MEDICATION TO PREVENT RELAPSE

There are four medicines commonly used specifically to prevent relapse to substance misuse, these being **naltrexone, disulfiram, acamprosate and buproprion** (*see Section C4, page 25*). Naltrexone is only licensed for the prevention of relapse to opiate misuse (in the UK), although there is increasing evidence to suggest that it is also effective in the prevention of relapse to alcohol misuse. Acamprosate and disulfiram are used solely to aid in prevention of relapse to alcohol misuse; buproprion aids in the prevention of relapse to nicotine misuse.

- Acamprosate may be prescribed routinely to aid in prevention of relapse to alcohol. It is best commenced during alcohol detoxification, but may be started at any time and continued through lapses to drinking.
- Naltrexone may also be prescribed routinely to aid in prevention of relapse to opiate misuse. It should usually be commenced with the support of specialist services who will administer a 'Narcan Challenge'.
- Disulfiram (Antabuse) is only suitable for prescription in selected cases.
- The effectiveness of both disulfiram and naltrexone is thought to be enhanced by the availability of a carer to supervise daily administration of the medication.

NALTREXONE

Naltrexone is an opiate receptor antagonist licensed in this country for the prevention of relapse to opioid drug misuse. It works by blocking the opiate mu (μ) receptor, preventing its activation by opioid receptor agonists such as heroin and methadone. Naltrexone is also sometimes used for prevention of relapse to alcohol, but is not licensed for this currently in the UK. It is usually prescribed orally, although a subcutaneous implant preparation is also available; the implant formulation has clear common-sense advantages for compliance, although it has not been researched in depth, and is currently available only in the private sector. A depot formulation is being trialled in the USA.

EFFECTIVENESS

Claims have been made that mean retention on naltrexone treatment is between one and six months (Kleber H, 1985), depending on patient selection and quality of adjunctive services. However, most studies of naltrexone use have shown high dropout rates and high relapse rates to heroin use (Jaffe J, 1995). A study by Bell et al (1999) found progressive attrition over the 3 month follow-up period with only 20% still using naltrexone after 3 months (one third of these admitted to occasional heroin use on-top of naltrexone). However, another 16% were abstinent without naltrexone use. Of the remaining 64%, 1/3 had relapsed to heroin use (23%), and over a half (37%) were on methadone. One patient had died from heroin overdose. Thus overall, despite the high attrition rate, only one quarter of patients were using illicit drugs in a dependent fashion at three months. This figure is lower than the rates of dependent heroin use commonly reported at 3 months following detoxification without naltrexone prescription.

As a rule of thumb, for an unselected population, maybe 20-40% of patients will be compliant with naltrexone at three months or non-compliant but abstinent from illicit substance misuse. Anecdotal evidence suggests that success is more likely if a carer is available to administer naltrexone and ensure compliance.

A recent Cochrane review (Kirchmayer U et al, 2000) concluded that there was not yet 'sufficient evidence to evaluate the efficacy of naltrexone treatment on opioid dependence, and further studies are needed before making a clear decision on whether to go on using it and enlarge its use as far as possible or to stop its use and concentrate on efficacious alternatives'.

SIDE-EFFECT PROFILE

Hepatotoxicity

In a placebo controlled trial using naltrexone doses six-fold that recommended for blockade of opiate receptors (300mg/day), five of 26 subjects developed elevations of ALT three to nineteen times their baseline values after three to eight weeks of treatment. There was no reaction in the placebo group subjects. All liver function tests returned to (or toward) baseline levels within a matter of weeks from cessation of naltrexone. The subjects with elevated liver enzymes were generally asymptomatic (Kleber H, 1985).

A study of naltrexone (at normal doses of 50mg daily) and methadone on 116 parenteral drug users with hepatitis C infection reported that neither methadone nor naltrexone resulted in increased levels of transaminases (Kleber H, 1985).

No cases of hepatic failure due to naltrexone administration have ever been reported.

DOSAGE GUIDANCE IN ABNORMAL LIVER FUNCTION (KLEBER H. 1985)

- All patients receiving naltrexone should have baseline liver function studies and then repeat tests once a month for the first 4 to 6 months. Patients with baseline liver abnormalities should be tested every 2 weeks for up to 6 weeks before going on to a once a month frequency.
- Do not start naltrexone if the AST is greater than approximately two times normal.
- Discontinue naltrexone if the AST rises to greater than 3 times normal unless some other cause is found (eg alcohol misuse).

