

SAFETY AND TOLERABILITY OF PHARMACOLOGICAL TREATMENT OF ALCOHOL
DEPENDENCE: COMPREHENSIVE REVIEW OF EVIDENCE

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ABSTRACT

Alcohol use disorders (AUD) cause significant morbidity and mortality worldwide, but pharmacological treatments for them are underused, despite evidence of efficacy. Acamprosate, naltrexone, nalmefene and disulfiram are all approved in one or more region for the treatment of alcohol use disorders. Baclofen currently has a temporary indication in France. Safety considerations for using psychopharmacological treatments in this patient group include the impact of concurrent alcohol consumption at high levels, multiple physical comorbidities which may interfere with pharmacological effects, distribution and metabolism, and concomitant medication for the treatment of comorbid physical and psychiatric conditions. The five drugs, including an extended-release injectable suspension of naltrexone, have different safety profiles which need to be balanced with the objective of treatment (initiation or continuation of abstinence, or reduction of drinking), individual patient preferences and comorbid conditions. Appropriate treatment will be based on the unique risk-benefit profile in each case.

KEY POINTS

- Acamprosate has an excellent safety profile and is recommended as first line treatment for patients wishing abstinence. Naltrexone and nalmefene are contraindicated with opioid- containing medication, but have reasonable tolerability
- The disulfiram–alcohol reaction is integral to its use, but careful patient selection and monitoring can mitigate safety risks
- Baclofen is a CNS depressant so there are potential concerns regarding overdose: it may have a role in patients with severe liver disease

1. Introduction

Alcohol use disorders (AUD) are common and disabling conditions, with 3.3 million deaths (5.9% of global deaths) and 5.1% of the global burden of disease and injury in 2012 attributable to them [1]. Alcohol dependence (ICD-10) or severe alcohol use disorders (DSM 5) is frequently under treated, with estimates of treatment in less than 25% affected of individuals in the USA [2] and 10% in Europe [3]. The mainstay of treatment is psychosocial [4] but there is a good evidence base for the effectiveness of pharmacological treatment in medically assisted alcohol withdrawal [5], in relapse prevention, and in reduction of alcohol consumption [4, 6-8].

Safety considerations for any medication include the pharmacokinetics of the drug; range of adverse drug reactions [9]; the patient population, including age, gender, ethnicity and interaction with underlying pathology, including co-morbid conditions; and interactions with other medications. In patients with alcohol dependence, the interaction of the treatment with alcohol consumption, the consequences of self-poisoning, and abuse liability, also need to be considered.

The focus of this article is on safety considerations of medications with an indication for relapse prevention or alcohol reduction in patients with alcohol dependence; specifically acamprosate, naltrexone, disulfiram, nalmefene and baclofen. Whilst AUD are frequently comorbid with other conditions, especially in treatment-seeking populations, there is limited evidence for the impact of comorbidity or the associated polypharmacy on safety considerations. Many of the medications with an indication for AUD have been tried in other substance use and behavioural addictions, but with insufficient efficacy to gain an indication and so are not reviewed here.

2. Literature review methodology

We conducted a systematic review informed by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines [10, 11]. All included and excluded studies in two recent systematic reviews of randomised controlled trials (RCTs) [4, 6, 7] were screened for potential eligibility. We reviewed papers published since 2010, to find studies which were not included in the NICE and Cochrane reviews. We searched PsychINFO, Medline and Embase with the terms ('alcohol' OR 'drinking') AND ('safety' OR 'toxicity' OR 'adverse effects' OR 'adverse events' OR 'overdose' OR 'tolerability' OR 'side effects' OR 'misuse' OR 'harm' OR 'hazard' OR 'contraindications' OR 'poisoning' OR 'complication' OR 'pharmacovigilance' OR 'phase four/4' OR 'post marketing surveillance' OR 'pharmacoepidemiology') for each of the following drugs:

acamprosate, naltrexone, disulfiram, nalmefene and baclofen. We included all papers with an abstract in English that met the inclusion criteria.

We also examined the bibliographic references of papers published after 2010 to ensure all relevant literature was included, and contacted key authors in the field with reference lists to ensure no key publications on safety and tolerability had been excluded (see Acknowledgements). We also reviewed any links from the European Public Assessment Reports (EPARs) and Summaries of Product Characteristics (SPCs) to published references.

We only included studies where alcohol dependence was the primary condition (thereby excluding ‘social drinkers’ and hazardous, harmful or abusive drinking) and safety/tolerability information was reported. Attribution of causality of adverse events requires a systematic approach to reporting, which is frequently lacking [12]. Given the complex interaction between subjective experience in patients with alcohol dependence and symptoms of alcohol withdrawal it is especially difficult to distinguish between alcohol-related symptoms and drug-related side effects, and so single case studies were excluded. Our complete search strategy is shown in Figure 1.

Insert Figure 1 about here

3. Acamprosate

Acamprosate (calcium acetylhomotaurinate) is licenced for relapse prevention in the UK, Australasia, North America and much of Europe. It modulates the N-methyl-D-aspartate (NMDA) receptor and indirectly enhances GABA function, both of which are altered during alcohol withdrawal and the early stages of abstinence [13]. A significant decrease in frontal lobe glutamate has been shown on magnetic resonance spectroscopy (MRS) in patients taking acamprosate in the early stages of abstinence compared with placebo [14]. This may account for the reduction in arousal, anxiety and insomnia (all negative reinforcers implicated in relapse back to heavy drinking) seen in patients taking acamprosate in the early stages of abstinence [8]. Acamprosate has low oral bioavailability (approximately 11%), is not protein bound, and is not metabolised by the liver, being excreted unchanged in urine [13]. The evidence base includes three recent systematic reviews and meta-analyses [4, 6, 15] demonstrating ‘moderate’ efficacy (relative risks of relapse 0.86 (95% CI: 0.81-0.91), 0.83 (95% CI:0.77-0.88) and 0.83 (95% CI:0.77-0.89), respectively) of acamprosate in relapse prevention.

