Treatment options for alcohol use disorders

GRAHAM PARSONS

In part one of our series on the management of alcohol use disorders (AUDs), published in the November issue, we explored the prevalence, harms and identification of AUDs. This second article looks at the pharmacological and psychosocial treatment options across the spectrum of AUDs.

Alcohol use disorders form a continuum of presentations that may require both pharmacological and psychological components of care. Alcohol dependency can often be treated in the community and in primary care but must be managed carefully and with the support of appropriately trained practitioners, as the consequences of a poorly managed medically-assisted detoxification can be significant.

Alcohol withdrawal syndrome

The presentation of alcohol withdrawal syndrome (see Figure 1) can vary from one patient to another but will generally be present for patients with a Severity of Alcohol Dependence Questionnaire (SADQ) score of 16 or above. In general, this is due to the CNS adjusting to the lack of alcohol, which has an inhibitory effect in the brain through its action on GABA receptors.

Alcohol withdrawal syndrome is not a uniform presentation and some patients may experience it worse than others and in different ways. The first symptoms and signs occur within six to 24 hours after the last drink has been consumed and peak within 24 to 48 hours. Symptoms include:

- Restlessness, anxiety, tremor and sweating
- Nausea and vomiting
- Headache
- Loss of appetite
- Insomnia
- Tachycardia, systolic hypertension
- Tactile, auditory and/or visual disturbances
- Seizures.

The severity of these symptoms can be assessed using the validated Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) and can be used to adjust the dose of the benzodiazepine prescribed, as appropriate (see below).
Delirium tremens is a toxic confusional state and represents the extreme manifestation of alcohol withdrawal syndrome. It peaks between 72 and 96 hours of alcohol consumption and results in the death of approximately 5% of patients presenting with it. Symptoms include:

- Disorientation
- Agitation
- Tachycardia (pulse rate >120bpm)
- Hypertension (20mmHg rise in systolic BP)
- Fever
- Visual and auditory hallucinations
- Marked tremor
- Sleeplessness
- Paranoid ideation.

Patients presenting with delirium tremens should be referred to hospital immediately but the best way to prevent this is to manage the detoxification effectively in conjunction with an alcohol specialist service using an appropriate dose of a benzodiazepine.

**Pharmacological management of alcohol dependency**

**Benzodiazepines**

Benzodiazepines are recommended for the management of alcohol withdrawal and detoxification by NICE, the British Association for Psychopharmacology (BAP) and the WHO. A Cochrane review by Amato et al. concluded that benzodiazepines perform better for seizure prevention than placebo (risk ratio 0.16) and show a “potentially protective benefit for many outcomes when compared with other drugs”. NICE recommends a fixed-dose regimen for community-based withdrawal. This involves prescribing a fixed dose of benzodiazepine, which reduces over 7 to 14 days depending on the level of severity of the alcohol dependency as defined by the SADQ. The starting benzodiazepine dose would be higher for severe dependency with a longer reduction regimen period. An example of the starting doses as determined by the SADQ score for different benzodiazepines is illustrated in Table 1.

In general, the choice of benzodiazepine will be determined by the prescriber’s familiarity and confidence with each drug. Chlordiazepoxide has historically been prescribed based on literature that states that it has a “low dependence-forming potential.” However, the short episodes of treatment required for alcohol detoxification makes many clinicians in the field consider this argument to be redundant. In terms of costs, it should be noted that chlordiazepoxide tablets are considerably more expensive than capsules (£49.50 vs £17.80 for 100 x 10mg tablets/capsules respectively) and therefore capsules should be used when possible.

Diazepam has the advantage that it can be prescribed on an instalment prescription (FP10MDA). Long-acting benzodiazepines (such as diazepam) are preferred as prophylaxis in those with a previous history of seizures. Many such patients would of course be excluded from a community alcohol detoxification (see Table 2). The shorter-acting benzodiazepines (oxazepam and lorazepam) can be used in cases of impaired liver metabolism, for example liver failure or in the elderly. A reduced dose should be considered in these cases and liver function monitored carefully.

When managing a benzodiazepine community-based assisted withdrawal programme, NICE also recommends the following:

- No more than two days of medication should be supplied at any time
- The patient should be monitored at least every other day and a family member or carer should preferably oversee the administration of the medication
- The benzodiazepine dose can be adjusted if the patient presents with severe withdrawal symptoms or over-sedation. This can be monitored using a validated tool such as CIWA-Ar.