OTHER PROBLEMS & SIDE-EFFECTS

The patient must be opiate-free for at least 7-10 days before induction onto naltrexone. Earlier induction can lead to a severe withdrawal syndrome associated with delirium. (This may not be the case in certain instances of in-patient induction under specialist care – see Section E7, page 79).

Naltrexone is contraindicated in acute hepatitis, liver failure and when there is a history of allergy to naltrexone. It should be used cautiously when there is hepatic or renal impairment, and in pregnancy and breast feeding. All patients must be warned that attempts to overcome the naltrexone blockade by use of very large amounts of opiates is dangerous and in rare instances may be lethal. Patients must also be warned that they will have lost tolerance to opiate use at the time of ceasing naltrexone, and that doses of heroin previously tolerated may now lead to overdose with possible respiratory depression and death.

Side-effects of naltrexone are largely similar to complaints associated with the opiate withdrawal syndrome; these include anxiety, insomnia, nausea, vomiting, joint and muscle pain, diarrhoea, sweating, lacrimation, fatigue, delayed ejaculation and reduced sexual potency. These effects will be expected to reduce in time and all would be reversible. Rashes occur occasionally and there has been a report of reversible idiopathic thrombocytopenia.

DOSAGE AND INDUCTION

Naltrexone should only be commenced when all opiate agonist drug has cleared from the brain; if it is started earlier an opiate withdrawal syndrome may be induced. In the case of heroin this translates into a day or so, but in the case of methadone use may mean waiting a week or more. In contrast to natural opiate withdrawal, naltrexone-induced withdrawal may occasionally lead to delirium with its associated risks. Best practice thus involves administering a dose of IM naloxone ('Narcan challenge' – *see appendix 11*, page 152) before commencement of oral naltrexone. The rationale here is to ensure that if an opiate withdrawal syndrome is induced then it will be short-lived (duration of action of naloxone is in the region of 30 minutes to 1 hour as opposed to a 24 hour duration of action of naltrexone). A dosage of 0.4mg IM followed by observation for 30 to 45 minutes will usually suffice. Any signs of opiate withdrawal occurring within this time will contraindicate commencement of naltrexone. Following a successful 'Challenge', naltrexone 25mg orally should be administered, increasing to 50mg daily thereafter.

The 'Narcan Challenge' may be arranged through referral to specialist services. Medication to manage acute opiate withdrawal and anaphylaxis should be available at sites/surgeries administering naloxone in such circumstances.

CONCLUSION

Naltrexone is generally a safe medicine to prescribe and probably reduces relapse rates to dependent opiate misuse following detoxification. There is a small risk of reversible elevation of liver enzymes which indicates the need to monitor liver function tests on a regular basis for the first period of treatment. As for all patients who have lost tolerance to opiates (as occurs after any detoxification), there is a risk of opiate overdose if the patient uses illicit heroin at pre-detoxification doses; patients should be reminded of this risk and warned not to attempt to overcome the naltrexone blockade.

ACAMPROSATE

Acamprosate is a putative anti-craving drug, licensed for use in alcohol dependency. Its exact mechanism of action is unknown, but it is thought to act via several mechanisms affecting multiple neurotransmitter systems. During alcohol withdrawal the central nervous system neurones enter a state of hyperexcitability (which leads to a classical withdrawal syndrome characterised by hallucinosis, paranoia, seizures and a generalised overactivity of the autonomic nervous system with high levels of anxiety, insomnia and tremor, sweating and gastrointestinal disturbance). Glutamate-mediated hyperexcitability may also occur, triggered by cues, during the post-withdrawal abstinence period.

At the neurobiochemical level, acamprosate's main action may be to cause a relative inhibition of this hyperexcitable state through a reduction of both glutamate release and receptor activation (glutamate is the major excitatory neurotransmitter). Interaction with the NMDA (glutamate) receptor is also associated with a reduction in calcium ion fluxes (through voltage-operated channels). Activity at the NMDA receptor may be as a 'partial co-agonist': low acamprosate concentrations enhance NMDA activity when this activity is low; but high acamprosate concentrations inhibit NMDA activity, when activity is high. This implies a non-linear dose-dependent effect. Acamprosate has a similar chemical structure to GABA (the major CNS inhibitory transmitter) and it may also act on the GABA presynaptic receptor to increase GABA activity in the synapse. Another inhibitory transmitter, taurine, may also have a role in alcohol withdrawal, and acamprosate has been demonstrated to increase taurine levels in rats.