Pharmacokinetic considerations and implications for safety

Acamprosate is derived from homotaurine, a nonspecific GABA agonist and calcium [13]. It is not metabolized by the liver and has no impact on drugs subject to hepatic metabolism, or which have an impact on the CYP450 system. It does not interact with alcohol, diazepam, oxazepam or imipramine [16], and there is no evidence of an interaction with disulfiram [17], although naltrexone increases its plasma levels *in vivo* [13]. It appears generally safe in patients with impaired hepatic function [13, 18]: in the RCTs reported here [19, 20] there were two deaths of patients on acamprosate, due to acute hepatic failure with pre-existing hepatic cirrhosis and carcinoma, respectively. Due to its predominately renal excretion, potential risks and benefits need to be considered on an individual basis in the elderly and patients with renal insufficiency, the recommendation being to start at a lower dose (333mg tds) and monitor renal function [16]. A major concern when treating patients with addictions is the abuse liability of drugs prescribed. There is no evidence of abuse liability in clinical studies, and none has been shown in animal models [21]. Acamprosate appears safe in overdose: there are reports from two studies of three patients taking intentional overdoses of 8-120 tablets with no 'untoward symptoms' [19, 22].

Acamprosate demonstrated a reasonable side effect profile in RCTs. Pharmacovigilance data [23] in 1.5 million patients indicated no serious adverse events, and a Cochrane review [6] found the most common side effects (significantly different to placebo) to be gastro-intestinal symptoms (see Table 1) especially diarrhoea (effect size 0.11[0.09-0.13]). If diarrhoea is severe, temporary dose reduction was beneficial [22, 24]. More recent studies not included in earlier meta-analyses [25, 26] confirm these earlier findings, diarrhoea being reported significantly more frequently in the acamprosate group, 1998mg/d ($p=.004$), and nervousness/ anxiety in the placebo group ($p=.002$) [26].

Insert Table 1 about here

Differences in how adverse events are collected has an impact on prevalence levels; where a 45-item checklist was used in addition to spontaneous reports [27], the reported number of adverse events was higher but was not significantly different between active medication (acamprosate 1998mg/d) and placebo. In studies where acamprosate (1998mg/d) was started before or during medically assisted withdrawal [28, 29] no significant differences in adverse effects from placebo were reported.

Pharmacological treatments for alcohol dependence

Two studies [30, 31] examined the tolerability of low (1.3g/d) and high dose (2.0g/d) acamprosate compared with placebo. Neither found a significant difference in dropouts due to adverse effects between the groups. Diarrhoea was reported significantly more frequently with acamprosate, and was dose-dependent (3.3%, 7.4%, 12.1%; $p < 0.01$) in the placebo, low and high dose acamprosate groups respectively in one study [30], and was frequent but not significantly different (39%, 43%, 48%) between the respective groups in the other [31].

The impact of combining acamprosate (1998mg/d) with naltrexone has been examined. One study [32] reported similar side effect profiles between groups with the exception of diarrhoea, and nausea, which showed significantly elevated scores in the combined group, where the daily dose of naltrexone was 50mg daily. A similar analysis of the COMBINE study data [33], using higher naltrexone doses (100mg daily), showed significantly increased levels, in the combined acamprosate and naltrexone group for nausea 42 % ($p < 0.001$), vomiting 18% ($p < 0.01$), diarrhoea 56% ($p < 0.001$), decreased appetite 25% ($p < 0.001$), somnolence 31% ($p < 0.05$), and abnormal liver function tests (AST/ALT 5x the upper normal limit) 2% ($p < 0.05$), when compared to placebo. Withdrawals due to adverse events were also greater (4%) in the combined group ($p < 0.05$).

Safety considerations in patients with comorbid psychiatric conditions

One small double-blind RCT of acamprosate for alcohol dependence in patients with schizophrenia spectrum disorders found no effect of acamprosate (1998mg/d) on measures of memory, attention, or executive function, or on psychotic symptoms [34]. The study was underpowered but the authors contend there were no specific safety concerns regarding acamprosate in this comorbid patient group. Another small double blind RCT in patients with alcohol dependence and bipolar (I or II) disorder maintained on mood stabilisers found rates of all adverse events to be comparable between acamprosate (1998mg/d) and placebo: one patient in each group was withdrawn due to persistent suicidality, and one patient in the acamprosate group had an anaphylactic skin reaction on initiation of the drug. There were no completed suicides in either group [35]. These studies suggest acamprosate is safe and tolerable in patients with bipolar disorder and schizophrenia, but the numbers in both studies are small and probably insufficient to exclude uncommon adverse events.

A meta-analysis of the acamprosate trial database examined the prevalence of depression (measured with the Hamilton Depression Rating Scale – HDRS) and differences between patients with and without depression [36]. Different versions of the HDRS were used across studies, so scores were standardized using linear transformation, and a cut-off of 17 to signify ‘moderate’ depression in the original HDRS-17 was standardized across scales to allow comparisons. Individual patient level data on 3354 patients from the 11 studies which had values for the HDRS at baseline and follow up were

analysed. The prevalence of moderate/ severe depression at baseline was 34.4% (range 29%-53%); the effect of acamprosate on mood was mediated by percentage days' abstinence, and no specific safety concerns were identified in the co-morbidly depressed subgroup.

A recent multi-centre double blind RCT conducted in Japan [25] showed similar incidences in reported adverse events across the groups. Diarrhoea was significantly more frequent with acamprosate, 1998mg/d, (12.9% vs 4.9%) but numerically more patients in the placebo group withdrew due to adverse events (6% vs 1.8%) during the administration period. A study in Chinese patients [37] found no differences in side effect profile between acamprosate (<60 kg, 1332 mg/d; ≥60kg, 1998 mg/d) and placebo; the most common side effects of the drug were diarrhoea (4.9%vs3.2%: $\chi^2=0.36$; $P=0.546$) and erythra (3.9% vs. 2.1%: $\chi^2=0.53$; $P=0.468$)- which all resolved without treatment. These studies suggest there are no obvious tolerability differences for acamprosate in Chinese or Japanese populations. A recent meta-analysis [38] concluded there were no gender differences in safety or tolerability for acamprosate.

4. Naltrexone

4.1 Oral naltrexone

Oral preparations are licenced for relapse prevention in the UK, Australia, Asia, USA and much of Europe. Naltrexone is rapidly absorbed and reaches a peak plasma concentration within one hour. It is subject to significant first pass metabolism, creating the primary active metabolite 6-beta-naltrexol, which has a half-life of 13 hours [39], the levels of which correlate with adverse events [40]. A substantial evidence base includes systematic reviews and meta-analyses, which demonstrate a significant effect for naltrexone over placebo on relapse rates in heavy drinking (RR 0.83; 95% CI:0.75 to 0.91) [4], and on relapse to any drinking at 3 months (RR=0.92, 95% CI=0.86-1.00) [15].

