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**Review article: pharmacotherapy for alcohol dependence: the  
why, the what and the wherefore**

*Short title: Pharmacotherapy for alcohol dependence*

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## Summary

### Background

The development of alcohol dependence is associated with significant morbidity and mortality. For the majority of affected people the most appropriate goal, in terms of drinking behaviour, is abstinence from alcohol. Psychosocial intervention is the mainstay of the treatment but adjuvant pharmacotherapy is also available and its use recommended.

### Aim

This review aims to provide an updated analysis of current and potential pharmacotherapeutic options for the management of alcohol dependence. In addition, factors predictive of therapeutic outcome, including compliance and pharmacogenetics, and the current barriers to treatment, including doctors' unwillingness to prescribe these agents, will be explored.

### Methods

Relevant papers were selected for review following extensive, language- and date-unrestricted, electronic and manual searches of the literature.

### Results

Acamprosate and naltrexone have a substantial evidence base for overall efficacy, safety, and cost-effectiveness while the risks associated with the use of disulfiram are well-known and can be minimized with appropriate patient selection and supervision. Acamprosate can be used safely in patients with liver disease and in those with co-morbid mental health issues and co-occurring drug-related problems. A number of other agents are being investigated for potential use for this indication including, baclofen, topiramate and metadoxine.

### Conclusion

Pharmacotherapy for alcohol dependence has been shown to be moderately efficacious with few safety concerns but it is substantially underutilized. Concerted efforts must be made to remove the barriers to treatment in order to optimize the management of people with this condition.

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## BACKGROUND

### Alcohol Misuse, Health and Societal Costs

Approximately 80% of the adult population in the United Kingdom (UK) consume alcohol.<sup>1</sup> The majority of people drink responsibly with no associated harmful effects. However, in England in 2014, 22% of men and 16% of women, amounting to some 10.3 million adults, consumed alcohol in a way that was potentially or actually harmful to their health and well-being.<sup>1</sup> It has been estimated that 5.9 % of the adult population in England (8.7% of men and 3.3% of women) are alcohol dependent.<sup>2</sup> Based on current population estimates this equates to some 3.2 million people, although the figure more frequently quoted is 1.6 million.<sup>3</sup>

In 2014/5 there were an estimated 1.1 million alcohol-related hospital admission in England, representing a 115% increase over 2003/4.<sup>4,5</sup> A total of 8,697 wholly attributable alcohol-related deaths were registered in the UK during 2014, two-thirds of which were attributed to alcohol-related liver disease.<sup>6</sup> However, a considerably higher estimate of 25,332 can be extrapolated from data provided by Public Health England based on a combination of all deaths relating to alcohol-specific conditions together with those where alcohol was causally implicated in some but not all cases.<sup>7</sup> The estimated cost of alcohol misuse to the National Health Service (NHS) is £3.5 billion per annum, while the overall costs of alcohol-related societal harm approximates to £21 billion per annum.<sup>8</sup>

In the United States of America (USA) the proportion of adults consuming alcohol is lower than in the UK at 46.3%.<sup>9</sup> The 12-month prevalence of alcohol dependence is estimated to be 3.8 % (men 5.4%; women 2.3%) while the estimated lifetime prevalence is 12.5% (men 17.4%; women 8.0%).<sup>10</sup> Alcohol dependence is associated with more than 85,000 deaths per year making it the third leading cause of preventable deaths in the USA;<sup>11</sup> the estimated annual cost to society is more than \$220 billion.<sup>12</sup>

### Alcohol Dependence: Definitions, Diagnosis and Natural History

A proportion of people consuming alcohol at harmful levels will develop alcohol dependence. This condition is characterized by craving; tolerance; a preoccupation with alcohol; continued drinking in spite of harmful consequences; and the development of a physiological withdrawal syndrome when alcohol is suddenly stopped or consumption reduced.<sup>13</sup> More exact definitions of this condition, which is officially recognized as a mental health disorder, are provided by the World Health Organization in the *International Classification of Diseases (ICD)*<sup>14</sup> and by the American

Psychiatric Association in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).<sup>15</sup> The ICD-10 and DSM-IV diagnostic criteria for alcohol dependence largely overlap and have high diagnostic concordance (Table 1).<sup>16</sup>

The diagnosis of alcohol dependence is usually made by reviewing the clinical history but this can be imprecise if the patient is unaware, or reluctant to reveal the extent of their problems with alcohol. However, questionnaires can facilitate the process. *The Alcohol Use Disorders Identification Test* (AUDIT),<sup>17</sup> for example, which was developed as a World Health Organization (WHO) collaborative initiative, is designed to identify people who have an alcohol use disorder; a score of  $\geq 8$  indicates hazardous/harmful drinking whilst a score of  $>16$  indicates alcohol dependence.<sup>17</sup>

Harmful alcohol use and alcohol dependence are relatively uncommon before the age of 15 but, thereafter, the prevalence increases steeply reaching a peak in the early twenties before declining. In one UK study the prevalence of alcohol dependence was 6% in 16 to 19 year olds, 8.2% in 20 to 24 year olds, 3.6% in 30 to 34 year olds, and 2.3% in 50 to 54 year olds.<sup>18</sup> Thus, substantial remission from alcohol dependence can occur, over time, often without intervention.<sup>19</sup> However, those who remain dependent in their forties tend to have a more chronic course; most studies find that 70 to 80% of people entering specialist treatment will relapse in the year after completing treatment, most likely in the first three months.<sup>20, 21</sup> Those who remain abstinent from alcohol for the first year after treatment have a relatively low risk of relapse thereafter.<sup>22</sup>

The long term prognosis for people entering specialist treatment is comparatively poor. Over a 10-year period about one third have continuing alcohol problems; a third show some improvement and a third have a good outcome defined as either abstinence or moderate drinking.<sup>23</sup> The mortality rate in this population is nearly four times the age-adjusted rate for people who are not alcohol dependent. Much of the excess mortality is accounted for by disorders associated with co-morbid tobacco use, including, cardiovascular disease and aerodigestive malignancies.<sup>23,24</sup>

## **The Treatment of Alcohol Dependence**

The severity of alcohol dependence can be assessed using the *Severity of Alcohol Dependence Questionnaire* (SADQ);<sup>25</sup> the information provided can facilitate clinical management.

The initial step in the treatment of alcohol dependence is withdrawal from alcohol. In some, but not all instances, medical assistance will be required to prevent or to treat the withdrawal symptoms;

benzodiazepines are the drugs most commonly employed to facilitate this process.<sup>13,26,27</sup> Expert guidance on the withdrawal process, including all aspects of patient safety and general well-being, is available from the UK National Institute for Health and Care Excellence (NICE).<sup>13,26</sup> People with mild dependence (SADQ score <15) do not usually need medically-assisted withdrawal; people with moderate dependence (SADQ 15 to 30) usually do need medical assistance, typically in a community setting;<sup>21</sup> while people who are severely alcohol dependent (SADQ score >30) will require medically-assisted withdrawal, typically in an inpatient or residential setting.

Withdrawal management is not a stand-alone process but should be the first phase of a longer term treatment plan. For the majority of people who are dependent on alcohol the most appropriate goal, in terms of alcohol consumption, is total abstinence. For people with significant psychiatric or physical co-morbidity, for example, a depressive disorder or alcohol-related cirrhosis, abstinence should always be the goal. Nevertheless, some people will not accede to this advice, preferring a goal of moderation. However, the more severe the level of dependence the less likely it is that a return to moderate or controlled drinking will be possible.<sup>22,28</sup> Thus, where a clinician believes that abstinence is the most appropriate goal they should strongly advise this course, but should not deny treatment if this advice is not heeded.<sup>21</sup>

Psychosocial intervention is the mainstay of the treatment for alcohol dependence.<sup>13</sup> In the UK, NICE has provided detailed guidance on the provision of psychosocial support tailored to reflect the severity of the dependence.<sup>13</sup> Services are delivered by both statutory and non-statutory providers and additional sources of support, such as self-help based interventions, are encouraged. NICE also recommends the use of adjuvant pharmacotherapy for people with moderate to severe dependence once they had been successfully withdrawn from alcohol.<sup>13</sup> They also recommend adjuvant pharmacotherapy for people with mild dependence who have either not responded to initial attempts to attain abstinence or have specifically requested it.<sup>13</sup>

Similar approaches to the treatment of alcohol dependence are employed in Europe,<sup>29</sup> the USA,<sup>30-32</sup> and Australia.<sup>33</sup> The latest French good practice recommendations,<sup>29</sup> published by the Société Française d'Alcoologie in partnership with the European Federation of Addiction Societies, recommend the use of pharmacological treatments, combined with psychosocial support, for relapse prevention in patients with alcohol dependence.<sup>29</sup> Likewise, in the USA, the Veterans Administration (VA),<sup>30</sup> National Institute on Alcohol Abuse and Alcoholism (NIAAA),<sup>31</sup> and Substance Abuse and Mental Health Services Administration (SAMHSA),<sup>32</sup> all advocate the use of

adjuvant pharmacotherapy, in combination with behavioural intervention or addiction-focused counselling, for the management of alcohol dependence. Finally, the Australian guidelines for the treatment of alcohol problems<sup>33</sup> stipulate that pharmacotherapy should be considered for all alcohol-dependent patients following detoxification---best used in association with psychosocial supports as part of an after-care treatment plan.

In this review the efficacy and safety of current and future potential pharmacotherapeutic agents for the management of alcohol dependence will be assessed; their use in clinical practice will be detailed; factors predictive of treatment outcomes, including compliance and pharmacogenetics, will be delineated; and the current barriers to treatment will be explored.

## **METHODS**

A general literature search was undertaken for articles on the generic topic '*treatment of alcohol dependence*'. In addition a specific language-unrestricted electronic search was undertaken of the Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Library, MEDLINE, EMBASE, and Science Citation Index for pharmacotherapeutic trials published between 1966 to October 2016; this was supplemented by manual searches of the bibliographies of relevant papers, specialist journals, conference proceedings, and trial registries.

## **RESULTS**

### **Licensed Pharmacotherapies for the Maintenance of Abstinence**

Disulfiram, acamprosate and naltrexone are the only pharmaceutical agents licensed for the maintenance of abstinence/relapse prevention in dependent drinkers in the majority of countries advocating the use of pharmacotherapy for the management of alcohol dependence (Table 2). Nalmefene has recently been licensed, in some countries, for use in people who are drinking at high risk levels who wish to reduce their alcohol consumption but not necessarily abstain.

#### **(i) Disulfiram**

Disulfiram has been used in clinical practice for the last 60 years; the oral preparation is licensed for relapse prevention in the UK, much of Europe, North America, Australia and parts of Asia. Despite its apparent efficacy, when used in compliant and/or supervised patients, overall its use remains controversial.

