



## Review

### Pharmacological interventions for alcohol relapse prevention

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(Received 09 December 2014 and accepted 08 February 2015)

**ABSTRACT:** Alcohol dependence is a chronic, debilitating disorder that is an important public health problem worldwide. Combined psychological and pharmacological treatment packages produce best outcomes in its management. In this paper we discuss the three NICE – approved relapse prevention medications used in treatment of alcohol dependence: acamprosate, naltrexone and disulfiram. We review the pharmacological profile, mode of action, pharmacokinetics, and safety and tolerability of each of these pharmacological interventions. We discuss how each intervention can be used in clinical practice and review the efficacy of each drug. No one drug is clearly superior to the other, and clinical factors and patient choice should inform the choice of drug.

**KEY WORDS:** *Alcohol; Dependence; Pharmacological treatment*

#### INTRODUCTION

Alcohol dependence is described in the International Classification of Diseases 10 as a 'cluster of physiological, behavioural, and cognitive phenomena in which the use of alcohol takes on a much higher priority for a given individual than other behaviours that once had greater value'<sup>1</sup>. Key characteristics of this syndrome include craving, physiological withdrawals, tolerance, loss of control and persistent use. Alcohol dependence exists on a continuum ranging from mild to moderate to severe and it can be a chronic relapsing condition. Alcohol dependence, affecting 6% of men and 2% of women in England, can have wide-ranging adverse consequences on the individual, family and wider society. After a successful withdrawal of alcohol (often by detoxification), for the management of those who are moderately or severely dependent on alcohol a combination of pharmacological and psychological interventions is recommended. In this paper we discuss three National Institute For Health And Care Excellence (NICE) - approved

medications (acamprosate, naltrexone and disulfiram) for use in alcohol relapse prevention<sup>2</sup>.

#### ACAMPROSATE

##### Pharmacological profile

Acamprosate (calcium acetylhomotaurinate, brand name Campral) is an amino acid (homotaurine) derivative. It is a calcium salt of N-acetyl homotaurine, and is structurally similar to neurotransmitters (both excitatory and inhibitory) such as glutamate, GABA ( $\gamma$ -aminobutyric acid), glycine and taurine.

##### Mode of Action

Acamprosate is thought to reduce processes related to alcohol withdrawal, as well as reducing the rewarding effects of alcohol<sup>3</sup>. Acamprosate has been demonstrated to bind to specific spermidine-sensitive sites that modulate the N-methyl-D-aspartate (NMDA) receptor in a complicated manner.

It is proposed that acamprosate normalises the dysregulation in neuronal firing by targeting both N-methyl-D-aspartate (NMDA) glutamatergic and GABA receptor activity. Chronic alcohol consumption leads to increased GABAergic activity, which is reduced during withdrawal.

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Chronic alcohol consumption also leads to increased synaptic expression of NMDA receptors (neuroadaptation). Sudden removal of alcohol leaves the NMDA-receptor system unopposed in a state of hyperactivity, which produces symptoms associated with acute alcohol withdrawal. By acting as an agonist on the GABA receptor, and by its actions centrally it restores normal activity. It is therefore thought to normalise the balance between excitatory and inhibitory pathways, and to alleviate discomfort following withdrawal.

Acamprosate is also hypothesised to act as a “partial co-agonist” at the NMDA receptor, where concentrations enhance activation when receptor activity is low, and high concentrations inhibit activation when receptor activity is high<sup>4</sup>. It is therefore thought to normalise the balance between excitatory and inhibitory pathways, and to alleviate discomfort following withdrawal. In this way, acamprosate is said to be a NMDA receptor modulator rather than a direct antagonist, potentially working via a spermidine-sensitive binding site<sup>5</sup>.

#### *Pharmacokinetics*

Acamprosate is poorly absorbed, and its bioavailability in humans is very low<sup>6</sup>. It is thought to be absorbed via a paracellular route<sup>7</sup> via the gastrointestinal tract and it is not protein bound or metabolised. It is also not metabolised by the liver; approximately 90% of the drug is excreted unchanged in the urine<sup>8</sup>. This is clinically important as it can be administered to patients with hepatitis or liver disease.

#### *Safety and tolerability*

Acamprosate is extremely safe and is generally well tolerated by patients. Occasional side effects include diarrhoea, nausea and vomiting; skin rashes are rarely seen, and more often than not most side effects are fleeting. Acamprosate has no abuse potential.