Pharmacokinetic considerations and implications for safety

There is limited evidence for a pharmacokinetic effect of naltrexone on other drugs. The cytochrome P450 enzyme system is not involved in metabolism of naltrexone or 6-beta-naltrexol, so interactions with drugs subject to hepatic metabolism are likely to be minimal [41]. Co-administration with acamprosate significantly increases acamprosate levels and side effects from acamprosate (see Acamprosate, section 3, above). Caution is advised for patients with liver dysfunction [4] and 5-10 fold increases in naltrexone plasma concentrations have been reported in patients with cirrhosis [41]. Although not experimentally tested, evidence from RCTs suggests the interaction with alcohol is not dangerous, and naltrexone has not been found to produce physical or psychological dependence [39]. The most important reaction from a safety consideration is with other opioid drugs, and patients need to be advised against their concomitant use. Data suggest the concurrent use of non-steroidal

analgesics with high dose naltrexone may account for the raised transaminases seen in early studies [42]. A study of naltrexone at 300mg in obese patients [43] reported elevated hepatic enzyme levels, but this was not repeated in patients with Huntington's disease [44] or eating disorders [45], or in patients with impulse control disorders treated with 200mg daily for up to a year, with limited use of analgesics [46]. Phase 2 studies showed no evidence of toxicity at doses of 800mg daily for one week [39]. A single RCT [47] reported a significant advantage for naltrexone 50mg daily over placebo in lipid profile (with reduced total cholesterol and triglyceride concentrations) in recently abstinent patients.

There are limited data on the impact of age on tolerability. In a single non-blinded RCT of naltrexone (100mg/d) and disulfiram (250-500mg/d) in Indian adolescents with alcohol dependence [48], side effects were reported as 'uncommon': 3 patients had self-resolving 'neuritis' in the disulfiram group and none in the naltrexone group (but no mention is made of how tolerability was assessed). A single study in patients aged over 50 years [49] showed no significant differences between placebo and naltrexone (50mg / day equivalent), sleep disturbance and anxiety being the most commonly reported effects.

Main summary of adverse effects

A Cochrane review [7] of 47 studies analysed available data on side effects that were documented in each study and calculated the risk differences (RD) for each of 46 different side-effects listed in between 2- 25 of the study reports. Table 2 shows the reported adverse events where there were significant risk ratios for naltrexone, and Table 3 the summary of side effects for which no difference was found between naltrexone and placebo. The most significant side effects attributable to naltrexone were nausea, vomiting, dizziness, abdominal pain, reduced appetite, and day time sleepiness.

Insert Table 2 about here

Insert Table 3 about here

The majority of studies have used naltrexone at 50mg daily, though some [50-55] have investigated the tolerability of 100mg naltrexone. Use of 150 mg naltrexone daily in patients with comorbid cocaine dependence [56] is discussed below, but a single open label study by Yoon et al. [57] evaluated the safety of 150mg daily in patients with alcohol dependence (titrated up from 25mg daily by week 3) over eight weeks. All patients were given prochlorperazine 10mg to reduce nausea in the first 3 days and use of 'over-the-counter' analgesics was restricted, which may have affected the observation of raised transaminases in studies of higher dose naltrexone in pathological gamblers

[58]. Yoon et al. [57] report that the most common side-effects (nausea, dizziness and drowsiness) occurred mainly in the early part of the study while patients were on the lower dose, and that 'higher doses did not increase the frequency or severity of side effects': hepatic transaminase profiles were stable.

RCTs assess safety considerations over a relatively small time frame, but a randomised single-blind trial of 50mg naltrexone versus acamprosate (no placebo) over one year [59] found that symptoms resolved after the first 2 weeks of the study, with no long term safety concerns.

Safety considerations for oral naltrexone combined with other medications

Polypharmacy increases safety concerns when prescribing a drug, but given only moderate effectiveness of licenced medications for treatment of alcohol dependence, the need to optimise outcomes has led to trials of combinations. The effect of acamprosate combined with naltrexone has been discussed above. A large study of naltrexone in combination with disulfiram [60], conducted in USA Veterans Administration (VA) outpatient clinics, included 254 patients with alcohol dependence comorbid with a major Axis I psychiatric disorder: patients were randomised (open label) to either 250mg disulfiram or placebo, and then subject to double blind randomisation to naltrexone (50mg/d) or placebo. Participating patients were therefore in one of four treatment groups: combined naltrexone and disulfiram, disulfiram only, naltrexone only, or placebo only. In the full sample, those in the combined group were significantly more likely to report abdominal pain, nausea, vomiting, numb limbs, pins and needles, irregular heart beat and restlessness (all $p < 0.05$) than either monotherapy medication. There were differences in side effect profiles within subsamples and these are discussed in the comorbidity section below.

Two small studies have examined the combination of ondansetron (a 5HT₃ antagonist) with naltrexone. Johnson et al. [61] added either naltrexone (50mg/d) or placebo to ondansetron for 8 weeks and reported no significant side effects. Myrick et al. [62] conducted a four-arm double-blind fMRI study, with naltrexone, ondansetron and placebo in combination for seven days. The main side effects (nausea-vomiting and dizziness) were significantly more likely in the naltrexone group, with no difference in side effects between the ondansetron or placebo groups.

Gabapentin (titrated to 1200mg/d) added to naltrexone (50mg/d) for the first 6 weeks of a 16-week treatment programme was compared with double placebo, after 4 days' abstinence. The combination group reported more daytime somnolence ($p=0.02$), blurred vision ($p=0.02$), and premature ejaculation ($p=0.02$), but improved sleep quality more than the other groups, and was overall well tolerated.

A 3-month open randomised three-arm comparative study of GHB and naltrexone (50mg/d) [63], singly and in combination (no placebo arm), reported a significantly higher side effect burden in the combination group than in the GHB group, specifically vertigo (5/18 vs. 2/20) and nausea (4/18 vs. 0/20). Five patients discontinued due to side-effects, three in the combination group and one in each of the other arms. The numbers are too small to be interpreted reliably but tolerability and safety in this combination require further study. Another Italian study [64] of uncertain design described 47 patients treated in 4 groups: escitalopram (20mg/d) only; naltrexone (50mg/d) + escitalopram (20mg/d); GHB (75mg/kg) + escitalopram (20mg/d); naltrexone (50mg/d) + GHB (75mg/kg) + escitalopram (20mg/d). Hyperalgesia was significantly more common in the naltrexone-treated groups when compared with the other groups. These findings need to be replicated in a larger sample with a placebo arm.