### ***Mode of action***

Alcohol is metabolized in the liver, *via* the enzyme alcohol dehydrogenase, to acetaldehyde and then to acetate *via* the enzyme acetaldehyde dehydrogenase (ALDH). Disulfiram is an oral ALDH inhibitor. The high levels of acetaldehyde which accumulate following alcohol ingestion in people taking disulfiram result in the development of a constellation of symptoms such as flushing, nausea, vomiting, tachycardia, hypotension, dyspnoea, dizziness and headache.<sup>34</sup> These symptoms appear approximately 5 to 15 min after alcohol consumption and last from 30 minutes to several hours. The intensity of the reaction varies with the amount of alcohol consumed and can prove fatal.<sup>35,36</sup> The fear of the unpleasant effects provoked by alcohol is believed to be the primary mechanism facilitating abstinence from alcohol.<sup>37,38</sup>

Disulfiram has been used in the treatment of cocaine addiction particularly in people with co-morbid alcohol-related problems.<sup>39-41</sup> It inhibits the enzyme dopamine  $\beta$ -hydroxylase, which converts dopamine to norepinephrine, and may reduce cocaine use because it inhibits the associated noradrenergic-mediated 'high'.<sup>42</sup>

### ***Efficacy***

There is no consensus on the optimal trial methodology for assessing the efficacy of disulfiram as a treatment for alcohol dependence. It has long been held that it can not be appraised fairly in double-blind randomized controlled trials (RCTs) because the psychological fear of provoking an unpleasant disulfiram-alcohol reaction is key to its effectiveness.

A number of systematic reviews and meta-analyses of the available trial data have been undertaken,<sup>13,41,43,44</sup> with a degree of consensus on treatment efficacy. The most comprehensive of these<sup>41</sup> included a total of 22 RCTs, published between 1973 and 2010, comparing the efficacy of disulfiram to no treatment, placebo or other pharmacological treatments, irrespective of blinding or supervision of medication. Based on the results of the open-label studies, where compliance was assured by supervision, disulfiram is a safe and efficacious treatment compared to no treatment or to other pharmacological agents.<sup>41</sup> However, no evidence of efficacy was found in blinded RCTs or where there was no supervision.<sup>41</sup>

### ***Safety***

The side-effects associated with use of disulfiram include: headaches, drowsiness, lethargy, peripheral neuropathy, optic neuritis, hepatotoxicity and psychosis.<sup>36,45,46</sup> In general the moderately severe side-effect profile can be offset by careful patient selection and supervision.

### ***Therapeutic use***

There are a number of contra-indications to the use of disulfiram including: cardiovascular disease, systemic hypertension, severe personality disorder, suicidal risk/psychosis, pregnancy/breast-feeding. Caution is also advised in the presence of renal failure, hepatic or respiratory disease, diabetes mellitus and epilepsy. NICE guidance suggests that disulfiram should be used as second-line treatment after acamprosate or naltrexone or if a strong preference for its use is expressed.<sup>13</sup> Treatment should be started at least 24 hours after the last alcoholic drink in a dose of 200 mg per day; warnings should be provided about the nature and seriousness of the interaction with ingested alcohol and the presence of alcohol in foodstuffs, perfumes and aerosol sprays. Supervision should be sought whenever possible. Treatment, if successful and relatively free from side-effects, may be continued long-term.

### **(ii) Acamprosate**

Acamprosate was introduced into clinical practice 30 years ago; the oral preparation is licensed for the maintenance of abstinence in alcohol dependent people in a wide range of countries including the UK, most of Europe, North America, Australia, parts of Asia and Africa and, most recently, Japan.

### ***Mode of action***

Acamprosate is the calcium salt of N-acetyl-homotaurine. Its mechanism of action is unclear although it has been ascribed to aspects of glutamatergic and/or GABA-ergic neurotransmission; it is most frequently referred to as a 'functional glutamate antagonist'.<sup>47</sup> Recently, however, it has been suggested that acamprosate has no direct neurotransmitter target and that the therapeutic effects associated with its use are due to the co-administered calcium moiety.<sup>48,49</sup> These findings have yet to be substantiated but the role of plasma and/or brain levels of calcium as a correlate or mediating factor in relation to the drug's efficacy may need to be further explored.<sup>49</sup>

### ***Efficacy***

The results of a large number of RCTs and meta-analyses<sup>13,44,50-53</sup> have shown that treatment with acamprosate, in conjunction with psychosocial support, significantly increases the proportion of alcohol dependent patients who remained completely abstinent from alcohol at 6 months. Mann *et al.*,<sup>50</sup> in a meta-analysis of 17 RCTs, involving 4087 participants, showed that 36.1% of patients receiving acamprosate achieved this endpoint compared with 23.4% of those receiving placebo;



overall the number needed to treat (NNT) to achieve continuous abstinence was 7.8 at 6 months and 7.5 at 12 months.<sup>50</sup>

A Cochrane review, including 24 RCTs with 6915 participants,<sup>51</sup> showed a significant beneficial effect of acamprosate on a number of outcome measures other than abstinence; thus its use was associated with a reduction in the return to *any* drinking with a NNT of 9; a reduction in the risk of any drinking to 86% of the placebo rate and an increase in the number of abstinent days by approximately three per month.<sup>51</sup>

### ***Safety***

Acamprosate is not metabolized in the liver and has no impact on drugs subject to hepatic metabolism or those which affect the cytochrome P450 system. Thus, it does not interact with alcohol and it is generally safe in patients with impaired hepatic function. However, as it is excreted predominantly *via* the kidney it should be used with care in people with renal insufficiency. Acamprosate is well tolerated.<sup>46</sup> Pharmacovigilance data in 1.5 million patients indicate no serious adverse events;<sup>54</sup> the most commonly reported side-effect is diarrhoea.<sup>50</sup> It does not have addictive potential and appears safe in overdose.<sup>47</sup>

### ***Therapeutic use***

Acamprosate is contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min) and in those who are hypersensitive to the drug or any of its components.

Guidelines in the UK,<sup>13</sup> France,<sup>29</sup> the USA,<sup>30,31</sup> and Australia<sup>33</sup> recommend that acamprosate is used as first-line treatment for alcohol dependence. It should be started as soon as possible after assisted withdrawal from alcohol in a daily divided dose of 1998 mg in people weighing >60 kg and of 1332 mg in those weighing <60 kg.<sup>13</sup> There is no need to adjust the dose in people with mild to moderate hepatic impairment, although dose adjustment is recommended in people with moderate renal impairment.<sup>13</sup> Treatment should continue for 6 months or longer in those deriving benefit who wish to continue; it can be continued if patients lapse but should be stopped if drinking persists beyond 4 to 6 weeks.<sup>13</sup>

### **(iii) Naltrexone**

Naltrexone has been used in the management of opioid dependence since 1984; it was first used to treat alcohol dependence in 1994. The oral preparation is licensed for relapse prevention in alcohol

dependent people in a wide range of countries including the UK, much of Europe, the USA, Australia and Asia.

### ***Mode of action***

Naltrexone and its active metabolite 6 $\beta$ -naltrexol act as opioid receptor antagonists, particularly at the  $\mu$ -opioid receptor. Its excretion is primarily renal. The mechanism of its beneficial effect in the treatment of alcohol dependence is not fully understood although it is believed to reduce the reward effects of alcohol by modulating the dopaminergic mesolimbic pathway.<sup>55,56</sup>

### ***Efficacy***

A substantial number of RCTs have been undertaken to examine the efficacy of naltrexone for the treatment of alcohol dependence. These have been the subject of a number of systematic reviews and meta-analyses employing varying inclusion criteria and drinking outcomes but, nevertheless, with broadly comparable results.<sup>13,44,52,54,57-59</sup> Thus, in alcohol dependent people who have been withdrawn from alcohol, naltrexone, in combination with psychosocial support, has a modest, albeit significant beneficial effect on relapse rates, and in reducing alcohol intake.

A Cochrane systematic review and meta-analysis, including 40 placebo-controlled RCTs of naltrexone, involving approximately 4500 participants, showed that treatment with naltrexone significantly reduced the risk of a return to heavy drinking to 83% of the placebo rate with a NNT of 9.<sup>58</sup> Treatment was also associated with a 4% reduction in the number of drinking days; a 3% reduction in the number of heavy drinking days; and a reduction in the amount of alcohol consumed, on drinking days, by about 11 grams. It did not, however, have a significant effect on the return to *any* drinking.<sup>58</sup> The effect on overall abstinence rates was not determined.

The results of a number of other meta-analyses confirm the effects of naltrexone in reducing the risk of a relapse to heavy drinking and the number of drinks consumed on drinking days;<sup>57-59</sup> some found that its use was, in addition, associated with a significant, albeit modest effect on the return to *any* drinking and overall abstinence rates.<sup>57,59</sup>

### ***Safety***

Naltrexone is metabolized in the liver *via* the enzyme dihydrodiol dehydrogenase predominantly to 6 $\beta$ -naltrexol; the metabolites are further conjugation with glucuronide. As naltrexone is not metabolized *via* the cytochrome P450 system interactions with drugs subject to hepatic metabolism are likely to be minimal. However, increased plasma naltrexone concentrations have been reported

in patients with cirrhosis. Naltrexone does not interact with alcohol and does not have addictive potential

The most commonly reported side-effects are nausea, vomiting, dizziness, abdominal pain, reduced appetite, headache and day-time sleepiness; these are dose-dependent and appear to be worse in women.<sup>46</sup> Hepatotoxicity has been reported in association with use of naltrexone in doses of >300 mg/day to treat obesity.<sup>60</sup> However, reviews of the available safety data have confirmed that hepatic toxicity is very unlikely to occur with the standard daily dose of 50 mg.<sup>13</sup>

The most important safety consideration in relation to naltrexone is its reaction with opioid drugs. Opioid receptor blockade persists for 48 to 72 hours after the last oral dose; thus, in an emergency non-opioid analgesia would have to be used for pain relief. If future use of opioids is anticipated, for example for elective surgery, then naltrexone should be discontinued ahead of time.