Acamprosate does not have significant drug interactions with many of the medications that are commonly used to treat alcohol dependence and other psychiatric disorders (including naltrexone, antidepressants, anxiolytics, and hypnotics)

#### **How to use in clinical practice**

The recommended dose of acamprosate is 666 mg three times daily (for those with bodyweight of 60 kg or over), and 666 mg in the morning, 333mg in the afternoon and 333 mg in the evening for those whose bodyweight is 60 kg or less. It can be started during or soon after withdrawal of alcohol. NICE recommends prescribing acamprosate for up to 6 months, or longer for those who are doing well on

it. It should be discontinued if drinking persists 4 to 6 weeks after commencing treatment.

#### **Efficacy**

A meta-analysis of 17 studies, with a total of 4087 individuals revealed that continuous abstinence rates from alcohol at 6 months were significantly higher in the acamprosate-treated patients<sup>9</sup>. At 12 months, the overall pooled difference between acamprosate and placebo for continued abstinence was 13.3%. The effect size in abstinence rates at 3, 6, and 12 months were 1.33%, 1.50%, and 1.95% respectively. A recent Cochrane review concluded that acamprosate was moderately effective in increasing abstinence after detoxification. It showed that acamprosate reduced the rate of patients returning to any drinking (relative risk [RR] 0.86, 95% CI 0.81-0.91; NNT = 9) and increased the cumulative abstinence duration by an average of 11 percent compared with the control group<sup>10</sup>.

#### **NALTREXONE**

##### **Pharmacological profile**

#### *Mode of action*

Naltrexone is an opioid antagonist, acting primarily on the mu receptors. It is hypothesised that naltrexone blocks the release of dopamine induced by alcohol consumption. This consequently reduces the rewarding effects of alcohol. In this way, naltrexone is thought to reduce craving to drink and loss of control, resulting in fewer relapses.

#### *Pharmacokinetics*

Following oral administration, naltrexone undergoes rapid and nearly complete absorption with approximately 96% of the dose absorbed from the gastrointestinal tract. Naltrexone is subject to significant first pass metabolism and oral bioavailability estimates range from 5 to 40%. The activity of the drug is thought to be due to the parent and the 6β-naltrexol metabolite, both of which are excreted primarily by the kidney.

#### *Safety and tolerability*

Naltrexone cannot be given to patients taking opioids. If opioids are required to treat pain, naltrexone should be discontinued. Some of the side effects of oral naltrexone are nausea, headache, and dizziness, which usually subside with continued use. Occasionally naltrexone can cause elevated liver enzymes and hence liver functions should be monitored periodically during naltrexone treatment. Naltrexone is contraindicated in acute hepatitis or liver failure.

## How to use in clinical practice

Naltrexone can be started soon after withdrawal of alcohol. The standard dose of naltrexone is 50 mg daily, usually starting at 25 mg for the first day or two. Prior to commencement it needs to be established that the patient is not on any opioid medication, and that liver functions are within reasonable limits. It is sensible to have a baseline liver function profile. Although routine blood monitoring is not advised it should be considered should clinical reasons indicate it. NICE recommends maintaining patients on naltrexone for 6 months and longer if they continue to benefit.

## Efficacy

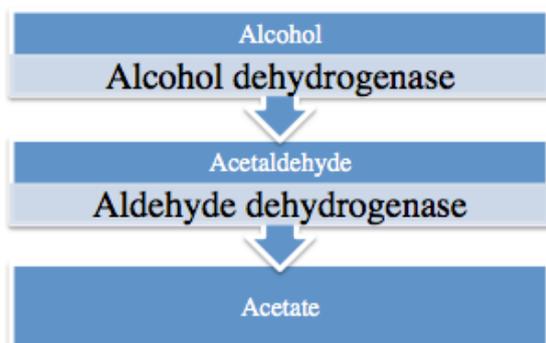
Naltrexone reduces the frequency and intensity of drinking, and helps in preventing a lapse become a relapse<sup>11</sup>. A Cochrane review of 50 randomised trials with 7793 alcohol dependent patients found that naltrexone significantly reduced the risk of returning to heavy drinking to 83% compared to the placebo group. Furthermore, the number of drinking days was decreased by approximately 4% and heavy drinking days by 3% in comparison to the placebo group<sup>12</sup>. The COMBINE study, the largest controlled clinical trial in the field of alcohol dependence, found that naltrexone was significantly more effective than placebo<sup>13</sup>.

