

## **Drugs for alcohol dependence**

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### **Abstract**

There is good evidence for the use of pharmacological treatments to improve outcomes in patients with alcohol use disorders (AUD). The management of acute withdrawal should include a high risk of suspicion for Wernicke–Korsakoff Syndrome, necessitating treatment with parenteral high-potency B vitamins (Pabrinex®). Benzodiazepines in reducing doses should be used in conjunction with a continuing treatment plan after detox (detox). The relapse prevention medications acamprosate and naltrexone should be considered in all patients with moderate to severe alcohol dependence wishing to maintain abstinence. Disulfiram can be considered as a second-line treatment, but should be initiated by a specialist. Nalmefene has been shown to be effective in patients with mild dependence wishing to reduce their alcohol consumption. Baclofen has a temporary indication in France, and may have a role in patients with co-morbid liver disease and anxiety, but its efficacy remains unproven.

### **Keywords:**

Acamprosate, alcohol dependence, baclofen, chlordiazepoxide, disulfiram, nalmefene, naltrexone, relapse prevention, thiamine

## Key Points

- In all patients presenting in alcohol withdrawal, have a high index of suspicion of Wernicke–Korsakoff syndrome and a low threshold for treatment
- Relapse prevention medication should be considered in all patients with moderate to severe alcohol dependence as part of a detox plan
- Alcohol use disorders present in a wide range of acute and community medical settings, are frequently co-morbid with other physical and mental illnesses and require immediate management
- Medication for these patients is often suboptimal, leading to missed opportunities to improve health outcomes

## Management of alcohol withdrawal

Patients presenting with symptoms of alcohol withdrawal require a quantified assessment of their alcohol use, including number of units of alcohol per day, duration of daily drinking, history of any previous seizures, and rating of severity of their alcohol withdrawal using a validated scale (e.g. revised Clinical Institute Withdrawal Assessment for Alcohol scale- CIWA-R) to assess the need for medically assisted detox (see Alcohol use disorders, pp xxx–xxx of this issue).

Unless a patient can be managed on a well-resourced unit where regular assessment of withdrawal symptoms can be undertaken, a fixed-dose reducing regimen of a benzodiazepine (diazepam or chlordiazepoxide) four times daily over 5–10 days is recommended over ‘symptom-triggered’ (as required) prescribing.<sup>1,2</sup> Patients should not be started on a medically assisted detox in the community unless there is adequate provision for monitoring and a clear management plan for the maintenance of abstinence. In patients with severe liver disease, a shorter acting benzodiazepine that is not metabolized in the liver (e.g. oxazepam or lorazepam) may be safer to reduce risk of encephalopathy and sedation. It is important to monitor the response to ensure that patients are neither over-sedated nor under-treated. Patients should be made aware of the risks of taking benzodiazepines together with alcohol and encouraged to develop a collaborative plan for remaining abstinent at the end of the assisted withdrawal period.

Wernicke–Korsakoff syndrome, caused by acute-on-chronic thiamine (vitamin B<sub>1</sub>) deficiency, can present while a patient is still drinking or during withdrawal, so a presumed diagnosis in any alcohol-dependent patient with confusion is advised.<sup>1,2</sup> Oral absorption of thiamine is low in this patient group; ensuring adequate doses of parenteral thiamine is a priority and is imperative before giving glucose infusions, which can cause Wernicke–Korsakoff syndrome in susceptible individuals. Oral thiamine (100 mg three times daily) should be continued for at least 6 weeks after detox until patients are eating normally (Table 1).

## Management of relapse prevention (Table 2)

After detox, as well as the behavioural and social adaptations that the patient should make to maintain abstinence from alcohol, neuroadaptation of the  $\gamma$ -aminobutyric acid (GABA) / glutamatergic systems continues as the brain adjusts to the alcohol free environment. As a result, patients can have heightened levels of anxiety and agitation, often leading to cravings for alcohol.

*Acamprosate* modulates the *N*-methyl-D-aspartate receptor and indirectly enhances GABA function; both of these are altered during alcohol withdrawal and the early stages of abstinence. *Acamprosate* is a first-line treatment and should be started by the end of detox to be most effective.

