared with 12% of placebo. The drug was well tolerated.

Memantine

Memantine is an N-methyl-d-aspartate (NMDA) receptor antagonist that may have potential for the treatment of alcohol disorders. Memantine has been shown to decrease alcohol craving in moderate drinkers. A double-blinded pilot study in the USA of memantine with 34 patients randomised to medication or placebo produced inconclusive results (Evans et al. 2007). Eighty percent of patients completed the 16-week trial; both groups significantly reduced their alcohol use, with no difference

between the groups. The authors conclude that there is no evidence from this pilot to support its use to reduce either alcohol consumption or relapse from abstinence.

Olanzapine

Similar results were found in a double-blind randomised parallel group trial of olanzapine (an antipsychotic) in Spain, where both placebo and treatment groups also received psychotherapy (Guardia et al. 2004). Olanzapine was well tolerated; side-effects were mostly weight gain (32%), increased appetite (25%), drowsiness (18%), constipation (11%) and dry mouth (11%). Both groups reduced drinking and no differences were found between groups on any of the measured psychological variables, in the relapse rate or in any other drinking variables.

Another trial was carried out in the USA by Hutchison et al. (2006) with 128 patients who were randomised to receive placebo or olanzapine with the aim of reducing craving. The patients were further analysed by sub-groups (those who had and did not have a particular allele (described as the seven-repeat allele of the DRD4 variable number of tandem repeats). Results of this study show that olanzapine reduced cue-elicited craving for alcohol in the DRD4-L (positive) individuals after 2 weeks of treatment. It also decreased the quantity of drinking over 12 weeks. It did not have this effect on the DRD4-S (negative) individuals. Side-effects from olanzapine included weight gain, with average weight gain being 6.5 lbs (approx 3 kilos) in the treatment group.

Aripiprazole

Finally, trials of aripiprazole have been recently reported. Aripiprazole is a dopaminergic/serotonergic agent with partial agonist properties at the D2 dopamine receptor and 5-hydroxytryptamine 1A (5-HT_{1A}) receptor and antagonist properties at the 5-HT_{2A} receptor.

Anton et al. (2008) conducted a randomised multi-centred double-blind, placebo-controlled study of efficacy and safety of aripiprazole in treatment of alcohol dependence. The primary efficacy measure was percentage of days abstinent over 12 weeks. Patients (n = 295) with DSM-IV alcohol dependence were randomised to placebo or oral aripiprazole in an increasing dose from 5mg to 30mg per day. Subjects also received weekly psychotherapy sessions. Time line follow-back method was used to measure alcohol consumption. More patients in the treatment group dropped out (41% vs 17% of controls); more dropouts in the treatment group were due to adverse effects than in the control group, and dropout also occurred sooner. Results indicated that aripiprazole patients consumed fewer drinks when they did drink and rated themselves as having fewer problems at study end. Statistically significant items favouring aripiprazole were 'made me not want to drink' (p = 0.034); 'felt better the next day if I did drink' (p = 0.010); and 'felt less high or intoxicated when I did drink' (p<0.0001). The authors conclude that this antipsychotic, or others, may be useful in treating alcoholism or other addictions.

Martinotti et al (2008) compared aripiprazole with naltrexone in a double-blind comparison trial of 75 patients who were committed to abstinence. Outcome measures were maintenance of abstinence and relapse to drinking, defined as 5 or more drinks on 5 days in a week; secondary was time to first drink, number of abstinent days and reduction in craving. Intention-to-treat analysis was used. Results: number of subjects alcohol free and relapsed during the study period were not significantly different in the two groups. The authors conclude that aripiprazole

was effective at flexible doses in improving alcohol-related outcomes, with a relapse rate and number of patients retained in treatment not significantly different from naltrexone.

Injectable naltrexone

Two randomised controlled trials were identified that tested intramuscular injection of naltrexone. Kranzler et al. (2004) conducted a multicentre trial of 315 patients who received a monthly injection of naltrexone or placebo for 12 weeks. Patients also received 5 sessions of motivational enhancement therapy. Outcomes of interest were self-reported alcohol use and GGT levels; 74% completed all injections, which were well tolerated. Results favoured the naltrexone group in reducing alcohol consumption and lowering GGT levels but did not reach statistical significance; however, the naltrexone group did have significantly fewer drinking days than the placebo group and a significantly greater abstinence rate (18% vs. 10%).