## DISULFIRAM

### Pharmacological profile

#### Mode of action

The primary pharmacologic action of disulfiram involves the disruption of normal alcohol metabolism. Alcohol is metabolised as shown below:



Unlike other medications for alcohol dependence, disulfiram does not affect brain opiate,  $\gamma$ -aminobutyric acid, or glutamate receptors directly. Disulfiram irreversibly inhibits the liver enzyme aldehyde dehydrogenase (ALDH), leading to the

accumulation of acetaldehyde. If alcohol is consumed once disulfiram is ingested, acetaldehyde accumulates in the blood resulting in the so-called unpleasant 'disulfiram-alcohol reaction'<sup>14</sup>. This reaction may persist for 30 minutes to several hours, or as long as alcohol remains in the blood.

#### Disulfiram-alcohol reaction

The reaction occurs approximately 10 minutes after ingestion of alcohol and can last from 3 minutes to 2 hours, varying from moderate to severe. Symptoms include nausea, throbbing headache, vomiting, chest pain, hypotension, flushing, sweating, thirst, dyspnea, tachycardia, vertigo, and blurred vision<sup>15</sup>. Severe aversive effects include respiratory depression, severe cardiac problems or seizures<sup>15</sup>.

#### Pharmacokinetics

Disulfiram is rapidly metabolised into its active metabolite, Me-DTC (S-methyl-N, N-diethylthiocarbamate). Approximately 80-95% of disulfiram is absorbed from the gastrointestinal tract. The fraction that remains unabsorbed is excreted (approximately 20%). The estimated half-life is 60-120 hours, thus it may take 1-2 weeks for total elimination from the body since the last dose<sup>16</sup>. The plasma half-life for Me-DTC is about ten hours, but the enzyme inhibiting effect of ALDH lasts considerably longer. The effect of the drug can thus persist for 7 to 14 days after discontinuation.

#### Safety and tolerability

As noted, if alcohol is consumed while a patient is on disulfiram, the concentrations of blood acetaldehyde will increase in proportion to alcohol intake, and the patient will experience the acetaldehyde syndrome (flushing, systemic vasodilation, respiratory difficulties, nausea, hypotension, and other symptoms). Prolonged administration of disulfiram does not produce tolerance, but rather, leads to increased sensitivity to alcohol (the longer a patient is treated with disulfiram, the more sensitive they become to alcohol)<sup>17</sup>.

Side effects are not common but may include drowsiness, nausea, halitosis and rarely allergic skin reactions or reduced libido. Rarely, disulfiram can cause acute hepatotoxicity and thus should be administered with caution, particularly for patients with liver disease. Disulfiram is contraindicated for those with psychoses or cardiac conditions including hypertension, as hypotension features in the disulfiram reaction. Contraindications are focused on avoidance of alcohol or alcohol-

containing deodorants, anti-perspirants, aftershaves, lotions, creams, food preparations, etc.

### Efficacy

Jorgensen *et al* in their meta-analysis found that disulfiram was helpful in reducing the number of drinking days, increasing abstinence in the short-term and slightly improving days to relapse compared to placebo, no disulfiram, or other treatments<sup>17</sup>. Disulfiram's effectiveness relies on the expectation of the disulfiram-alcohol reaction and thus the psychological component of the treatment is vital. There is evidence to suggest that patients who are motivated not to drink, have a longer drinking history, and are older, socially more stable or cognitively intact, may be more likely to adhere to medication<sup>18,19</sup>. A recent meta-analysis also concluded that disulfiram was significantly superiorly to the control when medication compliance was supervised<sup>20</sup>. Without supervision, treatment showed no significant efficacy. After combining 22 RCTs, the meta-analysis showed a significant success rate of disulfiram compared to controls.

### How to use in clinical practice

The recommended starting dose is 200 mg daily. Wherever possible it should be supervised, usually by a family member. Disulfiram should not be administered until the patient has abstained from alcohol for at least 24 hours. On stopping disulfiram, a patient should not drink alcohol for one week, as its effect can last for up to two weeks after the last dose. NICE recommends continuation of disulfiram for up to six months, or longer if beneficial.

### CONCLUSION

In summary, acamprosate, naltrexone and disulfiram are the only three drugs approved by NICE for use as alcohol relapse prevention agents. NICE recommends use of acamprosate or naltrexone as first line agents and disulfiram to be considered for patients 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'. There is no unequivocal evidence to suggest that any one of these three drugs is better than the other. It is also to be noted that all pharmacological treatments should be offered in conjunction with psychological interventions.

### Key points

1. Acamprosate, naltrexone and disulfiram are the only three alcohol relapse prevention medications approved by NICE.

2. NICE recommends using acamprosate or naltrexone as first line, and disulfiram only if the other two are not suitable or if the patient prefers disulfiram.
3. No one drug is clearly superior to the other, and clinical factors and patient choice should inform the choice of drug.
4. These pharmacological treatments should always be provided alongside structured psychological interventions.

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