Pharmacotherapy for alcohol dependence: status of current treatments
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The efficacy of medications for alcohol dependence remains modest, and there are no strong clinical predictors of treatment response. Approved medications include acamprosate (an N-methyl-D-aspartate receptor (NMDA) modulator), disulfiram (an acetaldehyde dehydrogenase inhibitor) and naltrexone (an opioid antagonist) while nalmefene (an opioid antagonist) is currently under review for approval in Europe. Clinical trials suggest that baclofen (a GABA-B agonist) and topiramate (an anticonvulsant) may be promising candidates, while several other drug candidates are currently evaluated at early clinical stages.

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Introduction
Alcohol use disorders (AUDs) (alcohol abuse and dependence) constitute the third leading cause of morbidity and mortality worldwide [1,2]. AUDs also rank high among the leading causes of decrements in disability-adjusted life-years and are responsible for a multitude of medical, psychological, social, economic and personal problems. The costs associated with alcohol amount to more than 1% of the gross national product in high income and middle income countries [3] much of which is accounted for by health care expenditures.

Alcohol dependence is a chronic relapsing disorder resulting from a complex interaction between genetics and environment. It is a heterogeneous disorder with a variety of phenotypes making it a challenge for any one-treatment to be effective for all individuals. In contrast to many other drugs of abuse, alcohol acts at multiple biological targets. These factors together pose unique challenges and simultaneously create multiple venues of possible targets for medication development.

The ultimate treatment goal for alcohol dependent patients is stable abstinence by prevention of relapse after detoxification [4]. A clinically significant reduction in alcohol consumption promoted by a specific pharmacological agent, with subsequent harm reduction is considered a valid intermediate goal on the way to full abstinence. Currently, there are three medications approved by both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) to treat alcohol dependence: disulfiram, oral naltrexone and acamprosate. The FDA has also approved the use of long-acting injectable naltrexone [5,6]. The EMA’s Committee for Medicinal Products for Human Use (CHMP) has recently recommended the granting of a marketing authorization also for nalmefene (Selincro®), a medicinal product intended for the reduction of alcohol consumption in adults with alcohol dependence (EMA, 2012). The overall effect size of the available drugs is moderate [7] and there is a crucial need for more effective treatments for AUD. The present review will summarize the research on currently approved medications and also discuss recent findings on other potential pharmacotherapies such as baclofen, prazosin, topiramate and varenicline.

Disulfiram
Disulfiram has been in use for the treatment of alcoholism since the 1940s, and was registered by the FDA in 1951. Disulfiram inhibits the enzyme acetaldehyde dehydrogenase, thereby preventing the metabolism of alcohol’s primary metabolite, acetaldehyde. In turn the accumulation of acetaldehyde in the blood causes unpleasant effects to occur if alcohol is ingested, which include sweating, headache, flushing, nausea and vomiting [8]. It is the association of these aversive symptoms with drinking alcohol that discourages the individual from further consumption. The accumulation of acetaldehyde poses serious medical risks and patients who are unable to abstain from drinking or for example, have compromised liver function should be advised against the treatment. One of the most cited disulfiram trials was conducted at a number of Veterans Administration hospitals across the United States in the 1980s. This 52-week trial with 605 alcohol-dependent men demonstrated that 250 mg disulfiram [9] had benefit over placebo in preventing relapse only in those patients who complied to treatment (20% of 577 who completed the study) but was ineffective in promoting continuous abstinence or in delaying the resumption of drinking. In a later study [10] with a focus on supervised treatment it was demonstrated that disulfiram (200 mg daily) enhanced treatment outcome when compared to the control group with regards to significantly higher number of abstinent days and a lower amount of drinks during the 6-month trial.
Evidence of efficacy of disulfiram is limited but the strongest predictor of an effect of treatment is observed in those trials that administered disulfiram under supervision [11,12]. In contrast to other approved pharmacotherapies, the strong psychological effects of disulfiram makes it a challenging drug to test in the gold standard double blind placebo controlled design, thereby making it difficult to compare treatment effects with the other approved medications. Overall, disulfiram does not target the core phenomenon of alcohol dependence and its clinical use is thereby limited.