A study by Garbutt et al. (2005) was also a multicentre trial, which took place over 6 months at 24 hospitals and clinics in the USA with 624 participants. This study used two doses of long-acting naltrexone 380mg and 190mg, vs. placebo, delivered in monthly intramuscular injections. Patients also received 12 sessions of low-intensity psychosocial intervention. The principal outcome measure was the rate of heavy drinking days. Intent-to-treat analysis was used. Results showed that 380mg of naltrexone resulted in a 25% decrease in heavy drinking, while 190mg doses resulted in 17% decrease compared to placebo, with the medication being well tolerated. Patients who entered with the goal of abstinence had a greater degree of reduction in drinking than those who aimed to reduce their drinking. These patients in both groups benefited more from the trial (placebo vs. both doses of naltrexone); however, patients who had already abstained when entering the trial benefited the most (see the study by O'Malley et al. 2007 below). Authors conclude that long-acting naltrexone is beneficial in the treatment of alcohol dependence.

Furthermore, patients who received 380 mg extended release naltrexone as part of the Garbutt et al. (2005) trial had significantly greater improvements from baseline in mental health ($p = 0.0496$), social functioning ($p = 0.010$), general health ($p = 0.048$), and physical functioning ($p = 0.028$), compared with placebo. Reductions in drinking from the baseline (percentage of drinking days and percentage of heavy drinking days in the last 30 days) were significantly ($p < 0.05$) correlated with improvements in quality of life (Pettinati et al. 2009).

O'Malley et al. (2007) analysed the data from a subgroup of patients who participated in the Garbut et al. (2005) study. The subgroup included patients with 4 days or more of voluntary abstinence before the injection of the extended release naltrexone ($n = 82$). Patients on 380 mg naltrexone ($n = 28$) has significantly better treatment outcomes when compared to placebo ($n = 28$), including a longer time to first drink (median of 41 days versus 12 days in placebo group) and to first heavy drinking event (>180 days vs 20 days respectively, $p = 0.04$). They also had only 0.7 drinking days per months, which is a 90% decrease when compared to 7.2 days in placebo groups ($p = 0.005$). The rate of continuous abstinence at six months was 32% versus 11% respectively ($p = 0.02$). The 190 mg dose of ($n = 26$) showed intermediate outcomes, indicating a dose-response effect. Therefore, a period of abstinence of as little as 4 days before commencement of treatment with the extended release naltrexone is sufficient to significantly prolong abstinence and reduce drinking in alcohol dependent patients.

Benzodiazepines

Benzodiazepines are not recommended for use beyond the withdrawal management period (See Chapter 5).

Antidepressants

Despite an expensive research into the role of SSRIs in treatment of alcohol dependence, there is limited evidence of their effectiveness (Johnson 2008). Their use in treatment of comorbid depression and alcohol dependence is discussed in 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

Pharmacological treatment is considered to be significantly more successful when the patient is receiving concurrent psychosocial treatment or structured medical supervision. Referral to a specialist alcohol and drug counselling service may be appropriate (see Chapter 6a: *Psychological Interventions* for more information).

Pharmacotherapy for relapse prevention should always be accompanied by close follow-up by the prescribing doctor.

Increasing medication adherence

Alcohol pharmacotherapy has been shown to be more effective than placebo among highly compliant participants (Volpicelli et al. 1997). However, adherence rates of alcohol dependent patients are generally low.

Poor medication adherence may be due to: adverse side effects; stigma attached to taking medication for an alcohol use disorder; no immediate reward for complying with these pharmacotherapies; fears about the safety and side effects of the medication (O'Malley 1998; Kranzler et al. 2000).

Adherence to pharmacotherapies may be assisted by:

- 1) 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
- 2) 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

- 3) Using motivational interviewing techniques to help the patient to identify their personal costs and benefits of taking the medication
- 4) Providing the patient with some take-home reading material about the medication
- 5) 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 to maintain abstinence.
- 6) 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 (Reid et al. 2005) (for the manual see Teesson et al. 2003).

Adherence may also be a problem in patients that 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 different patients. Decision of choice of medication includes:

- 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, treatment goals, capacity to adhere to treatment regime, concomitant medical conditions.

Resource factors: the cost of some medications will be prohibitive for some patients (e.g. topiramate, gabapentin, aripiprazole). Disulfiram treatment is best suited to individuals with social supports (e.g. family) who will help supervise medication adherence.

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