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REVIEW

# Practical outpatient pharmacotherapy for alcohol use disorder

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## Abstract

Alcohol use disorder (AUD) is commonly encountered in clinical practice. A combination of psychosocial intervention and pharmacotherapy is the cornerstone of AUD treatment. Despite their efficacy, safety and cost-effectiveness, clinicians are reluctant to prescribe medications to treat individuals with AUD. Given the high rate of relapse with psychosocial intervention alone, increasing patient access to this underutilized treatment has the potential to improve clinical outcome in this difficult-to-treat population. Herein, we provide practical pharmacotherapy strategies to improve treatment outcome for AUD. We review the efficacy and side effects of both on- and off-label agents with a particular focus on clinical applicability. Recommendations are supported by findings from randomized controlled trials (RCT) and meta-analyses selected to be representative, where possible, of current treatment guidelines. The goal of this paper is to help readers use pharmacotherapy with greater confidence when treating patients with AUD.

**Keywords:** alcohol use disorder, alcoholism, addiction, pharmacotherapy.

## Citation

Kim Y, Hack LM, Ahn ES, Kim J. Practical outpatient pharmacotherapy for alcohol use disorder. Drugs in Context 2018; 7: 212308. DOI: 10.7573/dic.212308

## Introduction

Alcohol use disorder (AUD) is a serious public health threat. It causes significant morbidity and mortality. Moreover, the economic burden of alcohol-related societal harm is nearly $250 billion annually in the United States (US) alone [1]. AUD as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2] is common with a lifetime prevalence of 29.1% [3]. The high prevalence of AUD and alcohol-related death worldwide warrants a focus on improving screening, treatment and access to care [4].

The mainstay of AUD treatment is psychosocial intervention [5,6]. However, unfortunately, the relapse rate is higher with psychosocial intervention alone as compared to in combination with pharmacotherapy [7]. This suggests a clear role for pharmacotherapy, used in conjunction with psychosocial treatment, to reduce relapse rates. A number of AUD medications have demonstrated reduction in heavy drinking and prolonged periods of abstinence [8]. Three medications are approved by the US Food and Drug Administration (FDA) for AUD treatment: disulfiram, oral and extended-release injectable naltrexone and acamprosate. Two other agents, gamma-hydroxybutyric acid and nalmefene, are approved in Europe. Several other agents are used off-label to treat the symptoms of AUD.

Despite their efficacy and cost-effectiveness, however, clinicians are often reluctant to prescribe medications to treat AUD. Fewer than 20% of people treated for AUD are prescribed FDA-approved medications at substance abuse treatment facilities and this is likely to be even lower for off-label agents [9,10]. Lack of knowledge or familiarity with the medications and doubts about their effectiveness may contribute to such a low utilization rate. Given the high rate of relapse and associated health and social burden, expanding awareness and knowledge of pharmacotherapeutic options, including off-label agents, has the potential to improve clinical outcome for individuals with AUD. This paper is a synthesized editorial to improve the readers' comfort level in prescribing medications to treat AUD, particularly for decreasing alcohol use and maintaining abstinence. We provide practical pharmacotherapeutic strategies to optimize treatment outcomes that are grounded in empirical evidence and incorporate consideration of comorbidities and side-effect profiles.

## Indication for pharmacotherapy and goal-setting

Most of the extant clinical trials were conducted on recently abstinent individuals with a DSM-IV-TR diagnosis of alcohol

dependence. DSM-IV-TR has since undergone a revision wherein alcohol abuse and alcohol dependence are integrated into a single disorder called AUD with mild, moderate and severe subclassifications. Although diagnostic crossover into DSM-5 is imprecise, alcohol dependence is roughly comparable to the moderate-to-severe subtype of AUD, whereas alcohol abuse is comparable to the mild subtype. Patients with AUD, particularly those with moderate-to-severe subtype, should be considered for adjuvant pharmacotherapy together with evidence-based psychosocial intervention [5,6,11].

The main goal of AUD treatment is either complete abstinence or reduction of heavy drinking (harm reduction), which is a proxy marker for harmful alcohol-related psychosocial consequences. Although controversy exists as to which is the preferred goal of AUD treatment, both options have benefits [12,13]. Goals should be developed with patients on a personalized basis. For individuals with severe comorbid psychiatric (e.g., bipolar disorder) or medical conditions (e.g., cirrhotic liver disease), clinicians should advocate strongly for complete abstinence as the treatment goal. Reduction of heavy drinking may be a more reasonable goal for ambivalent patients who lack the readiness to commit to abstinence [14]. Principles of motivational interviewing, together with flexibility and willingness to work with the patient's goals, can be helpful when working with these patients.

## Brief neurobiology of AUD

Given that existing treatments are moderately effective at best, clinicians must strive to optimize their understanding of the disorder and its underlying neuroscience. This means having a basic understanding of the effect of each agent on brain circuitry and its downstream effects. In line with our focus on clinical practice, we provide here a simplified overview. A more detailed neurobiology underlying AUD can be found elsewhere [15–18].

AUD medications alter the reinforcing effects of alcohol by affecting neurotransmitters that interact with the mesocorticolimbic reward pathway. Five neurotransmitters have been centrally implicated in AUD: dopamine, endogenous opioids, serotonin (5-HT), gamma-aminobutyric acid (GABA) and glutamate [18]. Alcohol indirectly increases dopamine levels in the mesocorticolimbic system and activates mu-opioid receptors in the brain. These effects are associated with the positive reinforcing and rewarding effects of alcohol. With chronic alcohol use, the brain adapts and the rewarding effects of alcohol-induced dopaminergic response are attenuated over time. Thus, the individual requires higher doses of alcohol to experience the rewarding effect, known as tolerance. In addition, alcohol increases the effects of GABA, a major inhibitory neurotransmitter, and inhibits the effects of glutamate, a major excitatory neurotransmitter in the brain. With chronic alcohol use, the GABA system is downregulated and the glutamatergic system is upregulated to counter the sedating, GABA-enhancing, glutamate-dampening effects of alcohol. This explains the hyperexcitable symptoms in the acute withdrawal phase that often require detoxification with benzodiazepines. The symptoms of acute alcohol withdrawal phase commonly start within hours from the last drink and typically subside within days without treatment. Symptoms include tremor, autonomic hyperactivity, nausea or vomiting, psychomotor agitation, and, in severe cases, seizures or delirium tremens [19]. For many patients with AUD, the acute withdrawal phase is followed by a protracted withdrawal phase that can last months to years. The symptoms of the protracted withdrawal phase include tremor, anxiety, insomnia, low energy, anhedonia and dysphoria [19,20]. It is theorized that this protracted withdrawal phase reflects a period of neural recovery from damage sustained by alcohol use [19]. This physiological resetting is known as allostasis, a bodily response to stress to reclaim homeostasis. Alcohol consumption during this period instantly relieves the unpleasant symptoms of this stress–response system and, thus, increases the relapse vulnerability of abstinent AUD patients.

## Practical prescribing strategies

Pharmacotherapy can be started either in the outpatient setting or during hospitalization for intoxication or withdrawal. Both abstinence and harm reduction approaches may be helpful. Collaborating with AUD patients to lower daily consumption may be helpful in working toward abstinence [21]. Pharmacotherapy is typically started after a patient has become abstinent from alcohol with inpatient or outpatient formal detoxification. However, it is also commonly initiated for individuals in an outpatient setting who are still consuming alcohol and have a goal of reducing their consumption. Table 1 concisely summarizes the dosing, side effects and other prescribing considerations of AUD medications discussed in this paper. Figure 1 is a suggested treatment algorithm for selection of agents that reflects the authors' perspective on AUD pharmacotherapy in the outpatient setting. Three agents are approved in the US, and we recommend providing initial consideration to these agents. Detailed guidelines for use of these agents can be found at the American Psychiatric Association Practice Guideline for the Treatment of Substance Use Disorders [22,23], Substance Abuse and Mental Health Services Administration guidelines [24], as well as the National Institute of Health and Clinical Excellence (NICE) guidelines [6].