### ***Therapeutic use***

Naltrexone is contraindicated in individuals taking or likely to take opioids. It is also contraindicated in people with acute hepatitis and acute or chronic liver failure. It should be used with caution in people with serum transaminase activities exceeding three times the upper reference range and in patients with renal failure. At present there is no consistent advice about monitoring of liver function tests in people receiving this drug but NICE guidance recommends that this should be considered in the elderly and the obese and that the drug should be discontinued immediately if the user feels unwell.<sup>13</sup>

Guidelines in the UK,<sup>13</sup> France,<sup>29</sup> the USA,<sup>30,31</sup> and Australia<sup>33</sup> recommend that naltrexone should be considered as a first-line treatment for alcohol dependence. Opioids should be stopped 7 to 10 days beforehand but treatment can be started while patients are still drinking and during medically-assisted withdrawal from alcohol. An initial dose of 25 mg/day is recommended increasing over a period of two weeks to a maintenance dose of 50 mg/day.<sup>13</sup> Treatment should be continued for 6 months or longer in those deriving benefit who wish to continue; it can be continued if patients lapse but should be stopped if drinking persists beyond 4 to 6 weeks.<sup>13</sup>

### **Combined treatment with acamprosate and naltrexone**

The effect sizes of acamprosate and naltrexone are modest and hence the effects of combining the two treatments has been explored.<sup>61,62</sup>

Keifer *et al.*,<sup>61</sup> randomized 160 severely dependent drinkers to acamprosate, naltrexone, acamprosate/naltrexone combined or placebo for 12 weeks; all participants received specific relapse prevention intervention. Both acamprosate and naltrexone and their combination had a positive treatment effect relative to placebo; the naltrexone/acamprosate combination was more effective than acamprosate alone but comparable in effect to naltrexone alone. Anton *et al.*,<sup>62</sup> randomized 1383 much less severely dependent drinkers to the same four arms of treatment for 16 weeks; participants were further randomized to receive one of two different types of behavioural therapy. Outcomes improved in all participant groups but were significantly better in those receiving naltrexone together with intensive behavioural therapy; combining treatments had no additional beneficial effect. Meta-analysis of these two trials confirmed that there were no significant differences in outcome favouring combined treatment.<sup>13,58</sup>

Co-administration of acamprosate and naltrexone results in a 33% increase in the peak plasma concentrations of acamprosate and a reduction in the time to reach peak plasma levels but has no effect on the pharmacokinetics of naltrexone. Thus, the incidence of diarrhoea and nausea was, as expected, significantly higher in the combined treatment groups, in both trials.<sup>58,61,62</sup>

#### **(iv) Nalmefene**

Nalmefene is an opioid system modulator which is structurally similar to naltrexone but it has a slightly different receptor profile. It was first introduced into clinical practice for the treatment of alcohol dependence in the early 1990s.<sup>63-65</sup> However, a meta-analysis of the three RCTs available from that time, which utilized daily doses in the 20 to 80 mg range, showed that although nalmefene had some beneficial effect on drinking outcomes none of these was significant.<sup>58</sup>

Subsequently the drug was remarketed and licensed, on the basis of a small number of additional industry-sponsored initiatives,<sup>66-70</sup> for use in people who were drinking harmfully and wanted to reduce, though not necessarily stop, their alcohol consumption. However, this so called ‘harm reduction’ approach to alcohol problems remain controversial.<sup>71</sup> Thus, although several studies have demonstrated that controlled drinking is possible and that moderation-based treatments may be preferred over abstinence-only approaches, the evidence base for using this approach is not strong.

Nevertheless, in 2013 nalmefene was approved by the European Medicines Agency as a treatment for alcohol dependence in people who wish to reduce their alcohol consumption but not necessarily abstain. It was granted a licence in Scotland in October 2013. In November 2014, NICE,<sup>72</sup> despite

concerns raised by its own Evidence Review Group,<sup>73</sup> recommended nalmefene, taken in a dose of 18 mg daily, as needed, together with psychosocial support, as a treatment option for people drinking at high risk levels who, although alcohol dependent, did not need medically-assisted withdrawal from alcohol and wished to reduce rather than stop alcohol. In France nalmefene is recommended as the first-line medication for reducing alcohol consumption in people who are alcohol dependent.<sup>29</sup> Regulators and advisory bodies in other European countries for example, Germany and Sweden, have not recommended nalmefene for this indication. The drug is not licensed for use in the USA or Australia

Palpaceur *et al.*,<sup>74</sup> have recently undertaken a meta-analysis of the efficacy and safety of nalmefene for the treatment of alcohol dependence. They included all available RCTs of nalmefene irrespective of publication status, primary outcomes and licensed indications.<sup>63-70</sup> Overall there was some evidence of a beneficial effect of nalmefene on the number of heavy drinking days per month and on total alcohol consumption but there were more withdrawals for safety reasons in the nalmefene-treated groups and the findings were not robust. There was no evidence of a beneficial effect of nalmefene on the health outcomes examined. The authors concluded that, at best, nalmefene has limited efficacy in reducing alcohol consumption but they were clearly aware of the limitations of their review and made specific recommendations for future studies.

The licensing and subsequent recommendations for the therapeutic use of nalmefene have been widely criticized.<sup>75,76</sup> The major objections raised include: (i) the target population was defined following an unplanned subgroup analysis of the available trials, thus departing from the intention-to-treat principle; (ii) the placebo comparator was inappropriate – the efficacy of nalmefene should have been compared with naltrexone which is used off- label for this indication; (iii) the supposed advantage conferred by nalmefene on alcohol consumption levels was of questionable clinical relevance; and, (iv) no evidence of wider harm reduction was sought or provided in the trials included for review.

As nalmefene is an opioid receptor antagonist the same precautions and guidance provided for naltrexone in relation to opioid usage should apply. The most commonly encountered side-effects are nausea, insomnia, dizziness, vomiting and fatigue. However, use of naltrexone has not been associated with evident hepatotoxicity. Naltrexone is considerably more expensive than the other drugs licensed to treat alcohol dependence, at least in the UK.

## Emerging Treatments for Alcohol Dependence

A number of other agents have been proposed and are currently under investigation as potential treatment options for alcohol dependence.<sup>77-82</sup> The majority already have a therapeutic profile and are being repurposed for use in this field. Of these baclofen, topiramate and metadoxine are the best known, but others with an evidence base include: (i) gabapentin: an inhibitor of presynaptic, voltage-gated sodium and calcium channels which is approved for the treatment of epilepsy and neuropathic pain; (ii) ondansetron: a serotonin 5-HT<sub>3</sub> receptor antagonist which is used to prevent nausea and vomiting in selected clinical situations; (iii) varenicline: a nicotinic receptor partial agonist which is used for smoking cessation; and, (iv) aripiprazole: an antipsychotic which is a partial dopamine agonist. None of these compounds is licenced for the treatment of alcohol dependence but can of course be used off-label.

### (i) Baclofen

Baclofen is a selective  $\gamma$ -aminobutyric acid (GABA)-B receptor agonist which was originally approved for the treatment of spasticity associated with multiple sclerosis and spinal cord lesions. Activation of GABA-B receptors might reduce anxiety and it was for this reason that it was identified as a potential treatment for alcohol withdrawal and dependence.

A number of placebo-controlled RCTs of baclofen, 30 to 60 mg/day, have been undertaken but with widely different results.<sup>83-88</sup> A series of trials undertaken by one Italian group,<sup>83-85</sup> including a trial in patients with cirrhosis,<sup>84</sup> showed significantly higher abstinence rates in participants receiving baclofen compared with placebo, together with improvements in other drinking outcomes.<sup>83,85</sup> However, studies undertaken in the United States,<sup>86</sup> Australia,<sup>87</sup> and Israel<sup>88</sup> showed no beneficial effects of baclofen over placebo on any drinking outcome, although a *post hoc* analysis of the Australian data showed that baclofen conferred some benefit, in terms of relapse behaviour, in a subgroup of patients with a co-morbid anxiety disorder.<sup>87</sup> Overall the drug was well-tolerated.

The divergent results of these studies have not been fully explained. One suggestion is that they may relate to the relatively low doses of baclofen used in the trials undertaken to date. Baclofen is rapidly absorbed and excreted primarily unchanged by the kidney but there is significant inter-subject variation in its pharmacokinetics, which could potentially be reflected in differences in population responses. This view was supported by the self-reported experience of a French physician who treated his own alcohol dependence and anxiety disorder with baclofen in a dose of 270 mg/day.<sup>89,90</sup> The consequent media interest resulted in an unprecedented demand, in France,

for off-label treatment with high dose baclofen.<sup>91,92</sup> In 2014, baclofen, in doses up to 300 mg/day, was authorized by the French Health Agency (FHA) as a second-line drug to prevent relapse or reduce drinking in people with alcohol dependence.<sup>93</sup> This authorization which is a specific measure known as a ‘temporary recommendation for use’ (TRU) requires centralized collection of follow-up data.<sup>93</sup>

Studies utilizing high doses of baclofen are now being reported. A German group randomized 56 alcohol dependent people to either baclofen titrated to 270 mg/day or placebo.<sup>94</sup> The mean daily dose of baclofen achieved during the 12 week high dose phase of the trial was 180 mg and during this phase abstinence rates were higher in those receiving baclofen than placebo (68.2% vs. 23.8%,  $p = 0.014$ ); baclofen also had a significant beneficial effect on overall abstinence rates during the 20 week trial (42.9% vs. 14.3%  $p=0.04$ ). However, there was no relationship between the individualized doses of baclofen and drinking behaviour outcomes suggesting that the efficacy of baclofen does not have a clear dose threshold. .

A multicentre RCT<sup>95</sup> undertaken in the Netherlands randomly assigned 151 alcohol dependent individuals to six weeks titration and ten weeks maintenance with either low-dose baclofen (30 mg/day), high-dose baclofen (up to 150 mg/day; mean 94 mg/day), or placebo. No significant differences were observed between the groups in the time to first relapse; the proportions who relapsed; the proportions who attained continuously abstinence; the cumulative abstinence duration; or the drop-out rates. Two important considerations need to be taken into account in relation to this trial *viz.*: (i) the drug dosage schedule and degree of psychosocial support differed between patients recruited from inpatient and outpatient facilities; and, (ii) the continuous abstinence rates were very high *viz.* high dose baclofen 62.5% cf. placebo 65.9%.

The results of two French high-dose baclofen studies, which will be pivotal in determining whether the TUR currently in place will be removed by the FHA or made official, have been reported but in abstract form only.<sup>96,97</sup> In the first of these – the ALPADIR study<sup>96</sup> - 320 alcohol dependent outpatients attending French specialist alcohol treatment clinics were randomized to baclofen (target dose 180 mg/day attained by 66%) or placebo using a 7-week titration, and 17 weeks maintenance paradigm. The proportions of patients who were continuously abstinent throughout the trial were similar in both groups *viz.* baclofen 11.9%; placebo 10.5%. Post-hoc subgroup analyses showed more evidence of benefit in the heaviest drinkers and when the outcome variable selected was the overall reduction in consumption.

The second of these French studies--the multicenter BACLOVILLE study—was designed to explore pragmatic risk reduction in a general practice.<sup>98</sup> A total of 320 attendees diagnosed as having an alcohol use disorder were randomized to treatment with baclofen, individually titrated to a maximum dose of 300 mg/day, or placebo for 12 months. There was no requirement for participants to be withdrawn from alcohol or to receive psychosocial support. The primary outcome, which was the proportion of patients who achieved WHO defined safe drinking levels (1-20 g/day for women and 1 - 40 g/day for men) was attained by 56.8% of the baclofen group and 36.5% of the placebo group (risk reduction 1.56 [95% CI 1.15, 2.11]; p = 0.004). At present no other information on outcome variables or safety is available.<sup>98</sup>

These four high dose baclofen studies are not directly comparable as they differ considerably in aspects of patient selection; study design and duration; dosage schedules and outcome variables. In addition the reporting of the two French studies is still incomplete. Thus overall conclusions about the efficacy of baclofen as a treatment for alcohol dependence can not be made at this time.

Baclofen and alcohol are both central nervous depressants so there are considerable safety concerns around use of this drug.<sup>46</sup> Fatigue, sleep disorders and vertigo/dizziness were more frequent in those taking the active drug particularly in the high-dose studies. Reports of further adverse event such as major sedation,<sup>99</sup> seizures,<sup>100</sup> mania,<sup>101</sup> and sleep apnoea<sup>102</sup> are increasing in parallel with increased use of this drug.