**Naltrexone**

Alcohol’s rewarding effect is mediated partly via release of endogenous opioid peptides [13] and one of the downstream effects of this is the activation of mesolimbic dopamine (DA) release in the nucleus accumbens, the key brain reward region [14]. Naltrexone (NTX), an opioid antagonist, blocks the intrinsic properties of psychoactive substances that act on the mu (μ), delta (δ) and kappa (κ) opioid receptor sites by competitively occupying them. It is known that alcohol acts on the opioid receptors and by blocking these sites; NTX prevents the reinforcing effects of alcohol [15]. When taken orally, NTX is quickly absorbed and undergoes first-pass metabolism in the liver. It is then converted to several metabolites. The main metabolite is 6β-naltrexol, which by itself reduces alcohol drinking in rats [16]. The mean elimination half-life of NTX is 3 hours while that of its metabolite is 13 hours. A PET study using 11C-carfentanil has shown a significant blocking of brain μ receptors for more than 72 hours following a single 50 mg dose of NTX [17]. Collectively, these properties contribute to the relatively long action of NTX. Data from human laboratory studies [18] have facilitated the understanding that NTX reduces relapse by blunting the ‘priming’ pharmacological effects of alcohol. This is also consistent with much of the clinical data in that naltrexone seems to be effective in preventing a ‘slip’ into alcohol use from becoming a full-blown relapse [15]. NTX was approved by the FDA for alcohol dependence in 1994. Apart from the early studies that led to the approval of naltrexone [19,20], the vast majority of the naltrexone studies have been multisite trials, conducted in the United States. A few meta-analyses and a Cochrane review [17,21,22,23] have evaluated the accumulated data on the efficacy of NTX. Typically, the studies have shown that oral NTX was superior to placebo in preventing relapse to heavy drinking after an initial abstinence period, in reducing craving and in increasing the percentage of abstinence days. One of the most consistent findings obtained with naltrexone is an increase in time to relapse. A few studies have provided data on the effect of a longer-term (6 months) NTX treatment [24,25] and overall the results demonstrated moderate evidence in favor of naltrexone concerning relapse rates, and no difference in the long-term effects on percentage of drinking days and time to first relapse.

Some distinct predictors of a positive response to NTX have been identified including, a positive family history of alcoholism [26], and high levels of craving and possessing a polymorphism (Asn40Asp) in the opioid receptor gene [27,28]. A challenge in medication trials such as with NTX has been compliance to treatment and studies have shown that there is a clear relationship between the beneficial effects of NTX in reducing alcohol relapse and compliance [24,29]. Moreover less compliant subjects did not show any effect from NTX treatment. This could also explain some of the heterogeneity in the findings regarding effectiveness of oral NTX. Therefore, enhancement of compliance either through behavioral intervention or the use of a different formulation could be the critical factor to help improve treatment outcome.

**Extended release naltrexone**

The pharmacokinetic properties of oral NTX lends to significant fluctuations in plasma levels (with oral daily dosing), requiring medication adherence above 85% in order to produce a therapeutic response [30]. NTX’s overall effectiveness may therefore be enhanced by optimizing its pharmacokinetic profile. By administering a deep intramuscular injection that releases NTX over several weeks, plasma levels would remain relatively constant and low enough to reduce the incidence of adverse events yet high enough for the desired anti-drinking effects [31].