## First-line agents

Both naltrexone and acamprosate are FDA-approved for the treatment of AUD. The key to selection starts with identification of concurrent opioid use and medical comorbidities. If the patient is currently using opioids to treat pain or the patient has acute hepatitis or liver failure, naltrexone is contraindicated and acamprosate may be a better option. Typically, acamprosate is best for maintaining sobriety once the patient has achieved abstinence. Renal impairment with creatinine clearance less than 30 mL per minute is a contraindication for acamprosate,

**Table 1. Pharmacotherapy for alcohol use disorder (AUD).**

| Medication[1] | Dosing[2] | Side effects and monitoring[3] | Medicolegal tips, other indications and contraindications[4] |
|---|---|---|---|
| **Naltrexone** | 50 mg once daily<br>380 mg monthly for intramuscular formulation | Nausea, vomiting, decreased appetite, anxiety, **hepatocellular injury, suicidality**<br>Injection site reactions for the intramuscular formulation<br>Monitor liver function | - Patient must be opioid-free for 7–10 days prior to initiation, as confirmed by negative urine test and/or naloxone challenge test<br>- Discontinue if opioid-based anesthesia is anticipated<br>- Warn patients of potential for hepatotoxicity<br>- Contraindicated in acute hepatitis or liver failure |
| **Acamprosate** | 333 mg tablets<br>2 tablets three times daily for weight ≥132 lbs and 2 tablets twice daily for weight <132 lbs<br>*Renal dosing | Diarrhea, nausea, flatulence, anxiety, depression, **suicidality**<br>Monitor renal function | - Contraindicated in patients with creatinine clearance less than 30 mL per minute |
| **Disulfiram** | Begin at 250 mg daily, may increase to 500 mg daily<br>*Variable starting doses | Disulfiram-alcohol interaction, metallic taste, dermatitis, sedation, headache, **psychosis, hepatotoxicity, hypotension**<br>Monitor liver function | - Patients must be educated about the effects if they drink, including potentially lethal hypotension, and that reactions may occur up to 2 weeks after discontinuing the medication, as well as with other forms of alcohol, including mouthwash and with cough syrup<br>- Contraindicated in patients who are intoxicated with alcohol, taking metronidazole, amprenavir, ritonavir, or sertraline, have psychosis or cardiovascular disease |
| Topiramate | Begin at 25 mg daily and increase to up to 150 mg twice daily<br>*Renal dosing | Sedation, dizziness, ataxia, paresthesia, psychomotor retardation, speech difficulties, tremor, nausea, cognitive function, **metabolic acidosis**<br>Monitor electrolytes | - Indicated for epilepsy, migraine prophylaxis, chronic weight management<br>- Non-FDA use for bipolar disorder, psychotropic drug-induced weight gain, binge-eating disorder<br>- Contraindicated within 6 hours of alcohol use |
| Gabapentin | Begin at 300 mg once daily and increase to up to 600 mg three times daily<br>*Renal dosing | Sedation, dizziness, ataxia, fatigue, tremor, xerostomia, constipation, weight gain, peripheral edema, **sudden death** (when used in epilepsy) **and suicidality**<br>Monitor renal function | - Indicated for post-herpetic neuralgia, adjunctive therapy in epilepsy, restless leg syndrome<br>- Non-FDA use for fibromyalgia, anxiety, bipolar disorder |
| Baclofen | Begin at 5 mg three times daily, may increase up to 10 mg three times daily | Dizziness, drowsiness, fatigue, weakness, **CNS depression, respiratory depression, seizures** | - Indicated for spasticity<br>- Non-FDA use for intractable hiccups |
| Nalmefene | 18 mg daily as needed 1–2 hours prior to anticipated drinking situation or as soon as possible after drinking | Nausea, vomiting, insomnia, fatigue, dizziness, **confusion, psychosis, dissociation** | - Not available in the US but approved for AUD in the EU<br>- Should not be chewed or crushed owing to potential for skin sensitization if medication comes in contact with skin |

*(Continued)*

**Table 1.** ***(Continued)***

| Medication[1] | Dosing[2] | Side effects and monitoring[3] | Medicolegal tips, other indications and contraindications[4] |
|---|---|---|---|
| Gamma-hydroxybutyric acid | Administer 50–100 mg/kg daily divided into 3–6 doses<br>*hepatic dosing | Dizziness, vertigo, sedation, headache, nausea, vomiting, enuresis, depression, **respiratory depression in overdose, psychosis, wandering at night** | - Indicated excessive sleepiness and cataplexy in narcolepsy<br>- Use with extreme caution given potential for abuse and/or diversion<br>- Providers must register with Xyrem REMS Program and use pharmacy that is specially certified |
| SSRI[5] | Depends on choice of the SSRI | Constipation, flatulence, insomnia, sedation, tremor, headache, dizziness, sweating, sexual dysfunction, **seizures, mania, suicidality** | - Indicated for mood, anxiety, obsessive compulsive disorders, eating disorders, but depends on the choice of SSRI<br>- Use with caution in patients with history of seizures or bipolar disorder |
| Varenicline | Begin at 0.5 mg daily, may increase up to 1 mg twice daily | Dose dependent nausea, vomiting, constipation, flatulence, insomnia, headache, abnormal dreams, depression, **suicidality** | - Indicated for nicotine dependence<br>- Carefully monitor for changes in behavior, depressed mood, agitation and suicidality |
| Ondansetron | Studies have used low doses (4 µg twice daily) but lowest dose available is 4 mg<br>*hepatic dosing | Headache, fatigue, constipation, diarrhea, dizziness, **dose dependent QT prolongation**<br>Monitor EKG in high risk patients | - Indicated for nausea/vomiting<br>- Avoid in patients with congenital long QT syndrome<br>- Use caution and monitor EKG in patients with electrolyte abnormalities, bradyarrhythmias, or CHF and those taking another QT prolonging agent |

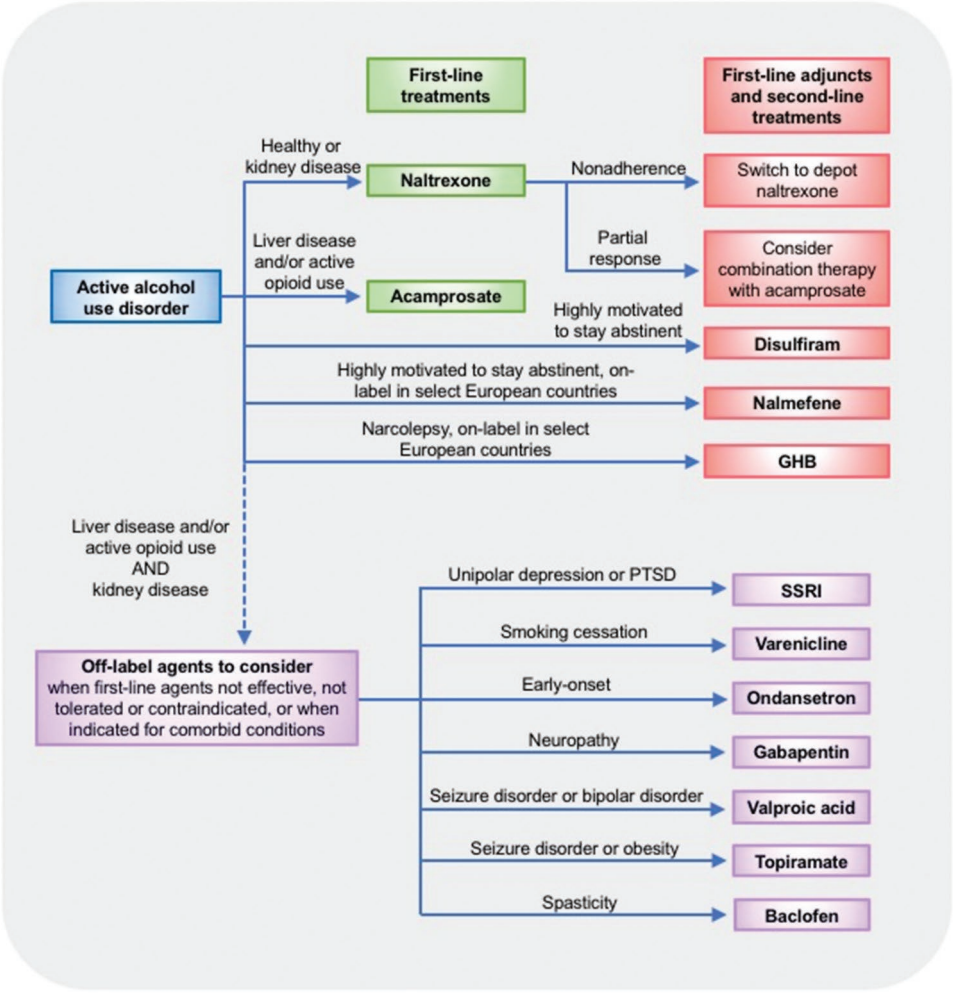
[1]FDA (U.S. Food and Drug Administration) approved medications for treatment of AUD indicated in bold.
[2]All dosing in oral route unless otherwise indicated.
[3]More common or notable side effects listed first, with serious but rare potential adverse effects to be aware of highlighted in bold.
[4]Specific medication allergy not listed for each medication to avoid redundancy, but prescribers should be aware of this contraindication.
[5]Selective serotonin reuptake inhibitors.
*Indicates drug dosing considerations for patients with hepatic or renal impairments.

and as such, baseline creatinine clearance should be evaluated. If the patient is still actively drinking, does not use opioids and has no hepatic impairment, the safest option is to initiate naltrexone. Naltrexone does not interact with alcohol and does not exhibit addictive potential.