## **(ii) Topiramate**

Topiramate is a potent antiepileptic with strong neuroprotective properties. It has many proposed targets of action, including facilitation of GABA-A receptor activity, and reduction of glutamate activity in  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and kainate receptors. Like many other drugs proposed for the treatment of alcohol dependence it is thought to reduce mesolimbic dopaminergic activity. A small number of RCTs of topiramate versus placebo, no treatment or an active comparator for the treatment of alcohol dependence have been undertaken and subjected to systematic review with or without meta-analysis.<sup>103,104</sup> A systematic review of topiramate versus placebo<sup>103</sup> including seven RCTs, involving 1,125 participants, demonstrated significant, though moderate, benefits of topiramate for abstinence and heavy drinking outcomes. A more generic Cochrane review of anticonvulsants in the management of alcohol dependence<sup>104</sup> included a separate analysis of six placebo-controlled RCTs of topiramate, involving 970 participants, and showed a modest but significant beneficial effect on heavy drinking and the



number of drinks per drinking day but a rather less robust effect on the number of abstinent days. Topiramate in a dose of 300 mg/day appears to be relatively well tolerated with the most common adverse effects being dizziness, paraesthesia, and anorexia. However, all the trials undertaken to date are short-term; with longer-term treatment there is potential, given the drug's safety profile, for the emergence of other side effects such as difficulties with memory and cognitive impairment.

### **(iii) Metadoxine**

Metadoxine (pyridoxal L-2-pyrrolidone-5-carboxylate) is an ion pair salt of pyridoxine and L-pyroglutamate. It is approved in several European countries, India, the Russian Federation, and Brazil for treating acute alcohol intoxication, based on its ability, when given as a single 900 mg intravenous dose, to facilitate the elimination of alcohol from blood and tissues.<sup>105</sup> Metadoxine has also been used to treat alcohol dependence based on its properties as a selective serotonin receptor subtype 5-HT<sub>2B</sub> antagonist and a monoamine-independent GABA modulator.<sup>106</sup> In an open label study patients treated with metadoxine, 1500 mg/day in divided doses, were significantly more likely to maintain abstinence at 3 months than untreated controls (44.8% vs. 21.6%;  $p < 0.004$ ).<sup>107</sup> In a randomized, open-label study in patients with severe alcoholic hepatitis survivors who received metadoxine, in addition to standard therapy, were significantly more likely to maintain abstinence at 6 months than those who did not (74.5% vs. 59.4%,  $p = 0.02$ ).<sup>108</sup> Metadoxine has an excellent safety record.<sup>109</sup> Its use needs to be further explored.

## **Pharmacotherapy in Specific Situations**

### **Alcohol-related liver disease**

The most important management goal for patients with significant alcohol-related liver injury is abstinence from alcohol. Nevertheless this aspect of their management, and in particular the use of adjuvant pharmacotherapy to achieve this goal, is inconsistently addressed in the literature with scant or no mention by some<sup>110,111</sup> but specific mention by others.<sup>112-114</sup>

No RCTs of the three main medications currently licensed for the treatment of alcohol dependence have been undertaken in people with significant alcohol-related liver injury. Of these acamprosate has the best safety profile.<sup>46,51,54</sup> It is not metabolised in the liver and there are no reported instances of hepatotoxicity. Further, Delgrange *et al.*,<sup>115</sup> reported, in a single dose RCT, that acamprosate does not adversely affect neuropsychiatric status in patients with Child's Grade A and B cirrhosis. Hepatotoxicity has not emerged as a clinical problem with naltrexone in standard doses,

although hepatotoxicity is a concern, in certain circumstances, when higher doses are used.<sup>60</sup> Patients with advanced liver disease are particularly vulnerable to naltrexone-induced hepatotoxicity<sup>116</sup> so its use in this situation would need to be monitored carefully. Use of disulfiram has been complicated by the development of hepatotoxicity which is associated with a mortality rate of 28%.<sup>117</sup> It is best avoided in patients with chronic liver disease.

Baclofen in a dose of 30 mg/day has been shown, in one RCT, to be a safe and effective treatment for alcohol dependence in patients with cirrhosis.<sup>84</sup> However, the study population was very carefully selected to excluded people with diabetes, hepatic encephalopathy, psychiatric co-morbidity and co-morbid drug misuse. Hence, the safety findings in this study may not be generalizable. In addition, much higher doses of baclofen are now being used to treat alcohol dependence but no information is available on the safety profile associated with these dose levels in patients with liver disease; until this information is available considerable caution should be exercised in use of this drug in this setting.

Topiramate has only rarely been linked to clinically apparent liver injury. However, as it is metabolized *via* CYP3A4 it may potentiate the hepatotoxicity associated with other drugs metabolised *via* this system. The anti-epileptic drug sodium valproate, for example, inhibits the first enzyme in the urea cycle and its use may be associated with the development of hyperammonaemic encephalopathy; co-medication with topiramate increases the circulating levels of free valproate and significantly increases the risk of this potentially fatal complication.<sup>118</sup>

Metadoxine has an excellent safety profile and has been shown to have utility not only to treat alcohol dependence but also alcohol-related liver disease. It accelerates the normalization of liver function tests and the liver appearance on ultrasound in individuals with alcohol-related steatosis, even in those who do not completely abstinent from alcohol.<sup>119</sup> In patients with severe alcoholic hepatitis treated with prednisolone the addition of metadoxine significantly improved survival, compared with prednisolone alone, both at 30 days (74.3% *vs.* 45.7%;  $p = 0.02$ ) and at 90 days (68.6% *vs.* 20.0%;  $p = 0.0001$ ).<sup>120</sup> The addition of metadoxine also significantly reduced the development/progression of hepatic encephalopathy (29.6% *vs.* 60.0%;  $p = 0.008$ ) and hepatorenal syndrome (31.4% *vs.* 54.3%;  $p = 0.05$ ).<sup>120</sup> These beneficial effects likely relate to the fact that metadoxine is an antioxidant and has also been shown to inhibit hepatic lipid accumulation and protect against glutathione depletion.<sup>121</sup> Further studies with this drug are clearly needed.

Both the American and European Associations for the Study of the Liver <sup>122,123</sup> recommend the use of acamprosate and naltrexone, in conjunction with psychosocial support, to decrease the likelihood of relapse in patients with alcohol-related liver disease. Future recommendations with regard to the use of baclofen in this setting will require a more extensive evidence base

### **Co-morbid psychiatric disorders and co-occurring drug misuse**

Psychiatric co-morbidity and co-occurring drug misuse are common in people with alcohol dependence. However, pharmacological intervention for alcohol dependence, in these situations, has received very little attention.<sup>13</sup>

People with alcohol dependence are frequently anxious and/or depressed but these symptoms often remit once they achieve abstinence or significantly reduce their alcohol intake.<sup>13</sup> Medication for depression and anxiety is often ineffective in people who are consuming significant amounts of alcohol either for relieving the psychiatric symptoms or for curbing the alcohol misuse.<sup>124,125</sup> In consequence, guidance from NICE recommends focusing on the management of the alcohol misuse as the first priority.<sup>13</sup> Acamprosate can be used to facilitate abstinence under these circumstances; it is well-tolerated; it does not interact with alcohol or have addictive potential; and is safe in overdose. Naltrexone and disulfiram both interact with alcohol and are less safe in these situations. If, however, symptoms of significant anxiety or depression remain after 3 to 4 weeks of abstinence from alcohol then patients should be referred appropriately for specific management of their mental health disorder.<sup>126</sup> People with alcohol dependence and significant co-morbid mental problems, such as schizophrenia or bipolar disorder, and those assessed to be at high risk of suicide, should be referred to a psychiatrist to make sure that effective assessment, treatment and risk-management plans are put in place.<sup>127</sup>

Alcohol and illicit drug dependence often co-occur. Treatment of the drug misuse must be optimised using psychosocial and/or pharmacological approaches, as appropriate, <sup>128</sup> but the alcohol misuse must also be specifically addressed. Naltrexone is not an option in individuals who have used or are using opioids and there are no published studies of acamprosate in opioid-dependent populations. Nevertheless, acamprosate is safe, well-tolerated and does not interact with the commonly used illicit drugs or with methadone or the antiviral agents use to treat co-morbid hepatitis C or HIV infection.

## **Predictors of Outcome**

The drugs currently available for the treatment of alcohol dependence have only modest effects and attempts have been made to optimise treatment by identifying people more likely to respond. These attempts are confounded by the so-called ‘placebo effect’ and by factors pertaining to adherence and compliance with treatment.

### **The placebo effect**

The placebo effect can confound efforts to determine treatment effectiveness in clinical trials. The greater the placebo group response the more difficult it is to demonstrate medication efficacy. The placebo response in trials of drugs for alcohol dependence appears to be even greater than, for example, trials in depression and schizophrenia. Further, more recent studies in alcohol dependence have shown greater placebo group improvement, an effect which persists even after controlling for several other moderators, including concomitant interventions. Thus, attempts will need to be made to more effectively isolate alcohol medication effects in future studies.<sup>129, 130</sup>

### **Compliance and adherence**

The clinical effectiveness of any medication is highly influenced by the degree of patient compliance and adherence to treatment regimens. Trials of drugs for the treatment of alcohol dependence, as in the addiction field generally, are characterized by high dropout rates and generally low levels of compliance with treatment.<sup>42, 51, 58</sup> However, very little information is available on the factors which affect compliance in this setting. Rohsenow *et al.*,<sup>131</sup> found that compliance with naltrexone was better in those who believed that the medication would help them maintain abstinence, and was not predicted by demographic or pre-treatment alcohol use, commitment to abstinence or perceptions about their own ability to abstain. Supervision or witnessing, which are employed primarily in patients receiving disulfiram, are a major determinant of compliance and hence effectiveness.<sup>42</sup>

### **Demography, drinking variables and co-morbidities**

A number of demographic variables, along with features of the drinking behaviour and potential co-morbidities, have been explored and several possible predictors of outcome identified, but the results are inconsistent. The most favourable results in people receiving unsupervised disulfiram were in those who were older; more socially stable; impulsive; and motivated.<sup>34,132</sup> Pooled data from seven placebo-controlled RCTs of acamprosate, involving 1485 participants, showed that there were no significant relationships between treatment outcome and gender, the age of onset, the

severity of dependence or family history.<sup>133</sup> A number of studies have reported that people with a family history of alcohol-related problems are more likely to benefit from naltrexone but other identified predictors such as high levels of craving, early age of onset, concomitant drug misuse and co-morbid depression are not as robust.<sup>134-136</sup> Mann *et al.*,<sup>137</sup> have shown, using functional cerebral MRI, that alcohol dependent people with high brain activity in the ventral striatum in response to alcohol cues had significantly better treatment outcomes with naltrexone. High cue reactivity as an ‘endophenotype’ might help to prospectively identify alcohol-dependent patients likely to respond to treatment. However, for obvious reasons, this approach is likely to be limited to studying the mechanisms of treatment responses.