Two studies have examined the effect of naltrexone combined with sertraline in alcohol dependent patients without comorbid depression. A double-blind RCT [65] of naltrexone (50mg/d) and sertraline (titrated to 100mg/d) found significantly increased rates of nausea, sleepiness and dizziness in the combined group. Farren et al. [66] conducted a similar study (naltrexone 100mg/d) and reported similar levels of common side effects between groups with the exception of sexual dysfunction, which was significantly more common in the combination group (68% vs 24%, $p < 0.001$). Finally a double blind study adding quetiapine (25-200mg daily) or placebo to naltrexone (50mg/d), showed no additional benefit or side effect burden beyond that of naltrexone [67].

Safety considerations for oral naltrexone in patients with comorbid psychiatric conditions

There is an emerging literature on the role of naltrexone in alcohol dependent patients with comorbid axis 1 psychiatric disorders. Naltrexone is not licenced for use in patients with comorbid psychopathology, but given the high prevalence they constitute an important area for safety considerations in clinical practice. Some data (of varying quality) is available for patients with alcohol dependence and comorbid cocaine dependence, depression, bipolar disorder, post-traumatic stress disorder (PTSD), psychotic disorders and eating disorders.

Cocaine and Alcohol Dependence (CAD)

Five RCTs have investigated the safety and efficacy of naltrexone in the treatment of comorbid alcohol and cocaine dependence (CAD) in relapse prevention [54, 56, 68] or abstinence initiation [55, 69]. None found any significant benefit for active medication (50mg/d [68, 69], 100mg/d [54, 55] 150mg/d [56]) in terms of outcomes for cocaine use, comorbid with alcohol, although this may have been masked by gender differences [56]. Pettinati et al. [56] investigated the effect of naltrexone 150mg vs placebo as a relapse prevention agent, and found that at higher dose there was significantly greater reporting of nausea in the naltrexone group (53.7% vs. 26.8%, $p < 0.05$), and in women more

than men on the active medication (52.1% vs. 35.3%, $p < 0.05$). A further analysis with 150mg/d [70] concluded that women with more severe psychiatric symptoms, and those with higher frequency of nausea were significantly more likely to discontinue treatment (OR = 23.89, and OR = 43.45, respectively), but the confidence intervals around these odds are broad. Pettinati et al. [54] also investigated naltrexone (100mg/d), disulfiram (250mg/d), both separately and combined, versus placebo in CAD patients. There were no serious medical complications or deaths during the study: headache, drowsiness, anxiety/irritability and nausea were the most commonly reported adverse events, but only nausea was significantly more frequent in the active medication groups ($p=0.01$). Increased sexual desire was more common in the combination medication group (33%) but not significantly more frequent than with placebo (28%).

Depression and alcohol dependence

The prevalence of depression co-occurrence has been found to range from 24%-48% in alcohol dependent men and women respectively, and ranges from 50-70% in clinical samples [71], but following detoxification and abstinence this substantially reduces [72]. Although the recommendation [4, 8] is to wait until the patient is 3-4 weeks abstinent from alcohol to reassess mood and need for treatment, both conditions often need to be addressed concurrently. Four RCTs have investigated naltrexone in this patient group.

Oslin et al. [73] examined older (aged 55 years or more) patients, post detoxification, who started naltrexone (50mg/d) or placebo. After 1 week, all patients still met criteria for depression and 50mg/d of sertraline was added, increased to 100mg/d after 1 week if tolerated, for 12 weeks. Adverse events were screened using a check list and although reporting of headache, anxiety, nausea, vomiting and decreased sexual function was common, none were more common with naltrexone / sertraline than with placebo sertraline group. Pettinati et al. [51] conducted a 4-arm RCT of sertraline (200mg/d), naltrexone (100mg/d) singly, in combination, and placebo: the most frequent serious adverse event was requiring inpatient detoxification, which correlated with a poor outcome rather than tolerability, and was significantly less frequent with combined naltrexone-sertraline group than in the other groups combined. There were no differences between groups in reports of symptoms of irritability, fatigue, decreased sexual desire, headache or nausea, but 7/42 (~17%) patients in the combined naltrexone /sertraline compared with only 1/40 (2.5%) in the placebo group withdrew due to adverse effects.

Adamson et al. [74] report a 12-week parallel-group trial in alcohol dependent patients with comorbid depression: 138 patients were randomised to citalopram (20mg/d) or placebo, increasing after week 1 if required, all patients then being prescribed naltrexone (50mg/d). Patients were not required to be abstinent at baseline. Overall 90.4% of the citalopram/naltrexone group and 87.7% of the placebo/naltrexone group reported one or more adverse events, with 'severe' events being more likely

in the citalopram group ($p=0.049$); most commonly difficulty sleeping, nausea, and low energy, although the latter was the only event that occurred more frequently with citalopram: two patients were withdrawn (one with suicidal ideation and one with severe abdominal cramps) both in the sertaline/naltrexone group.

Petrakis et al. [75] reported a sub-group of 139 patients with alcohol dependence and depression in the four-arm naltrexone (50mg/d) / disulfiram (250mg/d) study conducted in USA Veterans Administration (VA) outpatient clinics described above. There was no difference in adverse events between the groups, and the authors concluded that disulfiram and naltrexone were safe, both singly and in combination in this comorbid patient group.

Depression and Bipolar disorder and Psychoses

Two studies have examined the use of naltrexone (50mg/d) in patients with bipolar disorder [76, 77]. Petrakis et al. [77] reports a sub-analysis of 66 patients with 'psychotic spectrum disorder', 73% of whom had bipolar disorder (the remaining participants having schizophrenia or schizoaffective disorder). As expected, patients with psychotic spectrum disorders were significantly more likely to be prescribed atypical and/or typical antipsychotic (15% and 28.7% respectively), lithium (15%) or anticonvulsant (35%) medications than in the 'non-psychotic' group. This may have an impact on tolerability, with psychotic spectrum disorder patients significantly more likely to report abdominal pain, sweating and tremors than those in the non-psychotic spectrum group, whether they were on active treatment or placebo. A small double blind RCT in patients with bipolar disorder [76] added naltrexone or placebo to continued usual medication (lithium, anticonvulsants, antipsychotics and/or antidepressants): there was no interaction with valproate, and the change in side effect burden was not significantly different between adjuvant naltrexone and placebo. A small RCT of naltrexone (50mg/d) augmentation of 'treatment as usual' in patients with schizophrenia [78], concluded that naltrexone had no effect on psychotic symptoms and was well tolerated.