## Oral naltrexone

Naltrexone blocks the mu-opioid receptor that modulates the dopaminergic mesolimbic pathway, thereby dampening alcohol's pleasurable, reinforcing effects [18]. The starting dose is 50 mg/day for most patients, but prescribers may be more conservative for at-risk patients, using 25 mg/day as the starting dose, which can be increased over a period of 1–2 weeks to a maintenance dose of 50 mg/day [25]. Multiple meta-analyses of randomized controlled trials (RCT) have found that naltrexone reduces alcohol intake and relapse rates. The risk of heavy drinking has been shown to be reduced by 83% compared to placebo (number needed to treat [NNT]=9) with a 4% reduction in drinking days [26]. A 2014 meta-analysis reported a more modest benefit (NNT=12) to prevent return to heavy drinking for 50 mg/day of oral naltrexone [27]. The efficacy of naltrexone may be influenced by the presence of genetic predisposition, such as a single nucleotide polymorphism (SNP) in the mu-opioid receptor gene (OPRM1) and a variable number tandem repeat polymorphisms (VNTP) in the dopamine transporter gene (DAT1) [28–30]. Common side effects are nausea, headache, sedation and dizziness, which typically self-resolve with time. Given reports of elevated liver enzymes and low, but theoretical risk of hepatotoxicity, periodic liver enzyme monitoring is recommended. In addition, considering the mechanism of naltrexone as an opioid antagonist, it is contraindicated in patients using opioids. Treatment should not begin until the patient has been off opioids for more than a week. Naltrexone should also be discontinued if a surgical operation using opioid-based anesthesia is anticipated.

**Figure 1. Suggested treatment algorithm for alcohol use disorder (AUD).**




GHB, gamma-hydroxybutyric acid; PTSD, post-traumatic stress disorder; SSRI, selective serotonin reuptake inhibitor.

## Depot naltrexone

Depot formulation of naltrexone has been developed to improve adherence [25,31,32]. This formulation conveniently cuts dosing frequency from daily to monthly. It also avoids peak effects that may contribute to the higher likelihood of side effects. Three depot formulations are available (Vivitrol, Naltrel, Depotrex) of which only Vivitrol is approved in the US [33]. No head-to-head trials of these formulations are available. A large RCT of individuals receiving Vivitrol 380 mg monthly reduced heavy drinking by 25% compared to placebo [34]. Another multisite study involving a different depot formulation, Naltrel, did not replicate this result, but it did find that the medication increased the cumulative number of abstinent days during the 90-day treatment period compared to placebo (52.8 *vs* 45.6 days) [35]. Nevertheless, depot naltrexone is a useful agent when the patient receives benefit from oral naltrexone but has difficulty with adherence. Common side effects of Vivitrol are nausea, fatigue and decreased appetite. As with any depot formulation, clinicians should monitor injection-site reactions (e.g., pain, swelling, bruising, pruritus or redness) persisting for more than 2 weeks.

## Acamprosate

Acamprosate is often considered an 'artificial alcohol' or a 'functional glutamate antagonist.' This is because it inhibits the glutamate system and enhances the GABA system much like alcohol itself without the addictive properties of alcohol [25,36,37]. The typical dose is two 333 mg tablets three times a day, with lower recommended doses for patients with renal impairment. Multiple meta-analyses have found acamprosate to reduce alcohol consumption compared to placebo. Acamprosate decreased return to any drinking to 86% of placebo (NNT=9) and increased abstinence duration by 11% [38]. Another meta-analysis of largely European studies

found acamprosate increased 6-month abstinence rate (36.1 *vs* 23.4%) compared to placebo [39]. However, the Combining Medications and Behavioral Interventions (COMBINE) study [7] and its 1-year posttreatment drinking outcome study [40] did not show that acamprosate is more effective than placebo. Differences in study methodology between US and European studies may explain differing outcome [25]. Acamprosate has an excellent safety profile with diarrhea and fatigue being the most commonly reported side effects, which typically subside with use. It is not addictive and is safe in overdose. It is safe for patients with severe liver disease due to predominant renal excretion bypassing hepatic metabolism. Accordingly, acamprosate requires dose adjustment for renal insufficiency and it is contraindicated in patients with creatinine clearance less than 30 mL per minute.

## Second-line agents

Except for disulfiram, these agents are all off-label in the US. The agents discussed in this section are worth considering when naltrexone and acamprosate are ineffective or contraindicated. The evidence here is more mixed, and clinical judgment integrating mechanism, tolerability and comorbidity is essential. Informed consent must be obtained with a clear explanation about the off-label status, risks and benefits.

### Disulfiram

If the patient is motivated to stay abstinent and expresses a desire to try this agent, disulfiram may be an option. This medication does not promote abstinence by decreasing craving, but creates an aversive reaction to alcohol that discourages drinking [41]. Disulfiram blocks acetaldehyde dehydrogenase and prevents the breakdown of alcohol central metabolite, acetaldehyde. Acetaldehyde accumulation is responsible for the unpleasant physiologic reaction like flushing, nausea, vomiting, headache, palpitation and hypotension. These symptoms emerge approximately 10 minutes after alcohol ingestion and may last for several hours. The aversive reaction can be fatal due to hypotension [42,43] and, as such, this approach requires a clear commitment to total abstinence and patient education about covert forms of alcohol (e.g., mouthwash) to be avoided and duration of drug effects (up to 2 weeks after the last dose of disulfiram). The treatment starts, at least 12 hours after the last alcoholic drink at varying initial doses up to 500 mg/day for 1–2 weeks, after which the dose may be adjusted between 125 and 500 mg/day (average 250 mg/day) based on the severity of adverse effect [42].

The trial results for disulfiram are more mixed compared to naltrexone or acamprosate. In a 2014 meta-analysis (n=492), disulfiram was equivalent to placebo in return to any drinking or other primary outcome endpoints although none of the trials evaluated disulfiram efficacy under supervised treatment settings [27]. Earlier studies including one of US veterans (n=605) in a multicenter RCT for 52 weeks disulfiram also showed that disulfiram was not superior to placebo for abstinent days or time to first drink [44]. However, subgroup analysis in this study found that disulfiram reduced total drinking days. When disulfiram is taken routinely under supervised conditions, such as in a 12-week supervised head-to-head trial comparing disulfiram, naltrexone and acamprosate (n=243), disulfiram had a more significant reduction in heavy drinking days and longer abstinence periods [45]. This benefit faded with subsequent unsupervised treatment up to 52 weeks. In general, with proper supervision, disulfiram may benefit some AUD patients. When taken as directed without alcohol use, it is well tolerated. Common side effects of fatigue, drowsiness and headache typically self-resolve. Rare but serious side effects of hepatotoxicity and psychosis should be monitored with routine follow up and liver enzyme monitoring.

### Topiramate

Topiramate is an off-label agent for AUD. Its on-label indications are for seizure, migraine and obesity. If the patient has these comorbidities, topiramate is worth considering. Its main anti-AUD effects are mediated by the dampening of glutamate receptor activity and potentiation of inhibitory GABA-A receptor activity [46]. It is typically started at a low dose of 25 mg/day and slowly titrated up over several weeks to avoid side effects such as cognitive impairment and sedation. The maximum dose is 150 mg twice daily. A 2014 meta-analysis of topiramate *vs* placebo (n=691) resulted in a decrease in alcohol consumption [27], and other meta-analysis in the same year (n=1125) across 7 RCTs showed benefit for abstinence and heavy drinking [47]. Another large 2017 meta-analysis also found a reduction in total alcohol consumption with topiramate [48]. Adverse effects of topiramate include cognitive impairment, paresthesias, anorexia, fatigue, headache, drowsiness and depression.