### **Pharmacogenetics**

A number of studies have examined the role of the single nucleotide polymorphism (SNP) rs1799971 in the  $\mu$ -opioid receptor 1 gene (*OPRM1*) in relation to the response to treatment with naltrexone. Several, but not all, have reported a link between possession of the G allele of rs1799971 and better drinking outcomes. Anton *et al.*,<sup>138</sup> for example, showed that individuals carrying the G allele were more likely to attain abstinence and to have less heavy drinking days. However, Coller *et al.*,<sup>139</sup> found no significant association between rs1799971 genotype and any treatment outcome. Jonas *et al.*,<sup>140</sup> recently undertook a meta-analysis of eight trials, involving 1365 participants, which assessed rs1799971 genotype and the response to naltrexone and found no association between possession of the G allele and the return to *any* drinking or to the return to heavy drinking.

Karpyak *et al.*,<sup>141</sup> reported an association, in people treated with acamprosate, between abstinence length and polymorphisms in the glutamate receptor, ionotropic, N-methyl D-aspartate 2B (*GRIN2B*) gene, which encodes for the GluN2B subunit of the N-methyl-D-aspartate (NMDA) receptor. Carriage of the minor alleles of two SNPs, rs2058878 and rs2300272, which are in strong linkage disequilibrium, was associated with longer abstinence duration.

Kranzler *et al.*,<sup>142,143</sup> explored the relationship between the outcomes of treatment with topiramate and polymorphisms in the glutamate ionotropic receptor kainate type subunit 1 (*GRIK1*) gene, which encodes the GluK1 subunit of the glutamatergic kainate receptor. In alcohol dependent people who were homozygous for the C allele in rs2832407 treatment with topiramate resulted in a greater reduction in alcohol consumption than in carriers of the A allele. It has been suggested that

homozygosity for the C allele moderates peoples' desire to drink and increases their belief in their ability to abstain.<sup>142,143</sup>

The serotonin transporter (5-HTT) is encoded by the gene, solute carrier family 6 member 4 (*SLC6A4*). The promotor region of *SLC6A4* contains a polymorphism with short (S) and long (L) repeats in a 5'-HTT-linked polymorphic region (5'-HTTLPR). Johnson *et al.*,<sup>144</sup> showed that individuals homozygous for the L allele had better drinking outcomes following treatment with ondansetron than carriers of the S allele.

No studies have been undertaken, to date, to assess the clinical utility of genotype-guided medication selection or dosing strategies, and in only one, which was unfortunately substantially underpowered, were participants randomized to treatment with naltrexone or placebo by genotype.<sup>145</sup> Future studies may ultimately define a range of genetic variations that have clinical value in predicting response to the drugs used to treat alcohol dependence.

## **Barriers to Treatment**

Between 1.6 to 3.2 million people in England are alcohol dependent.<sup>2,3</sup> In 2014-15 only 150,640 (4.7 to 9.4%) of those affected received specialist treatment for their alcohol problems and this was only successfully completed in an estimated 47,900.<sup>146</sup> However, despite the fact that pharmacotherapy has been shown to be cost-effective this treatment approach is significantly underutilized.<sup>13</sup> Thus, in 2015, only 196,000 items were prescribed in primary care and NHS hospital settings throughout England although separate data were not available for naltrexone as it is also prescribed for drug use disorders. Overall acamprosate accounted for 71% of the prescribed items whilst nalmefene accounted for 2.2%.<sup>146</sup> While overall there has been a steady increase in the number of items dispensed this remains small given the size of the population at risk (Figure 1). Recent data from Australia show that only 3% of people with alcohol dependence receive pharmacotherapy and, of those only 15 to 25% receive the minimum period of 3 months treatment recommended in the National Guidelines.<sup>147</sup>

There are several possible barriers to the use of pharmacotherapy for the treatment of alcohol dependence (Table 3). Thus, for example, doctors may be reluctant to prescribe because they lack knowledge of or familiarity with the products available,<sup>148</sup> whilst certain statutory and non-statutory agencies may be reluctant to prescribe on philosophical grounds or simply because they are not able to (Table 3).

There are also other broader issues. Thus, the development of pharmaceutical agents to treat alcohol use disorders is hampered by an incomplete understanding of the neurobiological background of alcohol dependence and inconsistent results from genome wide association studies which have, overall, failed to identify robust, replicable targets for drug development. Further investigation and investment is clearly needed.

## **CONCLUSION**

Individuals with alcohol use disorders often fail to receive care, particularly evidence-based care, and there is clear evidence that although drug treatment for alcohol dependence is safe and cost-effective it is substantially underutilized. Efforts must be made to overcome the current barriers to treatment which, in large part, reflect unwillingness by doctors to prescribe these medications.

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## Statement of Interest

Neither author has any personal or financial interests to declare in relation to this article



## References

1. Health & Social Care Information Centre. *Health Survey for England, 2014*. Leeds: HSCIC, 2015. Available online at [www.hscic.gov.uk/catalogue/PUB19295/HSE2014-ch8-adult-alc-con.pdf](http://www.hscic.gov.uk/catalogue/PUB19295/HSE2014-ch8-adult-alc-con.pdf) [Accessed on 2 December 2016]
2. Health & Social Care Information Centre. *Adult Psychiatric Morbidity Survey, 2007*. Leeds: HSCIC, 2009. Available online at [www.hscic.gov.uk/pubs/psychiatricmorbidity07](http://www.hscic.gov.uk/pubs/psychiatricmorbidity07) [Accessed 2 December 2016]
3. Public Health England. *Alcohol Treatment in England 2013-14*. London: PHE 2014. Available online at [www.nta.nhs.uk/uploads/adult-alcohol-statistics-2013-14-commentary.pdf](http://www.nta.nhs.uk/uploads/adult-alcohol-statistics-2013-14-commentary.pdf) [Accessed 12 December 2015]
4. Public Health England. *Liver Disease Profiles*. London: PHE 2015. Available online at [www.fingertips.phe.org.uk/profile/liver-disease/data#page/0](http://www.fingertips.phe.org.uk/profile/liver-disease/data#page/0) [Accessed 2 January 2016]
5. Health & Social Care Information Centre. *Statistics on Alcohol, England 2016*. Leeds: HSCIC, 2016. Available online at [www.content.digital.nhs.uk/catalogue/PUB20999/alc-eng-2016-rep.pdf](http://www.content.digital.nhs.uk/catalogue/PUB20999/alc-eng-2016-rep.pdf) [Accessed on 2 December 2016]
6. Office for National Statistics. *Alcohol-related deaths in the United Kingdom, registered in 2014*. Newport: ONC, 2016. Available online at [www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2014](http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/causesofdeath/bulletins/alcoholrelateddeathsintheunitedkingdom/registeredin2014) [Accessed 17 December 2016]
7. Public Health England. *Local Alcohol Profiles for England*. London: PHE 2015. Available online at [www.fingertips.phe.org.uk/profile/local-alcohol-profiles/data#page/0](http://www.fingertips.phe.org.uk/profile/local-alcohol-profiles/data#page/0) [Accessed 2 January 2016]
8. House of Commons Health Committee. *Government's Alcohol Strategy*. London: The Stationary Office Ltd, 2012. Available online at [www.publications.parliament.uk/pa/cm/201213/cmselect/cmhealth/132/132.pdf](http://www.publications.parliament.uk/pa/cm/201213/cmselect/cmhealth/132/132.pdf) [Accessed 12 December 2015]
9. Teesson M, Baillie A, Lynskey M, *et al*. Substance use, dependence and treatment seeking in the United States and Australia: a cross-national comparison. *Drug Alcohol Depend* 2006;81:149–155.

10. Hasin DS, Stinson FS, Ogburn E, *et al.* Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry* 2007;64:830–842.
11. Mokdad AH, Marks JS, Stroup DF, *et al.* Actual causes of death in the United States, 2000. *JAMA* 2004;291:1238–1245.
12. Bouchery EE, Harwood HJ, Sacks JJ, *et al.* Economic costs of excessive alcohol consumption in the U.S., 2006. *Am J Prev Med* 2011;41:516–524.
13. National Institute for Health and Care Excellence. *Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. CG115*. London: NICE 2011. Available online at [www.nice.org.uk/guidance/cg115](http://www.nice.org.uk/guidance/cg115) [Accessed 12 December 2016].
14. World Health Organization. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization, 1992.
15. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV — 4th ed.* Washington DC: American Psychiatric Association, 1994.
16. Grant BF. ICD-10 and proposed DSM-IV harmful use of alcohol alcohol-abuse and dependence, United-States 1988: a nosological comparison. *Alcohol Clin Exp Res* 1993;17:1093-101.
17. Saunders JB, Aasland OG, Babor TF, de la Fuente JR, Grant M. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO Collaborative Project on Early Detection of Persons with Harmful Alcohol Consumption--II. *Addiction* 1993;88:791-804
18. Drummond DC, Oyefeso N, Phillips T, *et al.* *Alcohol Needs Assessment Research Project: The 2004 National Alcohol Needs Assessment for England*. London: Department of Health, 2005
19. Dawson DA, Grant BF, Stinson FS, *et al.* Recovery from DSM-IV alcohol dependence: United States, 2001-2002. *Addiction* 2005;100:281-292.

20. Hunt WA, Barnett LW, Branch LG. Relapse rates in addiction programs. *J Clin Psychol* 1971;27:445-456.
21. Raistrick D, Heather N, Godfrey C. *Review of the Effectiveness of Treatment for Alcohol Problems*. London: National Treatment Agency for Substance Misuse, 2006
22. Schuckit MA. Alcohol-use disorders. *Lancet* 2009;373:492-501.
23. Edwards G, Brown D, Oppenheimer E, *et al.* Long term outcome for patients with drinking problems: the search for predictors. *Br J Addict* 1988;83:917-927.
24. Marshall EJ, Edwards G, Taylor C. Mortality in men with drinking problems: a 20-year follow-up. *Addiction* 1994;89:1293-1298.
25. Stockwell T, Murphy D, Hodgson R. The severity of alcohol dependence questionnaire: its use, reliability and validity. *Br J Addict* 1983;78:145-155.
26. National Institute for Health and Care Excellence. *Alcohol-use disorders: diagnosis and management of physical complications*. CG100. London: NICE 2010. Available online at [www.nice.org.uk/guidance/cg100](http://www.nice.org.uk/guidance/cg100) [Accessed 12 December 2016]
27. Morgan MY. Acute alcohol toxicity and withdrawal in the emergency room and medical admissions unit. *Clin Med* 2015;15:486-489.
28. Edwards G, Gross MM. Alcohol dependence: provisional description of a clinical syndrome. *Br Med J* 1976;1:1058-1061.
29. Rolland B, Paille F, Gillet C, *et al.* Pharmacotherapy for Alcohol Dependence: The 2015 Recommendations of the French Alcohol Society, Issued in Partnership with the European Federation of Addiction Societies. *CNS Neurosci Ther* 2016;22:25-37.
30. U.S. Department of Veterans Affairs; U.S. Department of Defense. VA/DoD Clinical Practice Guideline for Management of Substance Use Disorders (SUD) 2009. Available online at [www.healthquality.va.gov/guidelines/MH/sud/sud\\_full\\_601f.pdf](http://www.healthquality.va.gov/guidelines/MH/sud/sud_full_601f.pdf) [Accessed 30 December 2016]
31. Pettinati HM, Weiss RD, Miller WR, *et al.* *Medical Management Treatment Manual: A Clinical Research Guide for Medically Trained Clinicians Providing Pharmacotherapy as*