PTSD and other co-morbid conditions

In a further sub-analysis of the VA group, Petrakis et al. [79] reported on 93 patients with PTSD (91 male): patients were more likely to report gastrointestinal ($p=0.05$), emotional, cold/ flu and neurological symptoms than those without PTSD (all $p < 0.02$). Patients with combined disulfiram (250mg/d) and naltrexone (50mg/d) in the PTSD group were significantly more likely to report cardiac or sexual side effects, and had higher post-traumatic re-experiencing symptoms, than those on either medication alone. There was one alcohol/disulfiram reaction in a patient in the combined disulfiram/naltrexone group. In a separate study [80], 88 patients were randomised to one of 4 groups: paroxetine (40mg/d) or desipramine (200mg/d), with naltrexone (50mg/d) or placebo, but there was no significant difference in side effect reporting between groups. Several studies have included

patients with co-morbid alcohol dependence psychiatric disorders [81-83]. None of these show significantly different side effect profiles from non-comorbid groups.

There is some evidence that naltrexone tolerability is worse in women. The observation of higher levels of nausea in women with CAD was discussed above. O'Malley et al. [84] reported a study of naltrexone (50mg/d) in 103 women (29 with comorbid eating disorders): no differences in adverse events across the medication or diagnostic group were found, but significantly more who reported any event were in the naltrexone group, and the most common significant individual events were decreased appetite, depression and dizziness. In an earlier open trial (naltrexone 50mg/d) [85] a regression analysis of 120 patients found younger age, female gender and less severe alcohol use were associated with increased nausea. Baros et al. [86] reported on pooled data from two earlier studies [87, 88] and found that women experienced more nausea on naltrexone (50mg/d) compared with placebo (38% vs 8%; $p=0.01$), though this had no impact on outcome, and concluded that reported sex differences may reflect study design rather than inherent pharmacological or biological differences in response. The naltrexone (50mg/d) studies have been conducted in a wide range of ethnic groups including Iranian [89], Taiwan Han [90], Indian and Chinese ethnic males in Singapore [91], American Indians and Alaskan Natives [92], Black African Americans, Hispanic Americans, Northern and Southern Europeans, and Australians: with no significant difference between groups in the observed safety profile.

4.2 The extended-release injectable suspension of naltrexone

The extended-release injectable suspension of naltrexone is currently only licensed in the USA, Russia, Ukraine, Azerbaijan, Kazakhstan, and Belarus. Its primary purpose is to improve compliance, as studies of oral naltrexone (50mg/d) show it to be superior to placebo only when compliance is greater than 80% [93] or 90% [94]. As the injectable suspension has reduced plasma levels and lower first pass metabolism, it is anticipated that levels of the metabolite 6-beta-naltrexol would be reduced, potentially reducing adverse effects [95].

Pharmacokinetic considerations and implications for safety

The main pharmacokinetic differences between long acting injectable naltrexone and the oral preparation are the lack of daily naltrexone peaks, and the reduced ratio of 6-beta- naltrexol. A preliminary double blind RCT [96] in which 15 alcohol dependent patients were given 206mg S/C naltrexone injection or 5 placebo injection after two weeks of oral naltrexone, followed by a washout period, found the main side effects to be pain and induration at the injection site in both groups, all other adverse events being comparable in frequency to those during the oral naltrexone period. A

small double-blind RCT [95] involving 30 participants (25 naltrexone 400mg IM monthly, 5 IM placebo monthly) found adverse event reporting to be similar to that with oral naltrexone, with the addition of injection site pain in 4/25 of the injectable naltrexone group, but in none with placebo injection. Two patients (8%) withdrew after the second naltrexone injection due to site injection induration and angioedema. As predicted, plasma concentrations of 6-beta- naltrexol were lower than after oral dosing, but this did not appear to reduce the side-effect burden. Kranzler et al. [97] randomised 215 patients to 300mg naltrexone IM followed by 150mg IM monthly or placebo for 3 months: 4% of patients in both groups withdrew due to injection site reactions. The most common adverse events were headache, nausea and fatigue; upper abdominal pain was more common with naltrexone group, and irritability and chest pain with placebo. There was a trend for pain to be more common in the naltrexone injection site. Garbutt et al. [98] conducted a 3-arm RCT of naltrexone 380mg IM, 190mg, or matching placebo: withdrawal due to adverse events occurred in 14.1% in the 380mg, 6.7% in the 190mg group, and 6.7% in the placebo group, due to dose-dependent rates of nausea, injection site reaction and headache. There were significant dose-dependent differences in reports of decreased appetite and dizziness. Two cases of pneumonia in the 380mg group were judged to be possibly related to medication. No effect of medication dose was found on increased levels of transaminases.

5. Disulfiram

Disulfiram acts by irreversible inactivation of liver acetaldehyde dehydrogenase (ALDH) enzymes. ALDHs catalyse the conversion of acetaldehyde into acetic acid during the metabolism of alcohol. Inactivation therefore results in an increased concentration of intracellular acetaldehyde, when alcohol is taken. Disulfiram also inhibits the conversion of dopamine to noradrenaline, and the depletion of noradrenaline in the cardiovascular system allows acetaldehyde to act directly on myocardial and vascular tissue to cause flushing, tachycardia and hypotension. Other symptoms of the disulfiram-alcohol reaction (DAR) include hyperthermia, headache, chest pain, and respiratory depression or hyperventilation which may be mild or life-threatening. There is substantial intra- individual variation in the severity of the DAR, due to variations in which polymorphisms are expressed or mutations are present in different parts of the alcohol oxidative pathway, and also to the complex metabolic pathway of disulfiram [99], which makes it hard to predict the response in any individual.

Pharmacokinetic considerations and implications for safety

Disulfiram is converted by gastric acid to diethyldithiocarbamate, which is a strong metal chelating agent [100] and may account for the mild but unpleasant side effect of ‘metallic taste’ [101]. Disulfiram is metabolized in the liver and inhibits the metabolism of drugs such as phenytoin

and warfarin which use the CYP450 and CYP2E1 systems, leading to increased levels [102]. It also inhibits the metabolism of chlordiazepoxide and diazepam (but not oxazepam), increasing their sedative effects [100, 103].