### Gabapentin

Gabapentin is another antiepileptic medication used off-label for AUD [49]. Its on-label indications are seizure and neuropathic pain. AUD patients for which gabapentin should be considered are those with comorbid neuropathy (typically alcoholic neuropathy or even diabetic neuropathy). It inhibits excitatory calcium channels and potentiates inhibitory GABA-B receptors. In a 12-week RCT involving recently abstinent alcohol dependent outpatients (n=150), gabapentin was found to increase abstinence rates without serious adverse side effects [50]. Gabapentin in combination with naltrexone was found to exhibit additive effects compared to naltrexone alone [51]. Doses of 900 and 1800 mg/day have been studied. Low-to-moderate doses (300–900 mg/day) are generally well tolerated while higher doses (1800 mg/day) can cause sedation and dizziness. Gabapentin is primarily cleared through renal excretion, and as such, monitoring renal function, including a

baseline level, is appropriate. Gabapentin also has the potential for misuse or abuse [52] that warrants monitoring.

## Baclofen

Baclofen is a GABA-B receptor agonist approved for spasticity treatment. Baclofen's efficacy for alcohol dependence has been more mixed than topiramate or gabapentin. Baclofen study doses range from 20 to 60 mg. Two RCTs (n=84, n=39) found baclofen to be associated with higher rates of abstinence compared to placebo [53,54]; whereas, another RCT (n=80) found no difference compared to placebo [55]. Baclofen was well tolerated in these studies without evidence of abuse or serious adverse effects. Adverse effects include nausea, vertigo and sleepiness. More serious side effects are hepatotoxicity, encephalopathy and hyperammonemia. Studies have also investigated high-dose baclofen (180–270 mg/day). However, the results varied and did not consistently demonstrate superior anti-AUD efficacy [56–58]. High-dose baclofen also runs the risk of sedation and additive CNS depressant effects when consumed together with alcohol.

## Nalmefene

Nalmefene is not available in the US but is approved for utilization in the EU for AUD. It is an opioid antagonist similar to naltrexone, but theoretically lasts longer, has greater bioavailability and no observed dose-dependent hepatotoxicity. A 2014 meta-analysis of three RCTs (combined n=608) demonstrated anti-AUD benefit using targeted dosing strategy (i.e., taken as needed before high-risk pro-drinking situations) [27]. One of the included trials (n=403) showed greater reduction of heavy drinking days with nalmefene compared to placebo (44 *vs* 32%) [59]. However, another subsequent 2015 meta-analysis of harm and benefit of nalmefene compared to placebo concluded that nalmefene has limited efficacy for alcohol consumption [60]. There are calls for post-approval randomized comparative studies and to even consider withdrawal of the AUD-treatment indication in Europe [61]. Common adverse effects of nalmefene are nausea, insomnia, fatigue and dizziness. A rare, but possible risk of psychosis and dissociation exists and warrants monitoring.

## Gamma-hydroxybutyric acid

Gamma-hydroxybutyric acid (GHB) is a naturally occurring neurotransmitter in the human brain that acts as an antagonist at GHB, GABA-B and GABA-A receptors [62]. It is on-label in the US and several European countries for the treatment of narcolepsy. It has been approved in Italy and Austria for relapse prevention in alcohol dependence and alcohol withdrawal syndrome. Only one double-blind RCT (n=82) has been conducted comparing 50 mg/kg/day of GHB with placebo in an outpatient setting of alcohol-dependent patients [63]. After 12 weeks, more patients in the treatment group were abstinent (31 *vs* 6%) or had reduced their drinking (42 *vs* 17%) as compared to the placebo group. A 2010 Cochrane review, including the double-blind RCT and several open-label trials comparing GHB with naltrexone and disulfiram concluded that, in the medium term (3–12 months), GHB appears favorable to naltrexone and disulfiram both in maintaining abstinence and preventing a craving based on a small amount of randomized evidence [64]. Vertigo and dizziness were the most frequently reported adverse reactions in these trials. The main concern with GHB is the potential for abuse and diversion, as well as potential craving for this drug. Consequently, it should be used with caution and careful monitoring.

## Varenicline

Varenicline affects the nicotinic acetylcholine receptors in the ventral tegmental area, specifically acting as a partial agonist at α4β2 and a full agonist at α7. It is approved for nicotine dependence in the US. It is unclear how this medication affects symptoms of AUD. However, studies have found evidence that varenicline modifies dopamine release in the nucleus accumbens [65]. A multisite RCT (n=200) found evidence to support the utilization of varenicline for reducing alcohol consumption and craving in patients with AUD [66]. The trial has found that varenicline is generally well tolerated with mild adverse effects, the most common of which are nausea, abnormal dreams and constipation. There have been case reports of new-onset or worsening psychiatric symptoms with varenicline use. Consequently, patients should be carefully monitored, although the trials in AUD have not found these effects. Patients with AUD for which varenicline should be considered are those with comorbid nicotine dependence. The target dose is 1 mg twice daily titrated from 0.5 mg/day over a week.

## Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitor (SSRI) antidepressants may be considered for individuals with comorbid psychiatric disorders. A meta-analysis of seven RCTs showed that the SSRIs adequately treat individuals with AUD and depression [67], while another meta-analysis showed that SSRIs were not more effective than placebo in treating AUD with comorbid depression [68]. Those with comorbid post-traumatic stress disorder (PTSD) may benefit from sertraline, particularly those with less severe AUD and early onset PTSD [69]. In a small study of participants (n=35) with comorbid AUD and major depressive disorder comparing the combination of escitalopram and aripiprazole to aripiprazole alone, Han et al. found that the combination was more effective at decreasing depressive symptoms and craving for alcohol [70].

## Ondansetron

Ondansetron is an anti-nausea agent that selectively blocks serotonin 5-HT3 receptors. Patients with early-onset alcohol dependence, defined as onset of problematic drinking at or

before age 25, tend to respond favorably to ondansetron at 4 µg twice daily [71–73]. In a RCT of male participants ages 18–60 years of age (n=102), 16 mg daily of ondansetron was superior to placebo in decreasing the proportion of heavy drinking days in the imputed sample but not in increasing proportion of abstinent days [74]. Because the dose range used in these studies has been broad, the optimal dosage is unknown. Ondansetron can be dosed twice daily. Major adverse effects are diarrhea, headache and fever. Dose-dependent QT prolongation may occur and, as such, electrocardiograph (EKG) monitoring and screening for underlying cardiac conditions are warranted.

## Combining pharmacotherapy

Combining medications that utilize different therapeutic mechanisms of action may be essential for patients with inadequate response to monotherapy. There is again a paucity of data for this approach and clinical judgment weighing the risks and benefits is needed. Studied combinations include (1) naltrexone and acamprosate, (2) naltrexone and ondansetron, and (3) naltrexone and sertraline. Two trials examining the combination of oral naltrexone and acamprosate showed mixed results. In one study (n=160), the combination led to fewer relapses and longer time to first drink compared to acamprosate monotherapy but not compared to naltrexone monotherapy [75]. The COMBINE study did not find any advantage of this combination over either monotherapy or placebo [7]. The combination of ondansetron and naltrexone for early-onset AUD led to reduced drinking compared to placebo. However, the combination was not compared to monotherapy of either drug [76]. A combination of naltrexone and sertraline has been shown to be more effective than naltrexone or sertraline monotherapy for maintaining abstinence in AUD patients with depression [77]. However, this combination was not shown to be superior to naltrexone in AUD patients without comorbid depression [78].

## Consideration of psychiatric comorbidity

AUD is highly comorbid with other psychiatric disorders. In patients with AUD, comorbid mood and anxiety disorders are common, as are comorbid schizophrenia and PTSD [3,79–81]. Failure to adequately address the comorbid psychiatric diagnosis leads to higher rates of adverse clinical outcome. For example, in patients with comorbid bipolar disorder and AUD, alcohol use increases the risk of suicide attempts, hospitalization and crime rates [82,83]. It is therefore important that clinicians have a high index of suspicion for psychiatric comorbidity.