- Part of the Treatment for Alcohol Dependence*. COMBINE Monograph Series, Volume 2. DHHS Publication No. (NIH) 04–5289. Bethesda, MD: National Institute on Alcohol Abuse and Alcoholism, 2004.
32. Center for Substance Abuse and Treatment. *Incorporating alcohol pharmacotherapies into medical practice* (Treatment improvement protocol (TIP); no. 49). Rockville, MD, Substance Abuse and Mental Health Services Administration (SAMHSA) 2009.
  33. Haber P, Lintzeris N, Proude E, *et al* on behalf of the Australian Government Department of Health and Ageing. *Guidelines for the Treatment of Alcohol Problems*. Sydney, University of Sydney 2009. Available online at [www.health.gov.au/internet/main/...nsf/.../AustAlctreatguidelines%202009.pdf](http://www.health.gov.au/internet/main/...nsf/.../AustAlctreatguidelines%202009.pdf) [Accessed 30 December 2016].
  34. Fuller RK, Branchey L, Brightwell DR, *et al*. Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. *JAMA* 1986;256:1449-1455.
  35. van Ieperen L. Sudden death during disulfiram-ethanol reaction. *S Afr Med J* 1984;66:165
  36. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. *Drug Saf* 1999;20:427-435.
  37. Krampe H, Ehrenreich H. Supervised disulfiram as adjunct to psychotherapy in alcoholism treatment. *Curr Pharm Des* 2010;16:2076-2090.
  38. Skinner M, Coudert M, Berlin I, *et al*. Effect of the threat of a disulfiram-ethanol reaction on cue reactivity in alcoholics. *Drug Alcohol Depend* 2010;112:239-246.
  39. Higgins ST, Budney AJ, Bickel WK, Hughes JR, Foerg F. Disulfiram therapy in patients abusing cocaine and alcohol. *Am J Psychiatry* 1993;150:675-676.
  40. Carroll KM, Nich C, Ball SA, *et al*. One-year follow-up of disulfiram and psychotherapy for cocaine-alcohol users: sustained effects of treatment. *Addiction* 2000;95:1335-1349.
  41. Skinner MD, Lahmek P, Pham H, Aubin HJ. Disulfiram efficacy in the treatment of alcohol dependence: a meta-analysis. *PloS one* 2014;9:e87366.
  42. Gaval-Cruz M, Weinshenker D. Mechanisms of disulfiram-induced cocaine abstinence: Antabuse and cocaine relapse. *Mol Interv* 2009;9:175-187.

43. Jørgensen CH, Pedersen B, Tønnesen H. The efficacy of disulfiram for the treatment of alcohol use disorder. *Alcohol Clin Exp Res* 2011;35:1749-1758.
44. Jonas DE, Amick HR, Feltner C, *et al.* Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014;311:1889-1900.
45. Malcolm R, Olive MF, Lechner W. The safety of disulfiram for the treatment of alcohol and cocaine dependence in randomized clinical trials: guidance for clinical practice. *Expert Opin Drug Saf* 2008;7:459-472.
46. Sinclair JM, Chambers SE, Shiles CJ, Baldwin DS. Safety and tolerability of pharmacological treatment of alcohol dependence: comprehensive review of evidence. *Drug Saf* 2016;39:627-645.
47. Kalk NJ, Lingford-Hughes AR. The clinical pharmacology of acamprosate. *Br J Clin Pharmacol* 2014;77:315-323.
48. Spanagel R, Vengeliene V, Jandeleit B, *et al.* Acamprosate produces its anti-relapse effects via calcium. *Neuropsychopharmacology* 2014;39:783-791.
49. Kufahl PR, Watterson LR, Olive MF. The development of acamprosate as a treatment against alcohol relapse. *Expert Opin Drug Discov* 2014;9:1355-1369.
50. Mann K, Lehert P, Morgan MY. The efficacy of acamprosate in the maintenance of abstinence in alcohol-dependent individuals: results of a meta-analysis. *Alcohol Clin Exp Res* 2004;28:51-63.
51. Rösner S, Hackl-Herrwerth A, Leucht S, *et al.* Acamprosate for alcohol dependence. *Cochrane Database Syst Rev* 2010;9:CD004332.
52. Donoghue K, Elzerbi C, Saunders R, *et al.* The efficacy of acamprosate and naltrexone in the treatment of alcohol dependence, Europe versus the rest of the world: a meta-analysis. *Addiction* 2015;110:920-930.
53. Plosker GL. Acamprosate: a review of its use in alcohol dependence. *Drugs* 2015;75:1255-1268.

54. Mason BJ. Acamprosate and naltrexone treatment for alcohol dependence: an evidence-based risk-benefits assessment. *Eur Neuropsychopharmacol* 2003;13:469-475.
55. Drobos DJ, Anton RF, Thomas SE, *et al.* Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers. *Alcohol Clin Exp Res* 2004;28:1362-1370.
56. Anton RF. Naltrexone for the management of alcohol dependence. *N Engl J Med* 2008;359:715-721.
57. Roozen HG, de Waart R, van der Windt DA, *et al.* A systematic review of the effectiveness of naltrexone in the maintenance treatment of opioid and alcohol dependence. *Eur Neuropsychopharmacol* 2006;16:311-323.
58. Rösner S, Hackl-Herrwerth A, Leucht S, *et al.* Opioid antagonists for alcohol dependence. *Cochrane Database Syst Rev* 2010;12:CD001867.
59. Jarosz J, Miernik K, Wąchal M, Walczak J, Krumpl G. Naltrexone (50 mg) plus psychotherapy in alcohol-dependent patients: a meta-analysis of randomized controlled trials. *Am J Drug Alcohol Abuse* 2013;39:144-160.
60. Mitchell JE, Morley JE, Levine AS, *et al.* High-dose naltrexone therapy and dietary counseling for obesity. *Biol Psychiatry* 1987;22:35-42.
61. Kiefer F, Jahn H, Tarnaske T, *et al.* Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo controlled study. *Arch Gen Psychiatry* 2003;60:92-99.
62. Anton RF, O'Malley SS, Ciraulo DA, *et al.* Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. *JAMA* 2006;295:2003-2017.
63. Mason BJ, Ritvo EC, Morgan RO, *et al.* A double-blind, placebo-controlled pilot study to evaluate the efficacy and safety of oral nalmefene HCl for alcohol dependence. *Alcohol Clin Exp Res* 1994;18:1162-1167.
64. Mason BJ, Salvato FR, Williams LD, Ritvo EC, Cutler RB. A double-blind, placebo-controlled study of oral nalmefene for alcohol dependence. *Arch Gen Psych* 1999;56:719-724.

65. Anton RF, Pettinati H, Zweben A, *et al.* A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. *J Clin Psychopharmacol* 2004;24:421-428.
66. Karhuvaara S, Simojoki K, Virta A, *et al.* Targeted nalmefene with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. *Alcohol Clin Exp Res* 2007;31:1179-1187.
67. Gual A, He Y, Torup L, *et al.* A randomised, double-blind, placebo-controlled, efficacy study of nalmefene, as-needed use, in patients with alcohol dependence. *Eur Neuropsychopharmacol* 2013;23:1432-1442.
68. Mann K, Bladström A, Torup L, Gual A, van den Brink W. Extending the treatment options in alcohol dependence: a randomized controlled study of as-needed nalmefene. *Biol Psychiatry* 2013;73:706-713.
69. van den Brink W, Aubin HJ, Bladström A, *et al.* Efficacy of as-needed nalmefene in alcohol-dependent patients with at least a high drinking risk level: results from a subgroup analysis of two randomized controlled 6-month studies. *Alcohol Alcohol* 2013;48:570-578.
70. van den Brink W, Sørensen P, Torup L, *et al.* Long-term efficacy, tolerability and safety of nalmefene as-needed in patients with alcohol dependence: a 1-year, randomised controlled study. *J Psychopharmacol* 2014;28:733-744.
71. Marlatt GA, Witkiewitz K. Harm reduction approaches to alcohol use: health promotion, prevention, and treatment. *Addict Behav* 2002;27:867-886.
72. National Institute for Health and Care Excellence. *Nalmefene for reducing alcohol consumption in people with alcohol dependence: evaluation report. TA325.* London: NICE 2014. Available online at [www.nice.org.uk/guidance/ta325](http://www.nice.org.uk/guidance/ta325) [Accessed 5 January 2016]
73. Stevenson M, Pandor A, Stevens JW, *et al.* Nalmefene for reducing alcohol consumption in people with alcohol dependence: an Evidence Review Group Perspective of a NICE Single Technology Appraisal. *Pharmacoeconomics* 2015;33:833-847.
74. Palpacuer C, Laviolle B, Boussageon R, *et al.* Risks and benefits of nalmefene in the treatment of adult alcohol dependence: a systematic literature review and meta-analysis of published and unpublished double-blind randomized controlled trials. *PLoS Med* 2015;12:e1001924.

75. Fitzgerald N, Angus K, Elders A, *et al.* Weak evidence on nalmefene creates dilemmas for clinicians and poses questions for regulators and researchers. *Addiction* 2016;111:1477–1487.
76. Naudet F, Palpacuer C, Boussageon R, Laviolle B. Evaluation in alcohol use disorders - insights from the nalmefene experience. *BMC Med* 2016;14:119-127.
77. Franck J, Jayaram-Lindstrom N. Pharmacotherapy for alcohol dependence: status of current treatments. *Curr Opin Neurobiol* 2013;23:692-699.
78. Caputo F, Vignoli T, Grignaschi A, *et al.* Pharmacological management of alcohol dependence: from mono-therapy to pharmacogenetics and beyond. *Eur Neuropsychopharmacol* 2014;24:181-191.
79. Litten RZ, Ryan M, Falk D, Fertig J. Alcohol medications development: advantages and caveats of government/academia collaborating with the pharmaceutical industry. *Alcohol Clin Exp Res* 2014;38:1196-1199.
80. Müller CA, Geisel O, Banas R, Heinz A. Current pharmacological treatment approaches for alcohol dependence. *Expert Opin Pharmacother* 2014;15:471-481.
81. Zindel LR, Kranzler HR. Pharmacotherapy of alcohol use disorders: seventy-five years of progress. *J Stud Alcohol Drugs Suppl* 2014;75 (Suppl 17):79-88.
82. Soyka M, Lieb M. Recent developments in pharmacotherapy of alcoholism. *Pharmacopsychiatry* 2015;48:123-135.
83. Addolorato G, Caputo F, Capristo E, *et al.* Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. *Alcohol Alcohol* 2002;37:504-508.
84. Addolorato G, Leggio L, Ferrulli A, *et al.* Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study. *Lancet* 2007;370:1915-1922.
85. Addolorato G, Leggio L, Ferrulli A, *et al.* Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol Alcohol* 2011;46:312-317.



86. Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. *Alcohol Clin Exp Res* 2010;34:1849-1857.
87. Morley KC, Baillie A, Leung S, *et al.* Baclofen for the treatment of alcohol dependence and possible role of comorbid anxiety. *Alcohol Alcohol* 2014;49:654-660.
88. Ponizovsky AM, Rosca P, Aronovich E, Weizman A, Grinshpoon A. Baclofen as add-on to standard psychosocial treatment for alcohol dependence: a randomized, double-blind, placebo controlled trial with 1 year follow-up. *J Subst Abuse Treat* 2015;52:24-30.
89. Ameisen O. Complete and prolonged suppression of symptoms and consequences of alcohol-dependence using high-dose baclofen: A self-case report of a physician. *Alcohol Alcohol* 2005;40:147–150.
90. Ameisen O. *Le Dernier Verre*. Paris, Denoël 2008.
91. Rolland B, Bordet R, Cottencin O. Alcohol-dependence: The current French craze for baclofen. *Addiction* 2012;107:848–849.
92. Dupouy J, Fournier JP, Jouanjus E, *et al.* Baclofen for alcohol dependence in France: Incidence of treated patients and prescription patterns-A cohort study. *Eur Neuropsychopharmacol* 2014;24:192–199.
93. Agence Française du Médicament et des produits de santé Recommandation temporaire d'utilisation (RTU) pour le baclofène - Point d'information 2014. Available online at <http://ansm.sante.fr/S-informer/Actualite/Une-recommandationtemporaire-d-utilisation-RTU-est-accordee-pour-lebaclofene-Point-d-information> [Accessed 30 December 2016]
94. Müller CA, Geisel O, Pelz P, *et al.* High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo-controlled trial. *Eur Neuropsychopharmacol* 2015;25:1167-1177.
95. Beraha EM, Salemink E, Goudriaan AE, *et al.* Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: A multicentre, randomised, double-blind controlled trial. *Eur Neuropsychopharmacol* 2016;26:1950-1959.

96. ALPADIR study (NCT01738282). *Efficacy and Safety of Baclofen for Maintenance of Abstinence in Alcohol Dependent Patients*. Available on line at [clinicaltrials.gov/show/NCT01738282](http://clinicaltrials.gov/show/NCT01738282) [Accessed 30 December 2016].
97. BACLOVILLE study (NCT01604330). *Baclofen for the Treatment of Alcohol Drinkers*. Available online at [clinicaltrials.gov/ct2/show/NCT01604330](http://clinicaltrials.gov/ct2/show/NCT01604330) [Accessed 30 December 2016].
98. Jaury P. Available on line at: [baclofentreatment.com/wpcontent/uploads/2016/09/ISBRA-16\\_Bacloville.mp3](http://baclofentreatment.com/wpcontent/uploads/2016/09/ISBRA-16_Bacloville.mp3). [Accessed 30 December 2016]
99. Rolland B, Labreuche J, Duhamel A, *et al*. Baclofen for alcohol dependence: Relationships between baclofen and alcohol dosing and the occurrence of major sedation. *Eur Neuropsychopharmacol* 2015; 25:1631–1636.
100. Rolland B, Deheul S, Danel T, Bordet R, Cottencin O. A case of de novo seizures following a probable interaction of high-dose baclofen with alcohol. *Alcohol Alcohol* 2012;47:577–580.
101. Geoffroy PA, Auffret M, Deheul S, Bordet R, Cottencin O, Rolland B. Baclofen-induced manic symptoms: Case report and systematic review. *Psychosomatics* 2014;55:326-332.
102. Olivier PY, Joyeux-Faure M, Gentina T, *et al*. Severe central sleep apnea associated with chronic baclofen therapy: a case series. *Chest* 2016;149:e127-e131.
103. Blodgett JC, Del Re AC, Maisel NC, Finney JW. A meta-analysis of topiramate's effects for individuals with alcohol use disorders. *Alcohol Clin Exp Res* 2014;38:1481-1488.
104. Pani PP, Trogu E, Pacini M, Maremmanni I. Anticonvulsants for alcohol dependence. *Cochrane Database Syst Rev* 2014;2:Cd008544.
105. Shpilenny LS, Muzychenko AP, Gasbarrini G, Addolorato G. Metadoxine in acute alcohol intoxication; a double-blind, randomized, placebo-controlled study. *Alcohol Clin Exp Res* 2002;26:340-346.
106. Fornai F, Grazia Alessandrì M, Bonuccelli U, Scalori V, Corsini GU. Effect of metadoxine on striatal dopamine levels in C57 black mice. *J Pharm Pharmacol* 1993;45:476-478.
107. Guerrini I, Gentili C, Nelli G, Guazzelli M. A follow up study on the efficacy of metadoxine in the treatment of alcohol dependence. *Subst Abuse Treat Prev Policy* 2006;1:35-40.

108. Higuera-de la Tijera F, Servín-Caamaño AI, Serralde-Zúñiga AE, *et al.* Metadoxine improves the three- and six-month survival rates in patients with severe alcoholic hepatitis. *World J Gastroenterol* 2015;21:4975-4985.
109. Addolorato G, Ancona C, Capristo E, Gasbarrini G. Metadoxine in the treatment of acute and chronic alcoholism: a review. *Int J Immunopathol Pharmacol* 2003;16:207-214.
110. Tilg H, Day CP. Management strategies in alcoholic liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2007;4:24-34.
111. Hazeldine S, Hydes T, Sheron N. Alcoholic liver disease – the extent of the problem and what you can do about it. *Clin Med* 2015;15:179-185.
112. Addolorato G, Mirijello A, Leggio L, Ferrulli A, Landolfi R. Management of alcohol dependence in patients with liver disease. *CNS Drugs* 2013;27:287-299.
113. Vuittonet CL, Halse M, Leggio L. Pharmacotherapy for alcoholic patients with alcoholic liver disease. *Am J Health Syst Pharm* 2014;71:1265-1276.
114. Rosato V, Abenavoli L, Federico A, Masarone M, Persico M. Pharmacotherapy of alcoholic liver disease in clinical practice. *Int J Clin Pract* 2016;70:119-131.
115. Delgrange T, Khater J, Capron D, Duron B, Capron JP. [Effect of acute administration of acamprosate on the risk of encephalopathy and on arterial pressure in patients with alcoholic cirrhosis]. *Gastroenterol Clin Biol* 1992;16:687-691.
116. Garbutt JC. Efficacy and tolerability of naltrexone in the management of alcohol dependence. *Curr Pharm Des* 2010;16:2091-2097.
117. Eneanya DI, Bianchine JR, Duran DO, Andresen BD. The actions and metabolic fate of disulfiram. *Annu Rev Pharmacol Toxicol* 1981;21:575-596.
118. Noh Y, Kim DW, Chu K, *et al.* Topiramate increases the risk of valproic acid-induced encephalopathy. *Epilepsia* 2013;54:e1-4.
119. Caballería J, Parés A, Brú C, *et al.* Metadoxine accelerates fatty liver recovery in alcoholic patients: results of a randomized double-blind, placebo-controlled trial. The Spanish Group for the Study of Alcoholic Fatty Liver. *J Hepatol* 1998;28:54-60.

120. Higuera-de la Tijera F, Servín-Caamaño AI, Cruz-Herrera J, *et al.* Treatment with metadoxine and its impact on early mortality in patients with severe alcoholic hepatitis. *Ann Hepatol* 2014;13:343-352.
121. Calabrese V, Calderone A, Ragusa N, Rizza V. Effects of metadoxine on cellular status of glutathione and of enzymatic defence system following acute ethanol intoxication in rats. *Drugs Exp Clin Res* 1996;22:17-24.
122. O'Shea RS, Dasarathy S, McCullough AJ. Practice Guideline Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Alcoholic liver disease. *Hepatology* 2010;51:307-328.
123. European Association for the Study of Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012;57:399-420.
124. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence. *JAMA* 2004;291:1887-1896.
125. Torrens M, Fonseca F, Mateu G, Farré M. Efficacy of antidepressants in substance use disorders with and without comorbid depression. A systematic review and meta-analysis. *Drug Alcohol Depend* 2005; 78:1-22.
126. National Institute for Health and Care Excellence. *Common mental health problems: identification and pathways to care. CG123*. London: NICE 2011. Available online at [www.nice.org.uk/guidance/cg123](http://www.nice.org.uk/guidance/cg123) [Accessed 12 December 2015]
127. National Institute for Health and Care Excellence. *Psychosis with substance misuse in over 14s: assessment and management. CG120*. London: NICE 2011. Available online at [www.nice.org.uk/guidance/cg120](http://www.nice.org.uk/guidance/cg120) [Accessed 12 December 2015]
128. Department of Health (England) and the devolved administrations. *Drug misuse and dependence: UK guidelines on clinical management*. London: Department of Health (England), the Scottish Government, Welsh Assembly Government and Northern Ireland Executive: 2007. Available online at [www.nta.nhs.uk/uploads/clinical\\_guidelines\\_2007.pdf](http://www.nta.nhs.uk/uploads/clinical_guidelines_2007.pdf) [Accessed 14 December 2015]

129. Litten RZ, Castle IJ, Falk D, *et al.* The placebo effect in clinical trials for alcohol dependence: an exploratory analysis of 51 naltrexone and acamprosate studies. *Alcohol Clin Exp Res* 2013;37:2128-2137.
130. Del Re AC, Maisel N, Blodgett JC, Wilbourne P, Finney JW. Placebo group improvement in trials of pharmacotherapies for alcohol use disorders: a multivariate meta-analysis examining change over time. *J Clin Psychopharmacol* 2013;33:649-657.
131. Rohsenow DJ, Colby SM, Monti PM, *et al.* Predictors of compliance with naltrexone among alcoholics. *Alcohol Clin Exp Res* 2000;24:1542-1549.
132. Baekeland F, Lundwall L, Kissin B, Shanahan T. Correlates of outcome in disulfiram treatment of alcoholism. *J Nerv Ment Dis* 1971;153:1-9.
133. Verheul R, Lehert P, Geerlings PJ, Koeter MW, van den Brink W. Predictors of acamprosate efficacy: results from a pooled analysis of seven European trials including 1485 alcohol-dependent patients. *Psychopharmacology* 2005;178:167-173.
134. Volpicelli JR, Clay KL, Watson NT, O'Brien CP. Naltrexone in the treatment of alcoholism: predicting response to naltrexone. *J Clin Psychiatry* 1995;56 Suppl 7:39-44.
135. Monterosso JR, Flannery BA, Pettinati HM, *et al.* Predicting treatment response to naltrexone: the influence of craving and family history. *Am J Addict* 2001;10:258-268.
136. Rubio G, Ponce G, Rodriguez-Jiménez R, *et al.* Clinical predictors of response to naltrexone in alcoholic patients: who benefits most from treatment with naltrexone? *Alcohol Alcohol* 2005;40:227-233.
137. Mann K, Vollstädt-Klein S, Reinhard I, *et al.* Predicting naltrexone response in alcohol-dependent patients: the contribution of functional magnetic resonance imaging. *Alcohol Clin Exp Res* 2014;38:2754-2762.
138. Anton RF, Oroszi G, O'Malley S, *et al.* An evaluation of  $\mu$ -opioid receptor (*OPRM1*) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. *Arch Gen Psychiatry* 2008;65:135-144.