Vivitrex®/Vivitol® (XR-NTX) is naltrexone formulated into polylactide-co-glycolide (PLG) [32], small-diameter (<100 μm), injectable microspheres, which contain other proprietary active moieties that lead to its extended-release properties lasting for several weeks [33]. Pharmacokinetic studies of XR-NTX in humans [34] have indicated that this extended-release formulation maintained stable, pharmacologically relevant plasma levels of NTX for at least 28 days. Pre-clinical studies have demonstrated that this formulation blocks central mu-opioid receptors for a period of approximately 4 weeks after a single injection [31]. The pharmacokinetic characteristics of a single-dose XR-NTX 380 mg versus oral NTX 50 mg are as follows: Cmax: 12.9 ng/mL vs. 10.6 ng/mL; elimination half time 7.0 days versus 1.0 hours (median) [35]. In addition, the intramuscular formulation yields a plasma area-under-the-curve monthly plasma accumulation of naltrexone that is approximately four-times that achieved with daily oral NTX [36]. As addressed in *Introduction*, alcohol dependence is the fourth leading cause of disability and is associated with considerable morbidity and mortality, and a recent study [37] evaluated the effect of XR-NTX also on a measure of quality of life using data from a multicentre efficacy trial of XR-NTX. The results of that study highlighted that 380 mg XR-NTX (as compared to 190 mg) led to significant improvements in the
domains of mental health, social functioning, general health, and physical functioning (Table 1).

In a 3-month multicentre trial in 315 patients, treatment with depot naltrexone led to a significant reduction in drinking days and greater rates of abstinence [38]. A subsequent study tested the effect of a long acting formulation at two doses, demonstrating a dose response effect of treatment with a 25% reduction in heavy drinking days compared to placebo. This effect was significant only for men [39]. The lack of effect in women was attributed to possible factors such as greater load of affective symptoms and higher placebo response.

The FDA approval of both oral and depot naltrexone includes a black box warning for the risk of liver damage. Caution on the use of naltrexone is advised especially in patients with significant liver problems [40]. The extended release formulation has lower risks of hepatotoxicity compared to the oral formulation because the drug does not undergo first pass metabolism in the liver.

### Nalmefene

Nalmefene is an opioid antagonist that is similar in structure to naltrexone but with a number of differences such as: longer plasma half-life (8–10 hours), more effective binding to central opioid receptors [41,42], higher bioavailability [43,44] and lower liver toxicity. Allowing patients to choose the goal of treatment be it abstinence or reducing their drinking, might enhance their motivation as a result of active engagement in the treatment plan. Treatment with nalmefene is positioned as an as-needed treatment regime (targeted use) and seems to be a feasible treatment approach in this patient population [45].

Apart from the study by Anton et al. [46], all other controlled clinical trials to date have demonstrated that treatment with nalmefene led to a reduction in heavy drinking [47,45]. More recently, results from a phase III clinical trial with 718 individuals treated with (18 mg)nalmefene or placebo for 24 weeks, (on an as-needed basis) demonstrated that at the end of month 6, treatment with nalmefene led to a 50% reduction in heavy drinking days and total alcohol consumption [48]. This is one of the largest controlled trials to evaluate the effect of pharmacotherapy utilizing the as-needed approach in the treatment of alcohol dependence. The findings from this phase III study have also been replicated in a subsequent phase III study in 718 patients [49].

Although the EMA’s ‘Guideline on the development of medicinal products for the treatment of alcohol dependence’, adopted by its Committee for Medicinal Products for Human Use (CHMP) in 2010, states that the ultimate treatment goal in alcohol-dependent patients is abstinence, the acceptance by the agency’s CHMP of the use of a study end point to be reduction in heavy drinking is clearly a paradigm shift in the field of treatment trials for alcohol dependence. Whether such an end point, will be accepted as clinically relevant also by the FDA is uncertain at this point.