**Carbamazepine**

NICE states that carbamazepine can be considered (outside its UK marketing authorisation) as an alternative to benzodiazepines for the treatment of acute alcohol withdrawal. In the UK, there is less clinical practice experience in using carbamazepine compared with benzodiazepines, resulting in a tendency to limit its use. A 2014 Cochrane review concluded that there was “insufficient” evidence to support the clinical use of anticonvulsants and recommended that clinicians “need to balance possible benefits/risk of treatment with anticonvulsants versus other medications as supported by evidence of efficacy”. BAP has expressed uncertainty about the role of carbamazepine in the alcohol detoxification process in the UK.

Carbamazepine may have a place in the management of patients who have previously had a sensitivity reaction to a benzodiazepine, have a significant past history of drug misuse (particularly benzodiazepines) or who do not wish to be treated with a family member or carer should preferably oversee the administration of the medication.
with benzodiazepines. It has been suggested that a carbamazepine loading-dose regimen could be an option in patients with untreated epilepsy; those with a history of more than two seizures during previous withdrawal episodes; or previous seizures despite adequate diazepam loading.8 These indications would preclude patients from a community alcohol detoxification (see Table 2).

The BNF recommends a dosage of 800mg carbamazepine daily in divided doses using the immediate-release formulation followed by a reduction to 200mg daily gradually over five days. The recommended duration of treatment is 7 to 10 days.11

**Thiamine and vitamin B compound oral formulations**

The significant health problems (Wernicke’s encephalopathy and Korsakoff syndrome) associated with thiamine depletion have been previously covered in part one of this series. NICE recommends that thiamine should be offered to people at high risk of developing, or with suspected, Wernicke’s encephalopathy and the dose should be “towards the upper end of the British National Formulary range”.3 The uncertainty around the dose range for thiamine is mirrored by a 2013 Cochrane review, which highlighted “insufficient evidence… to guide clinicians in determining the dose, frequency, route or duration of thiamine treatment for prophylaxis against or treatment of Wernicke-Korsakoff syndrome due to alcohol abuse”.12

Thiamine is not synthesised by humans and not stored in large quantities and therefore should be obtained regularly from the diet. When taken orally, bioavailability is limited and has been estimated at between 3.7% and 5.3%.13,14 Oral absorption in malnourished alcohol-dependent patients and in the presence of alcohol is also greatly reduced.15,16 Limited efficacy via the oral route may often be compounded by poor compliance with the three-times daily regimen needed. However, thiamine is rapidly absorbed when administered by intramuscular (IM) injection.

NICE recommends prophylactic oral thiamine for harmful or dependent drinkers:  
- If they are malnourished or at risk of malnourishment or  
- If they have decompensated liver disease or  
- If they are in acute withdrawal or  
- Before and during a planned medically-assisted withdrawal.9

NICE recommend prophylactic parenteral thiamine followed by oral thiamine for harmful, dependent drinkers or those with suspected Wernicke’s encephalopathy:  
- If they are malnourished or at risk of malnourishment or  
- If they have decompensated liver disease and in addition:  
  - They attend an emergency department or  
  - Are admitted to hospital with an acute illness or injury.9

This caution around the use of parenteral thiamine relates to the risk of serious allergic reactions (anaphylactic shock) associated with its use.17 Nevertheless, the risk associated with the IM thiamine preparation is currently estimated at less than 1 in 5,000,000.10 Considering this information and the limited bioavailability of oral thiamine, some specialist alcohol services support the use of Pabrinex Intramuscular High Potency Injection (containing ascorbic acid, pyridoxine, nicotinamide, thiamine and riboflavin) in the community, following a Wernicke-Korsakoff syndrome risk assessment (using a tool such as the Pabrinex Scoring System18 or the AlcoPath WEKP tool19) and provided certain conditions are in place (see Table 3). BAP recommend a prophylactic dose of one pair of ampoules once daily for three to five days or until no further improvement is seen for patients at high risk of Wernicke-Korsakoff syndrome.3

The use of vitamin B compound tablets is not recommended by NICE but the Royal College of Physicians (RCP) has highlighted that vitamin B deficiencies are “particularly common”, with pyridoxine (vitamin B6) deficiency reported in 50% of untreated alcoholics and riboflavin (vitamin B2) deficiency in 17%.20 However, there is a general consensus among experts that the treatment of thiamine deficiency remains the primary concern in this cohort.