EFFECTIVENESS

A 1997 review of acamprosate studies concluded the following:

- Oral acamprosate at 1.3 or 2g/day in 3 divided doses for 3 to 12 months was more effective than placebo in preventing alcohol relapse as measured by abstinence rates, duration of abstinence, continued abstinence following cessation of acamprosate (followed for up to 2 years), gamma-glutamyl transferase levels, and other clinical or biological end-points. Retention in treatment was also improved.
- Its efficacy seems dose-dependent.
- Efficacy may be enhanced by addition of disulfiram. One study with a 360 day treatment period, and 360 day acamprosate-free follow-up found more drink-free days with acamprosate + disulfiram, than with disulfiram alone, or no medication. There was no drug-drug interaction, or increase in side-effects.

SIDE-EFFECT PROFILE

Acamprosate is generally well tolerated; its commonest side-effects are diarrhoea, and mild/transient dermatological effects. Other potential side-effects include nausea, vomiting, abdominal pain, and fluctuation in libido. It has no abuse potential and no sedative, mood or cognitive effects.

PRESCRIBING

666mg tds orally, unless < 60kg when 666mg mane + 333mg bd is recommended. The standard duration of prescribing is one year. Acamprosate may be commenced during alcohol detoxification and the manufacturers recommend commencement on the second day of detoxification. It may also be continued through lapses to alcohol use if this is judged likely to enhance the likelihood of a return to abstinence.

CONCLUSION

Acamprosate has a positive profile in terms of proven effectiveness and good tolerability. Early results from a meta-analysis of randomised controlled trials demonstrate its effectiveness as compared to placebo, but also indicate that up to 17 patients would have to be treated for a single patient to remain abstinent who would otherwise have relapsed. There is no substantial data to indicate which kind of patient is likely to respond. However, acamprosate reduces alcohol consumption (rather than maintains total abstinence) in a greater number of patients. Acamprosate has not been directly compared to its main competitor for alcohol relapse prevention – naltrexone.

DISULFIRAM (ANTABUSE)

Disulfiram acts through the inhibition of the hepatic metabolism of alcohol leading to an escalation of plasma acetaldehyde levels. The rationale of prescribing is one of 'aversive therapy'. The following symptoms may result following alcohol consumption:

- **Flushing of the face.**
- **Pulsating headache.**
- **Vomiting.**
- **Breathing difficulties.**
- **Sweating and thirst.**
- **Blurred vision.**
- **Low blood pressure and dizziness.**
- **Confusion.**
- **The reaction may be fatal in rare instances.**

EFFECTIVENESS

Despite its common-sense advantages there is a surprising lack of quality evidence demonstrating that disulfiram increases abstinence rates. Anecdotal reports suggest success in individual cases especially where a relative or carer is available to supervise daily administration.

SIDE EFFECT PROFILE

There are reports of occasional rashes, tremor, headache, dizziness, peripheral neuropathies and psychosis. There is some evidence that disulfiram may precipitate liver damage, and liver function tests should be performed on a 3 to 6 monthly basis. It is contraindicated in pregnancy and breast-feeding, patients with a history of cardiovascular (including hypertension) or cerebrovascular disorder and in hepatic and renal failure. It should also usually be avoided in patients with a history of deliberate self-harm.

The unpleasant reaction can sometimes be triggered by the presence of alcohol in liquid medicines, remedies, tonics, foods and toiletries – patients must be warned to avoid close contact with or consumption of anything containing alcohol (*see appendix 9,* page129).

DOSAGE AND INDUCTION

Prescribing is usually commenced with a bolus dose of 800mg orally, decreasing to a maintenance dose of between 100mg and 200mg daily thereafter. Disulfiram should not be commenced within 24 hours of the last drink, and it is advisable to perform a breathalyser test before induction. Continuation will usually be for a period of 6 months to one year.

CONCLUSION

In contrast to naltrexone and acamprosate, there is little evidence of disulfiram's effectiveness in preventing relapse, and there are often contraindications to its prescription evident in patients with chronic alcoholism. Nevertheless it remains appropriate for prescription in selected cases.