Pharmacotherapy and psychosocial intervention are still the treatment of choice in managing comorbid psychiatric disorder and AUD. There are three different models of treating psychiatric patients with co-occurring AUD: sequential, parallel and integrated [84]. In sequential treatment, the more acute disorder is treated first, followed by the less acute comorbid disorder. This has historically been the norm of clinical practice. Moreover, in this model, AUD-specific treatment is often prioritized because pharmacotherapy targeting the comorbid psychiatric disorder first is often considered ineffective for individuals who are drinking heavily. In parallel treatment, both disorders are treated simultaneously by two different clinicians/teams of clinicians. Moreover, in integrated treatment, both disorders are treated simultaneously but by a single clinician/team of clinicians. There is increasing consensus that fully integrated care is preferred to parallel or sequential treatment in addressing both diagnoses and reducing arrest or hospitalization rates [85–88]. If there are community and/or healthcare system barriers to a fully integrated care, clinicians may choose an approach from available resources.

In choosing pharmacotherapy, one should consider efficacy and safety data, but with the awareness that the evidence base is much weaker in this population as research into AUD medications have historically excluded psychiatric comorbidities. A thorough discussion of efficacy and safety data is outside the scope of this paper, but a few notable findings are worth highlighting. For patients with AUD and depressive disorders, SSRIs may be effective for AUD as well as for the depression [67,68]. For patients with AUD and PTSD, sertraline may be of benefit in combination with behavioral intervention [89]. In patients with AUD and bipolar disorder, utilization of both lithium and divalproex compared to lithium alone has demonstrated efficacy for both symptoms of bipolar disorder and drinking outcomes [90].

Additional considerations when selecting medications for dually diagnosed patients are overlapping indications with co-morbid substance use disorder, side effects, drug–drug interactions, adherence and capacity to follow directions. Disulfiram, for example, should be used more carefully owing to the risk of psychosis, impulsivity and cognitive impairment. Topiramate, as well, is best avoided in patients with schizophrenia owing to its cognitive side effects. Intramuscular depot naltrexone should be given high priority for patients with serious chronic mental illness owing to high rates of nonadherence. Indeed, the treatment of dually diagnosed patients is complex and requires thoughtful consideration of risk–benefit ratio across a multitude of clinical and pharmacological factors. For particularly challenging cases, clinicians should consider referral to addiction specialists.

## Consideration of teratogenicity

Patients with AUD who are or become pregnant require careful consideration of the risks and benefits of treatment compared with nontreatment to both mother and fetus. Safety profiles in pregnancy are not well established for AUD medications owing to lack of adequate studies. Careful review of available data regarding harmful effects to the fetus and babies (through possible breast milk secretion) and risk–benefit discussion

with the patient is essential. When available, a referral to or a consultation with a reproductive medicine specialist is most appropriate.

## Combining medications with psychosocial treatments

There are no clinical trials comparing pharmacotherapy to psychosocial treatments for AUD. There is a lack of evidence to support 'pairing' of a particular pharmacotherapy with a specific psychosocial intervention. The COMBINE Study did not find either medication combined with psychosocial treatment (e.g., cognitive behavioral therapy [CBT], 12-step facilitation, motivational interviewing, etc.) to be superior to either medication monotherapy or psychosocial intervention without any medication [7]. We suggest offering any evidence-based psychosocial intervention available without necessarily attempting to pair it with a particular pharmacotherapy.

## Future directions: personalized medicine

As in other medical and psychiatric disorders, personalized medicine is gaining momentum as the future direction of patient care. It is well established that AUD is a heterogeneous disorder owing to the complex interaction of an individual's genetic makeup and environmental stress, which manifests in a wide spectrum of severity in drinking patterns, motivation for drinking, alcohol-related adverse consequences, and co-occurring psychiatric or substance use disorders [91,92]. It is, then, no surprise that we do not have one treatment that uniformly demonstrates effectiveness for every AUD patient. Research studies into personalized approaches to AUD consider genetic variations, epigenetic modifications, symptom clusters and brain imaging to tailor treatments to the idiosyncrasies of the individual patient. More research is needed, however, before this approach can be made widely available.

## Summary and concluding remarks

Pharmacotherapy is necessary despite the availability of effective psychosocial treatment options owing to high relapse rates with psychosocial intervention alone. Pharmacotherapy alters the reinforcing effects of alcohol and understanding of AUD neurobiology is useful for informed prescribing practice. Goals of treatment are either abstinence or reduction of heavy drinking (i.e., harm reduction) and both options have benefits. Moderate-to-severe AUD patients should be offered pharmacotherapy in addition to evidence-based psychosocial treatment. Any evidence-based psychosocial intervention may be offered and does not need to be paired with a specific drug treatment. Naltrexone and acamprosate are recommended for initial consideration. Depot formulation is available for naltrexone to improve adherence. Naltrexone is contraindicated for those with severe liver disease or with concurrent opioid use; acamprosate is recommended for individuals with a contraindication to naltrexone. Disulfiram should be reserved for those with high motivation to maintain abstinence and are willing to undertake supervised prescription. Off-label agents should be considered when on-label medications are ineffective, not tolerated, or contraindicated. For all medications, informed consent and careful consideration of comorbid medical and psychiatric diagnoses are critical to improve clinical outcome. Given the heterogeneity of the illness, tailoring treatment to the individual patient's unique history, makeup and symptomatology is important and will continue to gain momentum as the standard of care for clinical practice.

Pharmacotherapy for AUD is effective, cost-efficient and evidence-based. As there is no sweeping panacea for this heterogeneous and difficult-to-treat disorder, clinicians should have multiple treatment methods available in their toolbox to improve health outcomes. Expanding patient access to pharmacotherapeutic options is one such way that has the potential to be helpful for this population with unmet requirements.

**Disclosure and potential conflicts of interest:** The authors have declared that there are no conflicts of interest regarding this unfunded study. The International Committee of Medical Journal Editors (ICMJE) Potential Conflicts of Interests form for the authors are available for download at: http://www.drugsincontext.com/wp-content/uploads/2018/01/dic.212308-COI.pdf

**Acknowledgments:** Jungjin Kim conceived the idea, supervised the preparation of the manuscript, streamlined and provided the final edits. Youngjung Kim provided substantial contributions to the literature review, the writing of the manuscript and designed the final figure and the table. Laura Hack provided substantial contributions to the review and writing of the manuscript and the creation of the table. Elizabeth Ahn provided contribution to the literature review and writing of the manuscript.

**Funding declaration:** There was no funding associated with this article.



**Article URL:** http://www.drugsincontext.com/practical-outpatient-pharmacotherapy-for-alcohol-use-disorder

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**Provenance:** invited; externally peer reviewed.

**Submitted**: 4 December 2017; **Peer review comments to author:** 20 December 2017; **Revised manuscript received:** 14 January 2018; **Accepted:** 15 January 2018; **Publication date:** 7 February 2018.

**Drugs in Context** is published by BioExcel Publishing Ltd. Registered office: Plaza Building, Lee High Road, London, England, SE13 5PT.