### Acamprosate

Acamprosate, or N-acetyl homotaurine, is a functional N-methyl-D-aspartate receptor (NMDA) modulator. Although the mechanism of action for acamprosate is not well understood, its neurochemical effects have been attributed to its antagonism of NMDA glutamate receptors [50,51], which restores the balance between excitatory (glutamate) and inhibitory (GABA) neurotransmission [51] that is dysregulated following chronic alcohol consumption. Acamprosate has been shown to decrease dopamine hyperexcitability in the nucleus accumbens during alcohol withdrawal [52,53] and general neuronal hyperexcitability [50]. It is via these mechanisms that acamprosate is believed to reduce the withdrawal-associated distress and modify learned responses to alcohol cues [54]. Acamprosate has been used clinically in Europe for more than 20 years and was approved by the FDA as a pharmacological treatment for
alcohol dependence in 2004. In a meta-analysis of 17 published studies that included 4087 alcohol dependent individuals, continuous abstinence rates at 6 months were greater than for those who received placebo (acamprosate, 36.1%; placebo, 23.4%) [55]. In a multi-site trial in the USA, there was no overall evidence that acamprosate was superior to placebo among a heterogeneous cohort of alcohol dependent individuals [56]. A subsequent large multisite trial (COMBINE) also failed to find any therapeutic benefit of acamprosate compared with placebo on any drinking outcome measures in a medically managed setting [57]. The reasons for these negative findings, especially in light of numerous previous positive findings, are still being debated. Some of the possible explanations identified are discrepancies between the European and American studies with regard to patient characteristics, abstinence requirements before inclusion, and the intensity of psychosocial support [58,59]. More recently, a randomized placebo controlled trial (PREDICT) was conducted in Germany [60**] using the COMBINE protocol to identify what factors actually could influence medication response and in turn treatment outcomes (such as differences between countries, patient populations, etc.). The results of PREDICT demonstrated that treatment with acamprosate was not superior to placebo, thereby replicating the finding of the COMBINE study related to the effect of acamprosate.

The most recent Cochrane meta-analysis of acamprosate, with 24 randomized controlled trials of 6894 patients, indicated a statistically significant effect of acamprosate on the cumulative duration of abstinence (11% increase) and time to return to any drinking (14% less risk in the treatment group compared to placebo) [61]. A statistically significant difference between groups was also observed 3–12 months after treatment was discontinued. Overall, acamprosate has demonstrated effect sizes ranging from small to moderate in reducing alcohol consumption and subjective measures of alcohol craving, and promoting abstinence [62,63]. Because acamprosate is a drug taken three times a day, compliance is harder to obtain than with drugs taken once daily. Thus interventions directed towards abstinence motivation at the start of treatment are crucial for compliance to acamprosate and successful treatment outcome. More specifically a recent meta-analysis [64] demonstrated that the two most important variables that affected the efficacy of acamprosate were related to detoxification before the trial and having a goal of abstinence (i.e., as opposed to ‘controlled drinking’). Of interest is also the pooled analysis from seven trials in Europe including 1485 alcohol dependent patients which indicated that acamprosate was more beneficial in individuals with increased levels of anxiety, physiological dependence, negative family history, late age of onset, and female gender [65]. Importantly, a more recent sex-specific meta-analysis reported significant effects by acamprosate in both women and men with regard to rates of abstinence and medication compliance, with comparable tolerability profile in both genders [66*].