**The pharmacological management of other AUDs and aftercare planning**

**Acamprosate**

Acamprosate is recommended by NICE as an option following:  
- “Successful withdrawal… in combination with an individual psychological intervention… focussed specifically on alcohol misuse”  
- “Harmful drinkers and people with mild alcohol dependence who have not responded to psychological interventions alone, or who have specifically requested a pharmacological interven-

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**Table 1. Suggested benzodiazepine starting doses for alcohol detoxification**

<table>
<thead>
<tr>
<th>SADQ score</th>
<th>Moderate dependency</th>
<th>Severe dependency</th>
<th>Very severe dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td>15–29</td>
<td>15–25mg four times a day</td>
<td>30–40mg four times a day</td>
<td>50mg four times a day</td>
</tr>
<tr>
<td>30–40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>41–60</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Suggested benzodiazepine starting doses for alcohol detoxification**

<table>
<thead>
<tr>
<th>Initial dose of chlor Diazepoxide</th>
<th>Moderate dependency</th>
<th>Severe dependency</th>
<th>Very severe dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg four times a day</td>
<td>1000mg four times a day</td>
<td>1500mg four times a day</td>
<td>2000mg four times a day</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Initial dose of oxazepam</th>
<th>Moderate dependency</th>
<th>Severe dependency</th>
<th>Very severe dependency</th>
</tr>
</thead>
<tbody>
<tr>
<td>800mg four times a day</td>
<td>1000mg four times a day</td>
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Disulfiram
NICE recommends disulfiram, in combination with a psychological intervention, following a successful withdrawal, for service users with moderate and severe alcohol dependence who:
- Have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable or
- Prefer disulfiram and understand the relative risks of taking the drug.²

To optimise compliance, the dose of disulfiram should be supervised, as otherwise disulfiram is no better than basic support.³ This can be done by a carer or family member, who should be involved in the process.

Disulfiram blocks aldehyde dehydrogenase causing an accumulation of acetaldehyde if alcohol is consumed. This results in a number of adverse effects including nausea, flushing and palpitations, commonly termed the disulfiram-alcohol reaction (DAR). The DAR effects begin with facial flushing and throbbing in the head and neck. Respiratory difficulties, nausea, copious vomiting, sweating, thirst, chest pain, tachycardia, palpitations, marked hypotension, giddiness, weakness, blurred vision and confusion may follow. Severe reactions, including respiratory depression, cardiovascular collapse, cardiac arrhythmias, myocardial infarction, acute heart failure, unconsciousness, convulsions and sudden death, have been reported.²³ Patients should be advised to not consume alcohol 24 hours prior to starting disulfiram and for up to 14 days after stopping the drug. Alcohol in perfume, aerosol sprays and other cosmetic products, in addition to alcohol in food and medicine, may also cause a DAR.

Disulfiram should only be initiated by a specialist prescriber experienced in its use and at least 24 hours after the last alcoholic drink has been consumed. The usual dosage is 200mg daily but this can be increased after one week if the patient continues to drink and the 200mg daily dosage does not cause a sufficiently unpleasant reaction to deter drinking.² There is no evidence to guide how long to prescribe disulfiram but a period of 6–12 months seems reasonable, provided it is supported with regular reviews and psychosocial interventions.

Pabrinex Intramuscular High Potency injection should be administered by a trained doctor, nurse or pharmacist and their competency assessed by a competent clinician
- The clinician administering the Pabrinex IM high-potency injection should ensure their basic life support, including anaphylaxis training, is up-to-date
- Adrenaline 1:1000 IM injection should be available
- The clinician should remain with the patient for 15 to 30 minutes after the injection to ensure there are no untoward adverse effects
- The patient should be transported urgently to a hospital if they require further treatment

Naltrexone
NICE recommends naltrexone for the same conditions as acamprosate (see above).² The evidence base from several meta-analyses and systematic reviews suggests that naltrexone significantly reduces return to heavy drinking but does not necessarily improve cumulative or continuous abstinence rates.³

NICE recommends a starting dose of 25mg daily, aiming for a maintenance dosage of 50mg daily for a treatment period of “up to 6 months, or longer for those benefiting from the drug who want to continue with it”.² The Summary of Product Characteristics does not recommend a standard duration of treatment but recommends an initial period of three months and recognises that “prolonged administration may be necessary”.²²

Table 2. NICE criteria for inpatient or residential-assisted withdrawal

Drinking over 30 units of alcohol per day
- Having a score of more than 30 on the SADIQ
- Having a history of epilepsy, or experience of withdrawal-related seizures or delirium tremens during previous assisted withdrawal programmes
- Needing concurrent withdrawal from alcohol and benzodiazepines
- Regularly drinking between 15 and 30 units of alcohol per day and having:
  - Significant psychiatric or physical co-morbidities or
  - A significant learning disability or cognitive impairment

