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Medications Development for the Treatment of Alcohol Use Disorder: Insights into the Predictive Value of Animal and Human Laboratory Models

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Abstract

Development of effective treatments for alcohol use disorder (AUD) represents an important public health goal. This review provides a summary of completed preclinical and clinical studies testing pharmacotherapies for treatment of AUD. We discuss opportunities for improving the translation from preclinical findings to clinical trial outcomes, focusing on the validity and predictive value of animal and human laboratory models of AUD. Specifically, while preclinical studies of medications development have offered important insights into the neurobiology of the disorder and alcohol's molecular targets, limitations include the lack of standardized methods and streamlined processes whereby animal studies can readily inform human studies. Behavioral pharmacology studies provide a less expensive and valuable opportunity to assess the feasibility of a pharmacotherapy prior to initiating larger scale clinical trials by providing insights into the mechanism of the drug, which can then inform recruitment, analyses, and assessments. Summary tables are provided to illustrate the wide range of preclinical, human laboratory, and clinical studies of medications development for alcoholism. Taken together, this review highlights the challenges associated with animal paradigms, human laboratory studies and clinical trials with the overarching goal of advancing treatment development and highlighting opportunities to bridge the gap between preclinical and clinical research.

Keywords

addiction; valley of death; novel therapeutics

Introduction

Alcohol use disorder (AUD) has a major public health impact in the United States affecting nearly 18 million people and causing over 100,000 deaths annually (Bouchery et al., 2011; Grant et al., 2004; Harwood, 2000). Worldwide, alcohol abuse and misuse is the third

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leading risk factor for premature death and disabilities and is responsible for 4% of all deaths (2011). Although treatments for AUD have improved in past decades (Miller et al., 2011), there is still a great need to develop more effective interventions. Pharmacotherapies for AUD are used less often than psychosocial interventions (Fuller and Hiller-Sturmhofel, 1999), yet without a pharmacological adjunct to psychosocial therapy nearly three quarters of patients resume drinking within 1 year (Johnson, 2008). The limited use of pharmacotherapy for AUD is due, in part, to the relative lack of pharmacological options to successfully treat these disorders (Edlund et al., 2012). As such, development of effective treatments for AUD represents an important public health goal (Bouchery et al., 2011; Heilig and Egli, 2006; Johnson, 2010; Johnson et al., 2007; Steensland et al., 2007).

Litten and colleagues (2012) have argued that there are three overarching aims for ensuring the successful development of novel therapeutics for AUD: 1) improve the drug development process, 2) identify more effective therapeutics and/or use personalized medicine, and 3) enable the use of these novel medications in clinical practice (Litten et al., 2012). In order to achieve these goals, Litten and colleagues emphasize the importance of bridging the gap between preclinical and clinical research. In this paper, we will provide a perspective on medications development and a review of the pharmacotherapies for AUD that have been tested using animal paradigms, human laboratory paradigms and clinical trials focusing on the validity and predictive value of animal and human laboratory models of AUD. To do so, we will first discuss the neural targets of alcohol in relation to medications development including both the traditional targets such as ligand-gated ion channels and the endogenous opioid system, and novel targets such as ghrelin and neuropeptide Y (NPY). We will then delve into a review of the literature focused on identifying the challenges associated with animal paradigms, human laboratory studies and clinical trials with the overarching goal of advancing treatment development and highlighting opportunities to bridge the gap between preclinical and clinical research.

Neural Targets of Alcohol

One of the major obstacles for developing effective drugs for the treatment of AUD is that alcohol does not have a single molecular target but instead acts on a variety of different neurotransmitter receptors, ion channels, transporters and pathways in the central nervous system (CNS) to exert its behavioral effects [for review see (Gilpin and Koob, 2008; Koob and Volkow, 2010; Soderpalm and Ericson, 2013; Spanagel, 2009; Weiss and Porrino, 2002)]. Although not the focus of this review, we will briefly introduce some of the more prominent targets as they relate to medications development for AUD.