Rothstein & Clancy [104] reported an RCT of 58 inpatients prescribed disulfiram (500mg/d for 30 days, then 250mg/d), then randomized to adjuvant metronidazole (750mg) or placebo: 6/29 of those on co-prescribed metronidazole developed a 'confusional psychosis', reversible on discontinuation, with no benefit for the addition of metronidazole.

Undertaking an alcohol challenge in patients on disulfiram is not recommended in clinical practice. Rather, patients and carers should be given clear instructions about potential hazards, and sources of alcohol in consumables. In a controlled setting of 60 alcohol-dependent patients prescribed disulfiram (250mg/d), Kumaraswamy et al. [105] gave each an alcohol challenge: symptoms of the DAR started within 10-15 minutes and lasted between 90-240 minutes. Tachycardia, hypotension and transient ischaemic changes on ECG were most commonly noted, though 38% showed no significant ECG changes: all recovered, but those with hypotension required intravenous fluid stabilisation.

Overdose with disulfiram as a sole agent has relatively low toxicity, but given the irreversible effect on ALDH patients require observation until ALDH is active again. No abuse liability has been shown for disulfiram.

Main summary of adverse effects

The evidence base for disulfiram is less robust than for other medications licensed for the treatment of AUD: primarily due to difficulties (both ethical and pragmatic) in subjecting it to a double blind RCT (see Appendix III). However four RCTs conducted in alcohol dependent populations [106-109] (200mg/d [104], 250mg/d [105, 106] 800mg twice per week [107]), all found it to be generally well tolerated over 6-12 months, and not causing any hepatitis. Drowsiness was the only reported adverse event found significantly more frequently in patients taking 250mg disulfiram compared to 1mg (active control) or placebo [107]; altered liver function (elevated AST and bilirubin) was not related to disulfiram treatment, but significantly related to drinking status [108]. Similarly Chick et al. [106] found mean serum GGT dropped by 21 IU/L in patients on disulfiram but rose by a mean of 13 IU/L in those on a placebo vitamin C tablet. Headache, fatigue and skin rashes and an unpleasant aftertaste occurred more commonly with disulfiram group than placebo, and improved with dose reduction when that was undertaken [106, 109]. DARs were reported on 29 occasions [106] but none led to a dose reduction, and the authors concluded that disulfiram was well tolerated when given as part of a wider treatment programme. A small cohort study of more than 50 weeks duration (disulfiram 1.5g/week) [110] did not raise any long-term safety concerns. A more recent two-month prospective

cohort study in an Indian population (125mg/d) [111] showed an excess of skin rashes, supporting an earlier observation that there may be greater sensitivity to the adverse effects of disulfiram in Indian compared to Western patients [112]. A study in adolescents [113] found it to be well tolerated with no significant differences in reported adverse events between disulfiram (200mg/d) and placebo.

Early studies of disulfiram used much higher doses (1-3g daily) causing a higher burden of serious adverse effects and DAR, including death [112]. In one variable dose study, 500mg doses of disulfiram were much less tolerated than 250mg with all withdrawals due to adverse events in the 500mg group [114].

Safety considerations for disulfiram combined with other medications

Disulfiram has also been investigated in a number of studies of alcohol dependence with comorbid opioid substitution therapy (OST). An early study which was stopped after 12 weeks due to the small sample size [115] reported safety data in 35/82 study completers: all patients had been stable on methadone for at least three months before being randomized to 250mg disulfiram or placebo. No serious adverse events attributable to the combination of methadone and disulfiram were reported. In a recent prospective cohort study of 29 patients on OST at variable doses [116], in which participants were given disulfiram (100-300mg/d) for 6 months, 50% completed the study and three patients (10%) reported serious adverse reactions attributable to disulfiram, although there was no control group (see Appendix III).

Safety considerations for disulfiram in patients with comorbid psychiatric conditions

Two placebo-controlled studies have assessed the effects of disulfiram (250-500mg/d) in patients with alcohol dependence comorbid with cocaine use [117, 118]: the latter was discussed in the naltrexone section (above). Combining disulfiram with careful monitoring was considered safe with few serious adverse events. Laboratory studies of the disulfiram-cocaine-alcohol interaction in volunteers, have found that disulfiram increased cocaine levels and duration, with mild elevations of blood pressure and heart rate, which were not clinically significant [119]. The main evidence for using disulfiram in patients with alcohol dependence and comorbid Axis I disorders comes from the VA study reported by Petrakis et al. [60, 75, 79, 120] described above: none identified any specific concerns regarding the use of disulfiram in patients with psychotic spectrum disorders, PTSD or depression (see Appendix III). Earlier concerns about the potential for disulfiram to cause psychosis in vulnerable groups were based on doses of 1-3g [121] and have not been reported recently [8].

6. Nalmefene

Nalmefene is an opioid system modulator, structurally similar to naltrexone, but with a methylene group at the sixth carbon, where naltrexone has a ketone group. It has a slightly different receptor profile, acting as a mu receptor antagonist and kappa receptor partial agonist [122], but like naltrexone has no opioid mu agonist activity or abuse potential [123]. It is licenced in Europe for the reduction of alcohol consumption in patients not requiring medically assisted withdrawal.

Pharmacokinetic considerations and implications for safety

Nalmefene was originally developed to reverse the effects of opioid overdose and anaesthesia [122], and the benefits of opioid analgesics may not be felt if taken concomitantly with nalmefene. Like naltrexone there are no clinical safety concerns of co-ingestion with alcohol, and based on in vitro studies there are no relevant interactions with other drugs metabolised by the CYP450 and UGT systems. Potent inhibitors of the UGT2B7 system (e.g. diclofenac) if used chronically may increase nalmefene levels, but not with occasional use [124].

Nalmefene is extensively metabolized in the liver, largely by glucuronidation rather than transformation to a different metabolite; unlike naltrexone there is no identified risk of hepatotoxicity [125], but clearance of nalmefene was found to be significantly reduced in a small study of patients with liver disease, and inversely proportional to the level of hepatic pathology [126].

A Cochrane review [7] included a meta-analysis of the two earlier studies on nalmefene conducted in the USA. This found two adverse events reported significantly more frequently by patients on nalmefene than placebo were insomnia (Effect size 0.12 [0.05, 0.19]) and nausea (effect size 0.20 [0.14, 0.26])

Anton et al. [127] compared 5mg, 20mg and 40mg nalmefene with placebo, and Mason et al. [125] 20mg and 80mg doses of nalmefene with placebo. Patients on 80mg nalmefene were more likely to withdraw due to adverse effects but the occurrence of adverse drug reactions did not significantly differ between the groups.