Table 3. Minimum requirements for administering Pabrinex Intramuscular High Potency injection in the community (based on Thompson and Marshall²⁴)
Baclofen
NICE does not discuss the use of baclofen in the treatment of AUDs. Its use has been popularised recently, although the evidence base for its use still remains “insufficient.” NICE also cites evidence from an Italian randomised controlled trial of baclofen in cirrhotic alcohol-dependent patients wanting to be abstinent. The trial showed that baclofen at a dosage of 30mg daily significantly increased the number of subjects maintaining abstinence compared with placebo (71% vs 29%). However, NICE also cites a USA study that demonstrated “no superiority of baclofen in reducing heavy drinking or increasing abstinence.” NICE recommends that baclofen should be considered if a patient:
• Wants to be abstinent and
• Has high levels of anxiety and
• Has not benefited from or is unable to take acamprosate, naltrexone or disulfiram.

The unlicensed prescribing of baclofen for supporting abstinence following an alcohol detoxification should in general be limited to specialists familiar with its use for AUDs. As the adverse effects are predominantly at the start of treatment and are dose related, the dose should be started at 5mg three times daily and increased, if necessary, once or twice a week to a maximum dosage of 60mg daily.

Pragmatically, the length of treatment should mirror the advice on drugs used to support alcohol abstinence in NICE CG115; ie prescribe for a period of 6–12 months initially but this may be longer for those benefiting from the drug who want to continue it. Baclofen should be stopped if the patient is not responding to treatment but psychosocial interventions should continue. An abrupt withdrawal can cause a range of problems including psychiatric reactions and convulsions. It is therefore advised that, except in the case of serious adverse effects, a gradual dose reduction is undertaken over at least one to two weeks.

Nalmefene
Nalmefene is only licensed for use for the reduction of alcohol consumption in “adult patients with alcohol dependence who have a high drinking risk level, without physical withdrawal symptoms and who do not require immediate detoxification... in conjunction with continuous psychosocial support.” Although supported by NICE for use “within its marketing authorisation”, recent reviews have expressed concern about the evidence base supporting its use.

Shared care prescribing of drugs to support alcohol abstinence
Following a suitable period in specialist care, specialist prescribers may ask their primary care colleagues to take over the prescribing of acamprosate, naltrexone and disulfiram. This supports holistic care and the re-integration of patients into primary care as they move towards recovery.

When transferring patients to primary care, specialist prescribers should outline the roles and responsibilities of both the specialist prescriber and primary care prescriber. Drug information and referral mechanisms should also be provided to the primary care prescriber, which will enable them to take clinical responsibility for the prescribing of these drugs. This process is supported by the GMC, which recommends that prescribing should be based on the “patient’s best interests, rather than on [the prescriber’s] convenience or the cost of the medicine and associated monitoring or follow-up.”

Non-drug interventions for the management of AUDs
Psychological interventions should always be a component of aftercare planning following a medically-assisted withdrawal programme. NICE recommends individual psychological interventions, such as cognitive behavioural therapy (CBT) or behavioural therapies (focused on alcohol-related problems and consisting of one 60-minute session per week for 12 weeks), and group-based programmes, including social network and environment-based therapies. Self-help groups such as Alcoholics Anonymous (AA) or SMART Recovery can also be utilised.

For harmful drinkers and those with mild dependency (SADQ of 15 or below), similar programmes can be used. NICE also recommends brief or simple advice for patients who are drinking at hazardous or harmful levels (AUDIT scores 8 to 19). These sessions should last for 5–15 minutes and should be based on an evidence-based resource such as FRAMES:
• Feedback – on the service user’s level of risk of having alcohol problems
• Responsibility – for change lies with the service user
• Advice – provision of clear advice when requested
• Menu of options – exploration of options for change
• Empathy – warm, reflective and understanding approach
• Self-efficacy – optimism based on past achievement.

Extended brief interventions can be delivered by trained staff for adults who have not responded to the brief structured advice.

Summary
Benzodiazepines remain the main pharmacological intervention for supporting patients undertaking an alcohol detoxification programme but carbamazepine may also be an option in some circumstances. The role of thiamine in this process and to help prevent Wernicke-Korsakoff syndrome in some harmful drinkers cannot be underestimated.

A number of other drugs are also available to support patients following their alcohol detoxification and may also be used for selected patients who are harmful drinkers. These may be prescribed in primary care as part of a shared care arrangement or by prescribers with the necessary competencies to prescribe.

Non-drug interventions also remain an important element of treatment. These range from brief interventions for decreasing risk for harmful drinkers to CBT-based and self-help groups for...
dependent drinkers. Prescribers should be familiar with these interventions and where patients can access them within their locality.

References

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