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# References

1. Sacks JJ, Gonzales KR, Bouchery EE, Tomedi LE, Brewer RD. 2010 National and state costs of excessive alcohol consumption. Am J Prev Med. 2015;49(5):73–9. http://dx.doi.org/10.1016/j.amepre.2015.05.031
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, DSM-5. Arlington, VA, USA; 2013.
3. Grant BF, Goldstein RB, Saha TD, Chou SP, Jung J, Zhang H, Pickering RP, Ruan WJ, Smith SM, Huang B, Hasin DS. Epidemiology of DSM-5 alcohol use disorder: results from the national epidemiologic survey on alcohol and related conditions III. JAMA Psychiatry. 2015;72(8):757–66. http://dx.doi.org/10.1001/jamapsychiatry.2015.0584
4. Collaborators GBDCoD. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151–210. http://dx.doi.org/10.1016/S0140-6736(17)32152-9
5. Pettinati HM, Weiss RD, Miller WR, Donovan D, Ernst DB, Rounsaville BJ. Medical management treatment manual: a clinical research guide for medically trained clinicians providing pharmacotherapy as part of the treatment for alcohol dependence. Bethesda (MD): US DHHS; 2004. Available at: https://pubs.niaaa.nih.gov/publications/combine/index.htm [Last accessed: 12 January 2018].
6. Alcohol-Use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence. Leicester: National Collaborating Centre for Mental Health; 2011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22624177 [Last accessed: 12 January 2018].
7. Anton RF, O'Malley SS, Ciraulo DA, Cisler RA, Couper D, Donovan DM, Gastfriend DR, Hosking JD, Johnson BA, LoCastro JS, Longabaugh R, Mason BJ, Mattson ME, Miller WR, Pettinati HM, Randall CL, Swift R, Weiss RD, Williams LD, Zweben A, Group CSR. Combined pharmacotherapies and behavioral interventions for alcohol dependence: the COMBINE study: a randomized controlled trial. JAMA. 2006;295(17):2003–17. http://dx.doi.org/10.1001/jama.295.17.2003
8. Akbar M, Egli M, Cho YE, Song BJ, Noronha A. Medications for alcohol use disorders: an overview. Pharmacol Ther. 2017;pii:S0163-7258(17)30291-7. http://dx.doi.org/10.1016/j.pharmthera.2017.11.007
9. National Survey of Substance Abuse Treatment Services (N-SSATS): 2013, Data on substance abuse treatment facilities. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2014. Available at: https://wwwdasis.samhsa.gov/dasis2/nssats/2013_nssats_rpt.pdf [Last accessed: 12 January 2018].
10. Harris AH, Kivlahan DR, Bowe T, Humphreys KN. Pharmacotherapy of alcohol use disorders in the Veterans Health Administration. Psychiatr Serv. 2010;61(4):392–8. http://dx.doi.org/10.1176/ps.2010.61.4.392
11. Reus VI, Fochtmann LJ, Bukstein O, Eyler AE, Hilty DM, Horvitz-Lennon M, Mahoney J, Pasic J, Weaver M, Wills CD, McIntyre J, Kidd J, Yager J, Hong SH. The American Psychiatric Association Practice guideline for the pharmacological treatment of patients with alcohol use disorder. Am J Psychiatry. 2018;175(1):86–90. http://dx.doi.org/10.1176/appi.ajp.2017.1750101
12. Hasin DS, Wall M, Witkiewitz K, Kranzler HR, Falk D, Litten R, Mann K, O'Malley SS, Scodes J, Robinson RL, Anton R, Alcohol Clinical Trials Initiative Workgroup. Change in non-abstinent WHO drinking risk levels and alcohol dependence: a 3 year follow-up study in the US general population. Lancet Psychiatry. 2017;4(6):469–76. http://dx.doi.org/10.1016/S2215-0366(17)30130-X
13. Ritter A, Cameron J. A review of the efficacy and effectiveness of harm reduction strategies for alcohol, tobacco and illicit drugs. Drug Alcohol Rev. 2006;25(6):611–24. http://dx.doi.org/10.1080/09595230600944529
14. van Amsterdam J, van den Brink W. Reduced-risk drinking as a viable treatment goal in problematic alcohol use and alcohol dependence. J Psychopharmacol. 2013;27(11):987–97. http://dx.doi.org/10.1177/0269881113495320
15. Ostroumov A, Dani JA. Convergent neuronal plasticity and metaplasticity mechanisms of stress, nicotine, and alcohol. Annu Rev Pharmacol Toxicol. 2017;58:547–66. http://dx.doi.org/10.1146/annurev-pharmtox-010617-052735

16. Cui C, Noronha A, Morikawa H, Alvarez VA, Stuber GD, Szumlinski KK, Kash TL, Roberto M, Wilcox MV. New insights on neurobiological mechanisms underlying alcohol addiction. Neuropharmacology. 2013;67:223–32. http://dx.doi.org/10.1016/j.neuropharm.2012.09.022
17. Kyzar EJ, Pandey SC. Molecular mechanisms of synaptic remodeling in alcoholism. Neurosci Lett. 2015;601:11–9. http://dx.doi.org/10.1016/j.neulet.2015.01.051
18. Yardley MM, Ray LA. Medications development for the treatment of alcohol use disorder: insights into the predictive value of animal and human laboratory models. Addict Biol. 2017;22(3):581–615. http://dx.doi.org/10.1111/adb.12349
19. Trevisan LA, Boutros N, Petrakis IL, Krystal JH. Complications of alcohol withdrawal: pathophysiological insights. Alcohol Health Res World. 1998;22(1):61–6.
20. Martinotti G, Nicola MD, Reina D, Andreoli S, Foca F, Cunniff A, Tonioni F, Bria P, Janiri L. Alcohol protracted withdrawal syndrome: the role of anhedonia. Subst Use Misuse. 2008;43(3–4):271–84. http://dx.doi.org/10.1080/10826080701202429
21. Muckle W, Muckle J, Welch V, Tugwell P. Managed alcohol as a harm reduction intervention for alcohol addiction in populations at high risk for substance abuse. Cochrane Database Syst Rev. 2012;12:CD006747. http://dx.doi.org/10.1002/14651858.CD006747.pub2
22. Kleber HD, Weiss RD, Anton RF, Rounsaville BJ, George TP, Strain EC, Greenfield SF, Ziedonis DM, Kosten TR, Hennessy G, O'Brien CP, Connery HS, McIntyre JS, Charles SC, Anzia DJ, Nininger JE, Cook IA, Summergrad P, Finnerty MT, Woods SM, Johnson BR, Yager J, Pyles R, Lurie L, Cross CD, Walker RD, Peele R, Barnovitz MA, Gray SH, Shemo JP, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D, Work Group on Substance Use Disorders, Association Psychiatric Association. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry. 2006;163(8 Suppl):5–82. PubMed PMID:16981488
23. Kleber HD, Weiss RD, Anton RF, Jr., George TP, Greenfield SF, Kosten TR, O'Brien CP, Rounsaville BJ, Strain EC, Ziedonis DM, Hennessy G, Connery HS, McIntyre JS, Charles SC, Anzia DJ, Cook IA, Finnerty MT, Johnson BR, Nininger JE, Summergrad P, Woods SM, Yager J, Pyles R, Cross CD, Peele R, Shemo JP, Lurie L, Walker RD, Barnovitz MA, Gray SH, Saxena S, Tonnu T, Kunkle R, Albert AB, Fochtmann LJ, Hart C, Regier D, Work Group on Substance Use Disorders, Association Psychiatric Association. Treatment of patients with substance use disorders, second edition. American Psychiatric Association. Am J Psychiatry. 2007;164(4 Suppl):5–123. PubMed PMID:17569411
24. Medication for the treatment of alcohol use disorder: a brief guide. Rockville (MD): Substance Abuse and Mental Health Services Administration and National Institute on Alcohol Abuse and Alcoholism; 2015. Available at: https://store.samhsa.gov/shin/content//SMA15-4907/SMA15-4907.pdf [Last accessed: 12 January 2018].
25. Incorporating alcohol pharmacotherapies into medical practice. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2009. Available at: https://www.ncbi.nlm.nih.gov/books/NBK65180 [Last accessed: 12 January 2018].
26. Rosner S, Hackl-Herrwerth A, Leucht S, Vecchi S, Srisurapanont M, Soyka M. Opioid antagonists for alcohol dependence. Cochrane Database Syst Rev. 2010(12):CD001867. http://dx.doi.org/10.1002/14651858.CD001867.pub2
27. Jonas DE, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA. 2014;311(18):1889–900. http://dx.doi.org/10.1001/jama.2014.3628
28. Schacht JP, Anton RF, Voronin KE, Randall PK, Li X, Henderson S, Myrick H. Interacting effects of naltrexone and OPRM1 and DAT1 variation on the neural response to alcohol cues. Neuropsychopharmacology. 2013;38(3):414–22. http://dx.doi.org/10.1038/npp.2012.195
29. Schacht JP, Randall PK, Latham PK, Voronin KE, Book SW, Myrick H, Anton RF. Predictors of naltrexone response in a randomized trial: reward-related brain activation, OPRM1 genotype, and smoking status. Neuropsychopharmacology. 2017;42(13):2640–53. http://dx.doi.org/10.1038/npp.2017.74
30. Chamorro AJ, Marcos M, Miron-Canelo JA, Pastor I, Gonzalez-Sarmiento R, Laso FJ. Association of micro-opioid receptor (OPRM1) gene polymorphism with response to naltrexone in alcohol dependence: a systematic review and meta-analysis. Addict Biol. 2012;17(3):505–12. http://dx.doi.org/10.1111/j.1369-1600.2012.00442.x
31. Galloway GP, Koch M, Cello R, Smith DE. Pharmacokinetics, safety, and tolerability of a depot formulation of naltrexone in alcoholics: an open-label trial. BMC Psychiatry. 2005;5:18. http://dx.doi.org/10.1186/1471-244X-5-18
32. Volpicelli JR, Rhines KC, Rhines JS, Volpicelli LA, Alterman AI, O'Brien CP. Naltrexone and alcohol dependence. Role of subject compliance. Arch Gen Psychiatry. 1997;54(8):737–42. http://dx.doi.org/10.1001/archpsyc.1997.01830200071010
33. Gastfriend DR. Intramuscular extended-release naltrexone: current evidence. Ann N Y Acad Sci. 2011;1216:144–66. http://dx.doi.org/10.1111/j.1749-6632.2010.05900.x
34. Garbutt JC, Kranzler HR, O'Malley SS, Gastfriend DR, Pettinati HM, Silverman BL, Loewy JW, Ehrich EW, Vivitrex Study G. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. JAMA. 2005;293(13):1617–25. http://dx.doi.org/10.1001/jama.293.13.1617