**Baclofen**

Baclofen is a presynaptic gamma-aminobutyric-acid-B (GABA-B) receptor agonist that is mainly used to treat spasticity. It appears to act by modulation of G-protein-gated inwardly rectifying potassium channels (GIRK, Kir3) to suppress cortico-mesolimbic dopamine neurons [67]. The evidence for the efficacy of baclofen for alcohol dependence is largely based on three placebo controlled RCT’s, all at a dose of 30 mg [68]. In an early four-week trial in 39 subjects recruited from an inpatient detox unit, the authors found an increase in total abstinence and more abstinent days in the baclofen group [69]. Baclofen also showed superiority over placebo in a trial in 84 patients with liver cirrhosis (Child-Pugh grade A–C), with a doubling of the probability of being abstinent at treatment day 60 [70]. Finally, in a 12-week placebo controlled RCT in 80 patients recruited by advertisement, there was no significant effect on primary or secondary variables, with the exception of anxiety, which decreased in the baclofen group [71]. Importantly, in these three trials no serious adverse events were reported, nor were there any reports of increased craving, withdrawal symptoms or misuse of medication. In a recent case controlled study, higher doses of baclofen (75–125 mg daily) were tested in treatment-resistant alcohol dependent individuals with an improved drinking outcome post upward titration of the medication [72]. The optimal dosing of baclofen needs to be evaluated in future studies to address the issue of safety and effect on drinking outcomes with higher doses [72–74]. Because of the minimal liver metabolism and few side effects, baclofen has been recommended in a clinical guideline for the prevention of relapse to alcohol drinking in patients with alcoholic hepatitis [75]. In France, baclofen use has risen sharply over the last two years due to positive reports in the media [76]. This has caused the French medicines agency (AFSSAPS/ANSM) to warn against its use due to insufficient scientific data [77]. Collectively, the data currently available concerning the efficacy and tolerance of baclofen in alcohol-dependent patients do not support its use as first line medication but it may be considered in patients with liver cirrhosis when other medications are contraindicated.

**Topiramate**

Topiramate is a sulfamate substituted fructosepyranose derivative with several mechanisms of action that is currently used as an antiepileptic drug and as a second line treatment for migraine headache. It potentiates inhibitory GABA-A receptor-mediated input and antagonizes excitatory glutamatergic afferents to the mesocorticolimbic dopaminergic system, leading to reduced dopaminergic activity [78] and also interferes
directly with monoamine exocytosis [79]. Its efficacy as a relapse-preventing medication is largely based on the finding from a placebo-controlled trial of a dose of 300 mg, in 367 patients over 14 weeks. Using a conservative analysis, topiramate was significantly more efficacious than placebo in reducing the primary outcome, reduction in the percentage of heavy drinking days (8.44%; 95% confidence interval, 3.07–13.80%; \( P = .002 \)) [80]. This finding was further supported by two trials in which topiramate showed a significant (albeit modest) superiority over the comparator, naltrexone [81,82]. The effect of topiramate on heavy drinking is also currently being tested in HIV positive heavy drinkers (http://clinicaltrials.gov/show/NCT01764685). Topiramate has significant side effects (mainly related to the nervous system; e.g. paresthesias and cognitive dulling, but also fetal toxicity) that limit its use. Future research also needs to determine optimal dosing strategies [83].

Novel pharmacological targets

**Varenicline** is a partial agonist at the nicotine receptor used for smoking cessation. It reduces alcohol intake in preclinical models [84] and is of particular interest due to the high comorbidity of nicotine and alcohol dependence. While varenicline was associated with significantly reduced alcohol drinking and alcohol craving compared to placebo in both alcohol dependent smokers and non-smokers [85,86], another trial failed to detect any effect in a similar population [87].

Results from other ongoing trials are expected soon. OSU6162 belongs to a novel class of dopamine stabilizers characterized by the ability to suppress, stimulate, or not influence dopamine activity depending on the prevailing dopaminergic tone [88]. In rats, OSU6162 reduces voluntary ethanol consumption, ethanol withdrawal symptoms, operant ethanol self-administration, and cue-induced reinstatement of ethanol, and blunts ethanol-induced dopamine output in nucleus accumbens of ethanol-naïve rats [89]. A clinical trial of OSU6162 on cue induced alcohol craving in humans is currently in progress (EudraCT 2011-003133-34).

In addition to baclofen and topiramate, several other drugs that dampen the glutamatergic system or facilitate GABA transmission have been investigated in clinical trials. **Pregabalin** (S)-3-(aminomethyl)-5-methylhexanoic acid, CI-1008, S (+)-3-isobutyl GABA, is a presynaptic modulator of excitatory neurotransmitters including glutamate and monoaminergic neurotransmitters [90]. A randomized trial showed no differences in alcohol abstinence between pregabalin and the comparator, naltrexone [91] whereas hitherto no placebo-controlled study has been reported. **Gabapentin**, 1-(aminomethyl) cyclohexaneacetic acid is an anticonvulsant used for spasticity and epilepsy. In a 28-day placebo-controlled trial (\( n = 60 \)), gabapentin significantly reduced the number of drinks per day and mean percentage of heavy drinking days, and increased the percentage of days of abstinence [92]. Gabapentin may be more effective in patients experiencing withdrawal symptoms [93], and may improve outcomes over naltrexone alone during early stages of abstinence [94**].