139. Coller JK, Cahill S, Edmonds C, *et al.* *OPRM1* A118G genotype fails to predict the effectiveness of naltrexone treatment for alcohol dependence. *Pharmacogenet Genomics* 2011;21:902-905.
140. Jonas DE, Amick HR, Feltner C, *et al.* Genetic polymorphisms and response to medications for alcohol use disorders: a systematic review and meta-analysis. *Pharmacogenomics* 2014;15:1687-1700.
141. Karpyak VM, Biernacka JM, Geske JR, *et al.* Genetic markers associated with abstinence length in alcohol-dependent subjects treated with acamprosate. *Transl Psychiatry* 2014;4:e462.
142. Kranzler HR, Covault J, Feinn R, *et al.* Topiramate treatment for heavy drinkers: moderation by a *GRIK1* polymorphism. *Am J Psychiatry* 2014;171:445-452.
143. Kranzler HR, Armeli S, Wetherill R, *et al.* Self-efficacy mediates the effects of topiramate and *GRIK1* genotype on drinking. *Addict Biol* 2016;21:450-459.
144. Johnson BA, Ait-Daoud N, Seneviratne C, *et al.* Pharmacogenetic approach at the serotonin transporter gene as a method of reducing the severity of alcohol drinking. *Am J Psychiatry* 2011;168:265–275.
145. Oslin DW, Leong SH, Lynch KG, *et al.* Naltrexone vs placebo for the treatment of alcohol dependence: a randomized clinical trial. *JAMA Psychiatry* 2015;75:430–437.
146. Public Health England. *Adult substance misuse statistics from the National Drug Treatment Monitoring System (NDTMS) 2014-15.* London: PHE, 2015. Available online at [www.ndtms.net/Publications/downloads/Adult%20Substance%20Misuse/adult-statistics-from-the-national-drug-treatment-monitoring-system-2014-2015.pdf](http://www.ndtms.net/Publications/downloads/Adult%20Substance%20Misuse/adult-statistics-from-the-national-drug-treatment-monitoring-system-2014-2015.pdf) [Accessed 12 December 2016]
147. Morley KC, Logge W, Pearson SA, Baillie A, Haber PS. National trends in alcohol pharmacotherapy: Findings from an Australian claims database. *Drug Alcohol Depend* 2016;166:254-257.
148. Mark TL, Kranzler HR, Poole VH, *et al.* Barriers to the use of medications to treat alcoholism. *Am J Addict* 2003;12:281-294.

**Table 1. Comparisons between the ICD and DSM diagnostic criteria for alcohol dependence**

Criterion	ICD-10*	Criterion	DSM-IV*
1	Strong desire or sense of compulsion to use the substance	N/A	N/A
2	Impaired capacity to control use as evidenced by the substance often being taken in larger amounts or over a longer period than intended or by a persistent desire or unsuccessful efforts to control use	3	Persistent desire or one or more unsuccessful efforts to cut down or control drinking
		4	Drinking in larger amounts or over a longer period than the person intended
3	Physiological withdrawal	2	Physiological withdrawal
4	Tolerance	1	Tolerance
5	Preoccupation with substance use as manifested by important interests being given up or reduced or a great deal of time spent in activities necessary to obtain, take, or recover from the effects of the substance	5	Important social, occupational, or recreational activities given up or reduced because of drinking
		6	A great deal of time spent in activities necessary to obtain, to use or to recover from the effects of drinking
6	Persistent substance use despite clear evidence of harmful consequences	7	Continued drinking despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to be caused or exacerbated by drinking

\*In both the ICD-10 and the DSM-IV criteria, a diagnosis of alcohol dependence is made if three or more of the criteria are present together at some time during the previous 12 months

Abbreviations:

ICD-10: International Classification of Diseases, 10th Edition <sup>14</sup>

DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition <sup>15</sup>

N/A: Not Applicable

**Table 2. Essential details of the three drugs most widely licensed for the treatment of alcohol dependence**

Drug	Order	Contraindications	Precautions	Side-effects	Dosage	Duration	Comments
Disulfiram	Second-line	<ul style="list-style-type: none"> <li>• Cardiovascular disease</li> <li>• Systemic hypertension</li> <li>• Severe personality disorder</li> <li>• Suicidal risk or psychosis</li> <li>• Pregnancy &amp; breast-feeding.</li> </ul> <p><i>Caution</i> in the presence of renal failure, hepatic or respiratory disease, diabetes mellitus and epilepsy</p>	<p><i>Warnings:</i></p> <ul style="list-style-type: none"> <li>• Nature/seriousness of the interaction with ingested alcohol;</li> <li>• Alcohol in foodstuffs, perfumes, aerosol sprays</li> </ul>	<ul style="list-style-type: none"> <li>• Headaches</li> <li>• Drowsiness</li> <li>• Lethargy</li> <li>• Peripheral neuropathy</li> <li>• Optic neuritis</li> <li>• Hepatotoxicity</li> <li>• Psychosis.</li> </ul>	200 mg/day	Long-term if required	<p>Start 24 hr after last drink</p> <p>Treatment most effective if supervised or witnessed</p>
Acamprosate	First-line	Severe renal impairment (creatinine clearance <30 ml/min)		<ul style="list-style-type: none"> <li>• Diarrhoea</li> <li>• Anorexia</li> <li>• Flatulence</li> <li>• Nausea</li> <li>• Pruritus</li> <li>• Dry mouth</li> <li>• Paraesthesia</li> <li>• Fatigue</li> </ul>	<p>Weight:</p> <p>&gt; 60 kg 1998 mg/day</p> <p>&lt; 60 kg 1332 mg/day</p> <p>Reduce in moderate renal failure</p>	6 months, or longer	Safe for use in mild to moderate hepatic failure
Naltrexone	First-line	<ul style="list-style-type: none"> <li>• Acute hepatitis</li> <li>• Acute liver failure</li> <li>• Chronic liver failure</li> <li>• Use of/likely use of opioids</li> </ul> <p><i>Caution:</i> if serum transaminase activities exceeding three times the upper reference range and in patients with renal failure.</p>	<p><i>Warning:</i></p> <p>Naltrexone blockade persists for 48-72 hours after the last oral dose</p>	<ul style="list-style-type: none"> <li>• Nausea</li> <li>• Vomiting</li> <li>• Dizziness</li> <li>• Abdominal pain</li> <li>• Anorexia</li> <li>• Headache</li> <li>• Day-time sleepiness</li> <li>• Hepatotoxicity with high doses</li> </ul>	<p>Start with: 25 mg/day</p> <p>Maintenance 50 mg/day</p>	6 months, or longer	Stop opioids 7 to10 days before prescribing



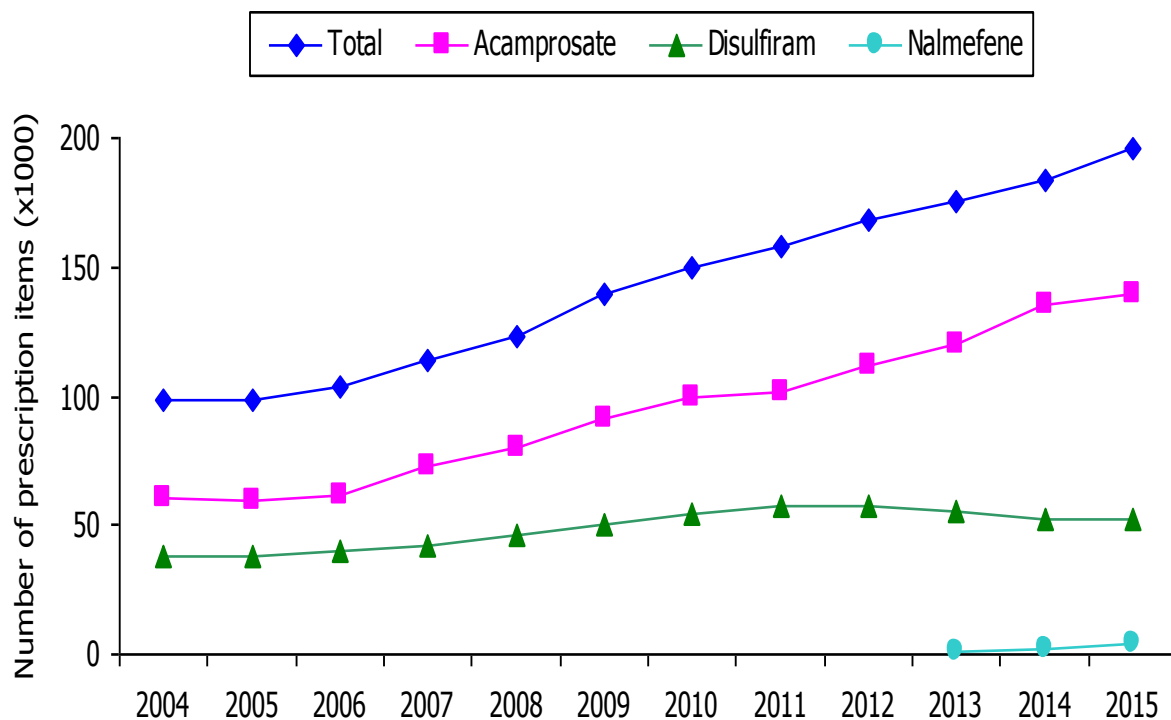
**Table 3. Barriers to the use of pharmacotherapy for alcohol dependence**

Barrier	Patients	Alcohol treatment services	Doctors
<b>Information</b>	Lack/poor awareness	Lack/poor awareness	Lack/poor awareness
		Lack/poor knowledge	Lack/poor knowledge
<b>Medication</b>	Reluctant to take	Lack of confidence in efficacy	Lack of confidence in efficacy
	Side-effects	Side-effects	Side-effects
		Cost	Cost
<b>Delivery</b>		Unable to prescribe ‘in-house’	No specific guidance available
		Unable to effectively monitor	Need for psychosocial support
			Lack of time
			Unable to effectively monitor
<b>Resources</b>	Cost of prescription		
<b>Philosophy</b>	Alternative addiction	‘Medicalises’ the condition	Ambivalence
		Against tenets of AA	

Abbreviation: AA: Alcoholics Anonymous

## Legend to Figure

**Fig. 1. Number of prescription items for the treatment of alcohol dependence prescribed in primary care in England 2004 to 2015**



Source: Adapted from the Prescribing Analysis and Cost Tool (PACT) from NHS Prescription Service of the NHS Business Services Authority Health and Social Care Information Centre <sup>146</sup>