35. Kranzler HR, Wesson DR, Billot L, Drug Abuse Sciences Naltrexone Depot Study G. Naltrexone depot for treatment of alcohol dependence: a multicenter, randomized, placebo-controlled clinical trial. Alcohol Clin Exp Res. 2004;28(7):1051–9. http://dx.doi.org/10.1097/01.ALC.0000130804.08397.29
36. Whitworth AB, Fischer F, Lesch OM, Nimmerrichter A, Oberbauer H, Platz T, Potgieter A, Walter H, Fleischhacker WW. Comparison of acamprosate and placebo in long-term treatment of alcohol dependence. Lancet. 1996;347(9013):1438–42. http://dx.doi.org/10.1016/S0140-6736(96)91682-7
37. Stahl SM. Prescriber's Guide: Stahl's Essential Psychopharmacology, 5th Edition. New York, NY, USA: Cambridge University Press; 2014.
38. Rosner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev. 2010(9):CD004332. http://dx.doi.org/10.1002/14651858.CD004332.pub2
39. 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(1):51–63. http://dx.doi.org/10.1097/01.ALC.0000108656.81563.05
40. Donovan DM, Anton RF, Miller WR, Longabaugh R, Hosking JD, Youngblood M, Group CSR. Combined pharmacotherapies and behavioral interventions for alcohol dependence (The COMBINE Study): examination of posttreatment drinking outcomes. J Stud Alcohol Drugs. 2008;69(1):5–13. http://dx.doi.org/10.15288/jsad.2008.69.5
41. Hald J, Jacobsen E. A drug sensitizing the organism to ethyl alcohol. Lancet. 1948;2(6539):1001–4. PubMed PMID:18103475
42. Suh JJ, Pettinati HM, Kampman KM, O'Brien CP. The status of disulfiram: a half of a century later. J Clin Psychopharmacol. 2006;26(3):290–302. http://dx.doi.org/10.1097/01.jcp.0000222512.25649.08
43. Chick J. Safety issues concerning the use of disulfiram in treating alcohol dependence. Drug Saf. 1999;20(5):427–35. http://dx.doi.org/10.2165/00002018-199920050-00003
44. Fuller RK, Branchey L, Brightwell DR, Derman RM, Emrick CD, Iber FL, James KE, Lacoursiere RB, Lee KK, Lowenstam I, Maany I, Neiderhiser D, Nocks JJ, Shaw S. Disulfiram treatment of alcoholism. A Veterans Administration cooperative study. JAMA. 1986;256(11):1449–55. http://dx.doi.org/10.1001/jama.1986.03380110055026
45. Laaksonen E, Koski-Jannes A, Salaspuro M, Ahtinen H, Alho H. A randomized, multicentre, open-label, comparative trial of disulfiram, naltrexone and acamprosate in the treatment of alcohol dependence. Alcohol Alcohol. 2008;43(1):53–61. http://dx.doi.org/10.1093/alcalc/agm136
46. Johnson BA, Ait-Daoud N. Topiramate in the new generation of drugs: efficacy in the treatment of alcoholic patients. Curr Pharm Des. 2010;16(19):2103–12. http://dx.doi.org/10.2174/138161210791516404
47. 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(6):1481–8. http://dx.doi.org/10.1111/acer.12411
48. Palpacuer C, Duprez R, Huneau A, Locher C, Boussageon R, Laviolle B, Naudet F. Pharmacologically controlled drinking in the treatment of alcohol dependence or alcohol use disorders: a systematic review with direct and network meta-analyses on nalmefene, naltrexone, acamprosate, baclofen and topiramate. Addiction. 2017;113(2):220–37. http://dx.doi.org/10.1111/add.13974
49. Pani PP, Trogu E, Pacini M, Maremmani I. Anticonvulsants for alcohol dependence. Cochrane Database Syst Rev. 2014(2):CD008544. http://dx.doi.org/10.1002/14651858.CD008544.pub2
50. Mason BJ, Quello S, Goodell V, Shadan F, Kyle M, Begovic A. Gabapentin treatment for alcohol dependence: a randomized clinical trial. JAMA Intern Med. 2014;174(1):70–7. http://dx.doi.org/10.1001/jamainternmed.2013.11950
51. Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, Randall PK. Gabapentin combined with naltrexone for the treatment of alcohol dependence. Am J Psychiatry. 2011;168(7):709–17. http://dx.doi.org/10.1176/appi.ajp.2011.10101436
52. Schifano F. Misuse and abuse of pregabalin and gabapentin: cause for concern? CNS Drugs. 2014;28(6):491–6. http://dx.doi.org/10.1007/s40263-014-0164-4
53. Addolorato G, Caputo F, Capristo E, Domenicali M, Bernardi M, Janiri L, Agabio R, Colombo G, Gessa GL, Gasbarrini G. Baclofen efficacy in reducing alcohol craving and intake: a preliminary double-blind randomized controlled study. Alcohol Alcohol. 2002;37(5):504–8. http://dx.doi.org/10.1093/alcalc/37.5.504
54. Addolorato G, Leggio L, Ferrulli A, Cardone S, Vonghia L, Mirijello A, Abenavoli L, D'Angelo C, Caputo F, Zambon A, Haber PS, Gasbarrini G. 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(9603):1915–22. http://dx.doi.org/10.1016/S0140-6736(07)61814-5
55. 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(11):1849–57. http://dx.doi.org/10.1111/j.1530-0277.2010.01273.x
56. Muller CA, Geisel O, Pelz P, Higl V, Kruger J, Stickel A, Beck A, Wernecke KD, Hellweg R, Heinz A. High-dose baclofen for the treatment of alcohol dependence (BACLAD study): a randomized, placebo-controlled trial. Eur Neuropsychopharmacol. 2015;25(8):1167–77. http://dx.doi.org/10.1016/j.euroneuro.2015.04.002