Drobes et al. [128] describe an 8-day trial to assess the impact of nalmefene (40mg/d), Naltrexone (50mg/d) or placebo in 125 alcohol dependent people. Patients in the nalmefene group reported significantly higher levels of poor sleep, irritability, trouble concentrating, decreased libido and headache than in either the naltrexone or placebo group. Whereas patients prescribed naltrexone reported significantly more nausea/ vomiting over the 6 days of medication.

There have been two large multi-centre double blind placebo-controlled three-month trials of nalmefene [129, 130] and one twelve-month safety trial [131] conducted in alcohol dependent patients, not in need of medically-assisted detoxification, but who wished to reduce or stop their alcohol consumption. Medication was taken on an 'as needed' basis, up to once daily. In the first study [130] patients were randomized to 18mg nalmefene or placebo: treatment-emergent adverse events were given as the reason for dropout in 91 patients; 69 (23%) in the nalmefene group (primarily dizziness, nausea, fatigue and headache), and 22 (7%) in the placebo group. Other common side-effects – namely sleep disorder, insomnia, vomiting, and hyperhidrosis, were twice as likely with nalmefene as with placebo, but most were of mild or moderate intensity, and occurred within 1 day of the first dose. Two patients committed suicide, both in the placebo group. In the second study [129], in which 341 patients were randomized to 18mg nalmefene and 337 to placebo, 68% and 59% respectively had treatment-emergent adverse events. Nausea, dizziness and insomnia occurred twice as often with nalmefene as with placebo. Dropout due to adverse events occurred in 5.9% of the placebo and 6.7% of the nalmefene group; a total of fourteen patients (4 placebo group, 10 nalmefene) had a psychiatric adverse event, but none was described as serious, and all settled. Two patients died, one in the nalmefene (cause unknown), and one in the placebo group (secondary to hepatocellular carcinoma).

In the 52-week safety study [131] 501 patients were randomized to nalmefene (18mg/d) and 164 to placebo. A similar pattern of treatment-emergent adverse events was reported (nausea, insomnia, dizziness vomiting and fatigue was reported twice as frequently as with placebo). The vast majority of adverse events (97%) were mild or moderate in intensity and occurred at the beginning of the study. Serious adverse events were reported in 5.4% of the placebo and 6.4% of the nalmefene group: the majority were not considered by investigators to be related to the study medication. Eighteen patients (1% on placebo and 3% on nalmefene) reported a psychiatric adverse event, 2 patients (both on nalmefene) had disorientation (one severe and one moderate). There were no differences between treatment groups, or changes over time for weight, ECG parameters or vital signs. At month 13 GGT and ALAT values remained higher in the placebo group.

Finally a sub-analysis of all patients at high or very high drinking risk levels combined from the 3 studies above [132], did not find any specific differences from the full population.

7. Baclofen

Baclofen is a GABA-B agonist used in the treatment of spasticity for many years. It currently has a 'temporary recommendation for use' in France for the maintenance of alcohol abstinence, or for the

reduction of consumption to low levels in patients with alcohol dependence who have not responded to other treatments [133]. Some studies demonstrate the effectiveness of baclofen in alcohol dependent patients [134-136] but are small and further trials are underway: current data inform the safety considerations presented here.

Pharmacokinetic considerations and implications for safety

The precise mechanism of baclofen is not fully understood. It is rapidly absorbed, and excreted primarily by the kidney unchanged, but there appears to be significant inter-subject variation in absorption and elimination. Although extensively used in patients with spasticity, safety considerations in patients with AUD may well differ. The lack of hepatic metabolism makes it potentially useful in patients with comorbid liver disease [137, 138]. Use in patients with renal disease, or in the elderly, who may have reduced renal capacity, has not been systematically studied. A case series of four alcohol dependent patients in India, developed morbilliform rashes on initiation of treatment which were dose dependent and resolved with drug cessation [139].

An early open RCT in Russia [140] which compared baclofen (37.5mg/d) with amitriptyline (75mg) or diazepam (15mg) in 'alcoholic patients with secondary affective disorders' who had been abstinent for 3-4 weeks, found it to have 'no side effects' but how this was assessed is not clear. There have now been seven subsequent double blind RCTs [134-136, 141-144] (see electronic supplementary Material): not all have demonstrated efficacy over placebo, but overall baclofen (30mg/d) appears well tolerated, and there have been no specific safety concerns including in patients with liver cirrhosis [135], or hepatitis C [138]. Indices of liver failure (AAT, bilirubin, INR and GGT) significantly improved in the baclofen group (due to reduced drinking), and there were no instances of encephalopathy, or craving for or liking of baclofen; and no evidence for a discontinuation syndrome [133, 134, 144]. More recent studies (baclofen doses ranged from 30-270mg/d) [136, 141-143] found that headache and drowsiness were most commonly reported, though not significantly more frequently with baclofen than with placebo.

Several studies have examined the impact of higher doses of baclofen. The first was a two-year observational study of 100 patients [145] in which the mean maximal dose of baclofen taken was 147mg/day (range 20 to 330mg). A wide range of side effects of mostly mild intensity were reported by 88% of patients, with no relationship between side effects and treatment response. In another prospective cohort study [146] involving 253 patients treated for up to one year, episodes of major sedation were recorded and the relationship between them investigated using a generalised estimating equation (GEE) model. The rate of sedation episodes increased with levels of alcohol and baclofen daily dose separately, and showed a significant interaction between the two. The first reported double blind RCT [136] of 56 patients individually titrated to daily doses of baclofen between 30-270mg reported that doses were well tolerated with no drug related serious adverse effects, and no

discontinuation symptoms, including craving. A small and retrospective case series suggested the existence of a 'baclofen withdrawal syndrome' [147] but this requires more robust prospective investigation. The same group also reported a nested cohort study of 23 alcohol dependent patients treated with high dose baclofen (mean dose 124.5 ± 67.2 mg/d) who also had borderline personality disorder [148]: those with comorbid personality disorder reported a significantly higher number of adverse events (65.2 vs. 6.5%; $p < 0.001$), and rate of treatment discontinuation after adverse events (52.2 vs. 8.6%; $p < 0.001$).