Alcohol dependence involves neural systems mediating behavioral stress responses [95**,96]. The effect on alcohol craving by the CRF1 antagonists, verucerfont (GSK561679) and pexacerfont (BMS-562086) is currently being evaluated in Phase-II clinical trials in anxious, stress-reactive alcoholic women (ClinicalTrials.gov Identifier: NCT01187511 and NCT01227980, respectively). LY686017 is a neurokinin-1 antagonist that blunts brain fMRI responses to cues associated with negative affect by modulating the stress-response system, and suppresses spontaneous and cue-induced alcohol cravings [97]. There are no published data on its clinical efficacy. Published and ongoing clinical trials of **prazosin**, an \( \alpha_1 \) antagonist, are based on animal studies demonstrating that prazosin reduces ethanol self-administration in alcohol preferring rats [98]. A 6-week pilot study was performed in 24 individuals (5 women) in escalating dose of prazosin (doses titrated \( \leq 16 \text{ mg/day} \), in divided doses) [99]. The results demonstrated that among the completers (20 completers, 3 women), self-reported drinking days were significantly fewer in the final 3 weeks with prazosin than with placebo. Among the 17 male completers, prazosin in the final 3 weeks was associated with significantly fewer self-reported drinking days and drinks per week. Larger studies are currently ongoing to evaluate the role of prazosin in AUD as well as AUD with comorbid PTSD.

Finally, **ondansetron**, a 5-HT3 antagonist used as an antiemesis prophylaxis before chemotherapy, has shown efficacy in reducing alcohol drinking in subgroups of patients with an early onset type of alcohol dependence in which serotonergic dysfunction may play a role [100]. Its clinical usefulness remains to be determined in replication trials. Recently, a few medication candidates have been abandoned for reasons of side effects (rimonabant) or lack of efficacy (aripiprazole).

References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


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The results of this study along with those of Gaul et al. (2013), led to the approval of nalmefene as a medication for alcohol dependence, with an as-needed dosing, with the goal of reducing hazardous drinking.


Weiss RD, O’Malley SS, Hosking JD, Locastro JS, Swift R: Do patients with alcohol dependence respond to placebo?


This study utilized a protocol similar to a large American study with a goal of conducting a replication efficacy trial in a different country. This is an important step towards evaluating the external validity of controlled trials since trials tend to report different findings for the same therapeutic agent in different countries, in individuals with the same diagnosis (but with potential differences with regard to culture, ethnicity etc that might affect the results).


Pharmacotherapy for alcohol dependence


Johnson BA: Recent advances in the development of treatments for alcohol and cocaine dependence: focus on topiramate and other modulators of GABA or glutamate function. CNS Drugs 2005, 19:873-896.


This pre-clinical study utilizes a voluntary long-term intermittent access model to evaluate the effect of a novel dopamine stabilizer on alcohol drinking in rats. This is the first study to report an effect by this compound on alcohol drinking. (−)-OSU6162 is currently being investigated clinically also as other neurobehavioral disorders, including alcohol dependence (EudraCT 2011-003133-34).


This is an example of the recent shift in addiction pharmacotherapy trials towards evaluating combinations of therapeutics that enhance treatment efficacy. In this specific study gabapentin was added to naltrexone to treat insomnia and mood instability. The results supported the hypothesis and in addition improved drinking outcomes.


This comprehensive review systematically evaluates findings from human laboratory models to assess their clinical utility in serving as predictors of relapse and how these methods are important tools in medication development.