57. Beraha EM, Salemink E, Goudriaan AE, Bakker A, de Jong D, Smits N, Zwart JW, Geest DV, Bodewits P, Schiphof T, Defourny H, van Tricht M, van den Brink W, Wiers RW. Efficacy and safety of high-dose baclofen for the treatment of alcohol dependence: a multicentre, randomised, double-blind controlled trial. Eur Neuropsychopharmacol. 2016;26(12):1950–9. http://dx.doi.org/10.1016/j.euroneuro.2016.10.006
58. Reynaud M, Aubin HJ, Trinquet F, Zakine B, Dano C, Dematteis M, Trojak B, Paille F, Detilleux M. A randomized, placebo-controlled study of high-dose baclofen in alcohol-dependent patients-The ALPADIR Study. Alcohol Alcohol. 2017;52(4):439–46. http://dx.doi.org/10.1093/alcalc/agx030
59. Karhuvaara S, Simojoki K, Virta A, Rosberg M, Loyttyniemi E, Nurminen T, Kallio A, Makela R. 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(7):1179–87. http://dx.doi.org/10.1111/j.1530-0277.2007.00401.x
60. Palpacuer C, Laviolle B, Boussageon R, Reymann JM, Bellissant E, Naudet F. 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(12):e1001924. http://dx.doi.org/10.1371/journal.pmed.1001924
61. Naudet F, Palpacuer C, Boussageon R, Laviolle B. Evaluation in alcohol use disorders – insights from the nalmefene experience. BMC Med. 2016;14(1):119. http://dx.doi.org/10.1186/s12916-016-0664-9
62. Skala K, Caputo F, Mirijello A, Vassallo G, Antonelli M, Ferrulli A, Walter H, Lesch O, Addolorato G. Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. Expert Opin Pharmacother. 2014;15(2):245–57. http://dx.doi.org/10.1517/14656566.2014.863278
63. Gallimberti L, Ferri M, Ferrara SD, Fadda F, Gessa GL. gamma-Hydroxybutyric acid in the treatment of alcohol dependence: a double-blind study. Alcohol Clin Exp Res. 1992;16(4):673–6. http://dx.doi.org/10.1111/j.1530-0277.1992.tb00658.x
64. Leone MA, Vigna-Taglianti F, Avanzi G, Brambilla R, Faggiano F. Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses. Cochrane Database Syst Rev. 2010(2):CD006266. http://dx.doi.org/10.1002/14651858.CD006266.pub2
65. Schacht JP, Anton RF, Randall PK, Li X, Henderson S, Myrick H. Varenicline effects on drinking, craving and neural reward processing among non-treatment-seeking alcohol-dependent individuals. Psychopharmacology (Berl). 2014;231(18):3799–807. http://dx.doi.org/10.1007/s00213-014-3518-1
66. Litten RZ, Ryan ML, Fertig JB, Falk DE, Johnson B, Dunn KE, Green AI, Pettinati HM, Ciraulo DA, Sarid-Segal O, Kampman K, Brunette MF, Strain EC, Tiouririne NA, Ransom J, Scott C, Stout R, Group NS. A double-blind, placebo-controlled trial assessing the efficacy of varenicline tartrate for alcohol dependence. J Addict Med. 2013;7(4):277–86. http://dx.doi.org/10.1097/ADM.0b013e31829623f4
67. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. JAMA. 2004;291(15):1887–96. http://dx.doi.org/10.1001/jama.291.15.1887
68. Iovieno N, Tedeschini E, Bentley KH, Evins AE, Papakostas GI. Antidepressants for major depressive disorder and dysthymic disorder in patients with comorbid alcohol use disorders: a meta-analysis of placebo-controlled randomized trials. J Clin Psychiatry. 2011;72(8):1144–51. http://dx.doi.org/10.4088/JCP.10m06217
69. Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K. Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 2005;29(3):395–401. http://dx.doi.org/10.1097/01.ALC.0000156129.98265.57
70. Han DH, Kim SM, Choi JE, Min KJ, Renshaw PF. Adjunctive aripiprazole therapy with escitalopram in patients with co-morbid major depressive disorder and alcohol dependence: clinical and neuroimaging evidence. J Psychopharmacol. 2013;27(3):282–91. http://dx.doi.org/10.1177/0269881112472563
71. Kranzler HR, Pierucci-Lagha A, Feinn R, Hernandez-Avila C. Effects of ondansetron in early- versus late-onset alcoholics: a prospective, open-label study. Alcohol Clin Exp Res. 2003;27(7):1150–5. http://dx.doi.org/10.1097/01.ALC.0000075547.77464.76
72. Johnson BA, Roache JD, Javors MA, DiClemente CC, Cloninger CR, Prihoda TJ, Bordnick PS, Ait-Daoud N, Hensler J. Ondansetron for reduction of drinking among biologically predisposed alcoholic patients: a randomized controlled trial. JAMA. 2000;284(8):963–71. http://dx.doi.org/10.1001/jama.284.8.963
73. Johnson BA, Roache JD, Ait-Daoud N, Zanca NA, Velazquez M. Ondansetron reduces the craving of biologically predisposed alcoholics. Psychopharmacology (Berl). 2002;160(4):408–13. http://dx.doi.org/10.1007/s00213-002-1002-9
74. Corrêa Filho JM, Baltieri DA. A pilot study of full-dose ondansetron to treat heavy-drinking men withdrawing from alcohol in Brazil. Addict Behav. 2013;38(4):2044–51. http://dx.doi.org/10.1016/j.addbeh.2012.12.018
75. Kiefer F, Jahn H, Tarnaske T, Helwig H, Briken P, Holzbach R, Kampf P, Stracke R, Baehr M, Naber D, Wiedemann K. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. Arch Gen Psychiatry. 2003;60(1):92–9. http://dx.doi.org/10.1001/archpsyc.60.1.92
76. Ait-Daoud N, Johnson BA, Prihoda TJ, Hargita ID. Combining ondansetron and naltrexone reduces craving among biologically predisposed alcoholics: preliminary clinical evidence. Psychopharmacology (Berl). 2001;154(1):23–7. http://dx.doi.org/10.1007/s002130000607

77. Pettinati HM, Oslin DW, Kampman KM, Dundon WD, Xie H, Gallis TL, Dackis CA, O'Brien CP. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. Am J Psychiatry. 2010;167(6):668–75. http://dx.doi.org/10.1176/appi.ajp.2009.08060852
78. Farren CK, Scimeca M, Wu R, Malley SO. A double-blind, placebo-controlled study of sertraline with naltrexone for alcohol dependence. Drug Alcohol Depend. 2009;99(1–3):317–21. http://dx.doi.org/10.1016/j.drugalcdep.2008.06.006
79. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, Goodwin FK. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA. 1990;264(19):2511–8. http://dx.doi.org/10.1001/jama.1990.03450190043026
80. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006;67(2):247–57. http://dx.doi.org/10.4088/JCP.v67n0211
81. Compton WM, Thomas YF, Stinson FS, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV drug abuse and dependence in the United States: results from the national epidemiologic survey on alcohol and related conditions. Arch Gen Psychiatry. 2007;64(5):566–76. http://dx.doi.org/10.1001/archpsyc.64.5.566
82. Oquendo MA, Currier D, Liu SM, Hasin DS, Grant BF, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). J Clin Psychiatry. 2010;71(7):902–9. http://dx.doi.org/10.4088/JCP.09m05198gry
83. Webb RT, Lichtenstein P, Larsson H, Geddes JR, Fazel S. Suicide, hospital-presenting suicide attempts, and criminality in bipolar disorder: examination of risk for multiple adverse outcomes. J Clin Psychiatry. 2014;75(8):e809–16. http://dx.doi.org/10.4088/JCP.13m08899
84. Assessment and Treatment of Patients with Coexisting Mental Illness and Alcohol and Other Drug Abuse. SAMHSA/CSAT Treatment Improvement Protocols. Rockville (MD): Substance Abuse and Mental Health Services Administration; 1994.
85. Ziedonis DM. Integrated treatment of co-occurring mental illness and addiction: clinical intervention, program, and system perspectives. CNS Spectr. 2004;9(12):892–904, 25. http://dx.doi.org/10.1017/S1092852900009718
86. Mangrum LF, Spence RT, Lopez M. Integrated versus parallel treatment of co-occurring psychiatric and substance use disorders. J Subst Abuse Treat. 2006;30(1):79–84. http://dx.doi.org/10.1016/j.jsat.2005.10.004
87. Weiss RD, Griffin ML, Kolodziej ME, Greenfield SF, Najavits LM, Daley DC, Doreau HR, Hennen JA. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. Am J Psychiatry. 2007;164(1):100–7. http://dx.doi.org/10.1176/ajp.2007.164.1.100
88. Mills KL, Teesson M, Back SE, Brady KT, Baker AL, Hopwood S, Sannibale C, Barrett EL, Merz S, Rosenfeld J, Ewer PL. Integrated exposure-based therapy for co-occurring posttraumatic stress disorder and substance dependence: a randomized controlled trial. JAMA. 2012;308(7):690–9. http://dx.doi.org/10.1001/jama.2012.9071
89. Hien DA, Levin FR, Ruglass LM, Lopez-Castro T, Papini S, Hu MC, Cohen LR, Herron A. Combining seeking safety with sertraline for PTSD and alcohol use disorders: A randomized controlled trial. J Consult Clin Psychol. 2015;83(2):359–69. http://dx.doi.org/10.1037/a0038719
90. Sylvia LG, Gold AK, Stange JP, Peckham AD, Deckersbach T, Calabrese JR, Weiss RD, Perlis RH, Nierenberg AA, Ostacher MJ. A randomized, placebo-controlled proof-of-concept trial of adjunctive topiramate for alcohol use disorders in bipolar disorder. Am J Addict. 2016;25(2):94–8. http://dx.doi.org/10.1111/ajad.12346
91. Litten RZ, Ryan ML, Falk DE, Reilly M, Fertig JB, Koob GF. Heterogeneity of alcohol use disorder: understanding mechanisms to advance personalized treatment. Alcohol Clin Exp Res. 2015;39(4):579–84. http://dx.doi.org/10.1111/acer.12669
92. Sanchez E, Cruz-Fuentes C. Cognitive control and negative and positive valence systems in the development of an NIMH RDoC-Based model for alcohol use disorder. Alcohol Clin Exp Res. 2016;40(1):214–5. http://dx.doi.org/10.1111/acer.12920