*Naltrexone* is an opioid antagonist, which acts indirectly to reduce craving, and has been

found to be more effective in the prevention of return to heavy drinking than the maintenance of abstinence. It may therefore be the first-line choice in those who are unlikely to achieve abstinence immediately. Patients should be advised against the concomitant use of opioids. It has a better tolerability profile in men, and therefore should be started at a half dose (25 mg daily) in women.

*Disulfiram* acts by irreversible inactivation of acetaldehyde dehydrogenase (ALDH) enzymes in the liver. It is a second-line choice and should only be started by specialists in motivated patients who have had a thorough risk assessment. It takes approximately 5 days for new ALDH to be made, and patients are at risk of an aversive reaction to alcohol during this time. Earlier reports (in the 1950s) of it causing or worsening psychosis have not been seen since doses have been reduced to 200 mg daily (from 2 g).<sup>3</sup> Patients taking disulfiram should be warned about the interaction between disulfiram and alcohol, which can manifest as flushing, nausea, palpitations and, more seriously, arrhythmias, hypertension and collapse.<sup>2</sup>

*Nalmefene* is another opioid antagonist, differing from naltrexone in that it is a partial agonist at the kappa ( $\kappa$ ) receptor. It has a licence for the reduction of alcohol consumption in individuals with mild dependence who do not need an immediate detox. It can be used on an 'as required' basis when patients fear they are at risk of drinking. It does not need to be started within specialist services and, as with the other medications, should be given alongside psychosocial support.

*Baclofen* is a GABA-B agonist, although its precise mechanism of action is not fully understood. It is excreted primarily unchanged by the kidney, but there appears to be significant inter-subject variation, and the therapeutic dosing window is not yet clear. Baclofen is a central nervous system depressant so there are potential concerns regarding overdose, but it may have a role in patients with severe liver disease and anxiety.<sup>3</sup>

Insert Table 12 here

## **Table 1 Management of Wernicke–Korsakoff syndrome (WKS)<sup>4</sup>**

### **Have a low threshold for treatment**

**Prophylactic treatment** for patients at risk of WKS should be:

• **One pair of i.m./i.v. ampoules of high-potency B-complex vitamins (Pabrinex®) daily for 3–5 days**

(Thiamine 200–300 mg i.m. daily can be given if Pabrinex® is unavailable)

**Therapeutic treatment for presumed/diagnosed WKS** consists of:

Give 2-3 pairs of i.v. ampoules (*i.e.* 4-6 ampoules) of high-potency B-complex vitamins *three times daily for 2 days*

- If no response, discontinue treatment
- If signs/symptoms respond, continue one pair of i.v. or i.m. ampoules daily for 5 days *or for as long as improvement continues*

i.m., intramuscular; i.v., intravascular.

**Table 2 Medications licensed for use in the treatment of alcohol dependence**

<b>Medication</b>	<b>Standard adult dose</b>	<b>Cautions</b>	<b>Duration</b>	<b>Main Use</b>
Acamprosate	666 mg (two tablets) t.d.s	Elderly patients, renal insufficiency. Check LFTs	6–12 months. Stop if relapse of >6 weeks	Maintenance of abstinence
Naltrexone	50 mg daily	No concomitant opioid use, reduced tolerability in women. Check LFTs	6–12 months. Stop if relapse of >6 weeks	Prevention of relapse to heavy drinking
Disulfiram	200 mg daily. Can start with loading dose if required	Patient needs to be aware of avoiding alcohol in all products (e.g. perfume, mouthwash). Risk assessment required. Improved effectiveness if 'witnessed'	6--12 months. Stop immediately on resumption of drinking	Maintenance of abstinence
Nalmefene	18 mg, as required, up to once daily	No concomitant opioid use	Up to 6 months	Reduction of alcohol consumption
Baclofen *(therapeutic dose not established)	Starting dose 5 mg t.d.s. Doses above 90 mg daily not advised *	Serious respiratory depression in overdose, especially with alcohol. Potential for own withdrawal syndrome	Not established	'Temporary recommendation for use' in France for maintenance of alcohol abstinence

LFT, liver function test; t.d.s., three times daily.

## KEY REFERENCES

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