The main safety considerations relate to co-administration with other CNS depressants (e.g. opioids, benzodiazepines, tricyclic antidepressants) and anti-hypertensives. The increase in prescriptions for baclofen for AUD has resulted in its use in more episodes of self-poisoning. The clinical presentation of baclofen overdose is related to its inhibitory neurotransmitter effects, and includes coma, hypotonia, respiratory depression, seizures and cardiac abnormalities, and at higher doses autonomic effects such as hypertension and CNS depression [149]. In a consecutive series of 23 self-poisoning presentations to a regional toxicology service in Australia [150], in which baclofen doses consumed ranged between 80- 2500mg, seizures were reported in 4 cases (3 on baclofen only), 16 patients required to ICU, and 11 required intubation (median 32 hours). Baclofen doses less than 200mg were not associated with severe effects but delirium, seizures and coma occurred at higher doses, include 6 of the 7 patients who co-ingested alcohol. A recent report compared 14 consecutive emergency presentations in alcohol dependent patients treated with baclofen following intentional poisoning to 56 matched patients presenting with overdose from another neurodepressant medicine [151]. Alcohol co-ingestion occurred in 78.6% of baclofen poisoned patients compared with 48.2% in the control group ($p = 0.07$): they were significantly more likely to be admitted to ITU, and to require mechanical ventilation. A retrospective review of 12 patients admitted following baclofen overdose (ranging between 140-800mg; median 340mg) [149] noted 10 patients had made previous suicide attempts, that benzodiazepines and alcohol were frequently co-ingested, and there was a dose-dependent relationship in the severity of medical symptoms.

8. Discussion

Summary of main findings

Acamprosate appears safe and well-tolerated for the maintenance of abstinence in alcohol dependent patients, with no significant safety concerns across a wide range of patient groups including those with major mental illness. It is safe in overdose, and when taken with alcohol. Its main side effect is diarrhoea which settles within a few days, or with dose reduction if severe. Acamprosate plasma

levels and side effects are increased by naltrexone, and potentially in the elderly and those with significant renal insufficiency. It is recommended as a first line treatment for the maintenance of abstinence [4, 152].

Early concerns about oral naltrexone causing hepatotoxicity have not been replicated in patients with alcohol dependence, although monitoring is still advised [4], and use of non-steroidal analgesics should be limited. It has a moderate side effect burden, specifically gastro-intestinal symptoms, headache and drowsiness/fatigue, which are dose dependent, and appear to be worse in women. There are no significant safety concerns regarding use of naltrexone in patients with alcohol dependence comorbid with depression but some evidence that combining it with sertraline makes naltrexone less tolerable at higher doses (100mg naltrexone, 200mg sertraline) although this may be more effective. Combinations with acamprosate, disulfiram, ondansetron, gabapentin, olanzapine and sertraline were all safe although increased the side-effect burden. However, the risk-benefit ratio for combining naltrexone with citalopram or GHB is less certain and requires further investigation. Taken together, the hypothesized benefits on tolerability from the injectable formula do not seem to have been realised, and in addition there are substantial adverse events at the injection site. The potential benefit of injectable naltrexone over the oral preparation appears to be related to improved adherence rather than improved tolerability, and other safety considerations remain untested.

The safety profile of nalmefene is similar overall to that of naltrexone, but its action as a partial agonist at the opioid kappa receptor may account for the increased reporting of CNS symptoms (dizziness, insomnia, disorientation). There are no significant concerns regarding use in patients with liver pathology, and the clinical trials specifically tested its co-ingestion with alcohol and found this to be safe.

Several reviews of the safety of disulfiram [100, 106, 153] have concluded that the moderately severe side effect profile for disulfiram <250mg daily can be mitigated by careful patient selection and supervision, for those patients (including those with co-morbid cocaine addiction) in whom it may be effective. The DAR remains potentially serious if both disulfiram and alcohol are taken at high doses.

There are substantial safety considerations regarding self-poisoning with baclofen, particularly in conjunction with alcohol, as both are CNS depressants and if taken at high levels timely medical intervention is needed to prevent respiratory depression. Concomitant prescribing with other CNS depressants requires a careful risk benefit assessment, and evidence to date suggests that it is safer for use to maintain rather than initiate abstinence in those with no suicidal tendencies. It may have a

particular role in the treatment of alcohol related liver disease. Optimal therapeutic doses, along with the relative safety risks of higher doses, have yet to be established

In addition to the medications reviewed here, other medicines are being investigated in patients with alcohol dependence, including ondansetron (discussed above) and topiramate. The first trial (using 300mg topiramate daily) found it to have significant side effects (including paraesthesiae, nausea, cognitive impairment and headache) which were reduced when a lower dose (200mg/d) and slower titration were used [154, 155].

Areas of uncertainty

Use of clinical trial data to examine safety and tolerability has the advantage of comparison with placebo, and more systematic recording of adverse events. This is particularly necessary in patients with alcohol dependence who have high placebo responses to treatment and a high incidence of adverse events [132, 156, 157]. However RCTs typically exclude patients with significant physical or psychiatric comorbidity [100] which obscures potential safety concerns in the wider group of patients seen in clinical practice. In patients with alcohol dependence especially, any medication to initiate abstinence or reduce drinking needs to have good evidence for the safety of the drug combined with alcohol, which seems well established for nalmefene [132] but less clearly for baclofen [146]. For medications that aim to promote abstinence from alcohol the safety profile needs to be weighed against the risks to the patient of relapse [112], but the prescriber also needs to take into consideration potential interactions with concomitantly prescribed medications in a patient group with considerable physical and psychiatric comorbidity. Baclofen is a good example of how the ‘repurposing’ of drugs in a different patient group may alter the safety profile, as was also seen in early reports of hepatotoxicity of naltrexone in non-alcohol dependent obese patients. Improved and more consistent reporting of case reports and case series may help identify significant safety concerns [12, 158] that do not come to light in clinical trials.

Conclusions

Alcohol dependence is responsible for a substantial burden of disease. Pharmacotherapy is underused in its treatment despite evidence of moderate effect [156], similar to that in other conditions [159]. Acamprosate, naltrexone, nalmefene have a substantial evidence base for being generally well tolerated, and disulfiram risks are well known and can be mitigated with appropriate patient selection and supervision. There are some positive initial reports regarding baclofen in patients with alcohol

Pharmacological treatments for alcohol dependence

dependence, but its safety profile, including its therapeutic dose range, interaction with other CNS depressants and abuse liability, have yet to be established.

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