A long-standing belief is that alcohol interacts with the mesolimbic dopamine (DA) pathway to produce its behavioral effects [for review see (Gonzales et al., 2004; Pierce and Kumaresan, 2006)]. Specifically, DA release in the nucleus accumbens (NAc) is thought to be central in the motivation and positive reinforcement associated with acute alcohol administration. Alcohol causes an increase in synaptic DA concentration in the NAc similar to other drugs of abuse (Di Chiara and Imperato, 1988; Gessa et al., 1985). Importantly, many of the targets described below do indirectly affect DA neurotransmission.

Ligand-gated ion channels are widely held to play an important role in ethanol-induced behaviors [for review see (Dopico and Lovinger, 2009; Harris et al., 1995; Spanagel, 2009)]. Research in this area has focused on investigating the effects of ethanol on two large superfamilies of ligand-gated ion channels. The first is the Cys-loop superfamily including nicotinic acetylcholine receptors (nAChRs), 5-hydroxytryptamine type 3 receptor (5-HT_3Rs), $GABA_A$Rs and glycine receptors. Varenicline, an FDA-approved smoking cessation aid, is a full and partial agonist at several nAChR subtypes and has been shown to attenuate the reinforcing effects associated with alcohol in both mice (Blomqvist et al., 1996; Steensland et al., 2007) and humans (Fucito et al., 2011; Litten et al., 2013; Mitchell et al., 2012c), while others suggest it might be effective in reducing alcohol consumption by exacerbating the negative effects of alcohol (Childs et al., 2012; Kamens et al., 2010). Ondansetron, a 5-HT_3R antagonist has been shown to decrease alcohol intake in preclinical studies (Tomkins et al., 1995) and decrease alcohol intake in early onset alcoholics in several clinical trials (Johnson et al., 2000; Kranzler et al., 2003) possibly through decreasing alcohol craving and diminishing the pleasurable effects associated with alcohol [for review see (Ye et al., 2001)]. The second superfamily of ligand-gated ion channels that are targets for alcohol action is the glutamate superfamily with members including α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), kainate receptors and N-methyl-d-aspartate receptors (NMDARs) [for review see (Dodd et al., 2000; Moykkynen and Korpi, 2012; Tsai and Coyle, 1998)]. Acamprosate, one of three FDA approved medications for AUD, is an NMDAR antagonist and has been shown to prevent relapse in alcohol dependent individuals acting as an anti-craving medication [for review see (Littleton, 1995; Witkiewitz et al., 2012)]. Additionally, memantine, another NMDAR antagonist, currently used in the treatment of moderate to severe dementia, has shown great promise in preclinical studies (Piasecki et al., 1998; Sabino et al., 2013), yet the sole clinical study conducted on memantine for AUD yielded negative results (Evans et al., 2007).

P2X receptors (P2XRs) constitute a third superfamily of ligand-gated ion channels that are becoming a focus of investigation in neuroscience and alcohol studies [for review see (Asatryan et al., 2011)]. Preclinical studies suggest that ivermectin, a selective, positive allosteric modulator of P2X4R, is able to decrease alcohol self-administration in wildtype mice using multiple models of alcohol intake but to a lesser extent in P2X4R knock out mice (Wyatt et al., 2014; Yardley et al., 2012).

Another well-known target of alcohol in the CNS is the endogenous opioid system [for review see (Gianoulakis et al., 1996; Herz, 1997)]. There are 3 known opioid receptor subtypes: μ, δ, and κ. In addition to endogenous opioid peptides: β-endorphins, enkephalins, and dynorphins, exogenous ligands, such as morphine, also act on the opioid receptors. Naltrexone, one of the three drugs approved by the FDA for the treatment of AUD, blocks opioid receptors and is believed to decrease the reinforcing effects of alcohol [for review see (Johnson, 2008)]. Nalmefene, another opioid receptor antagonist with a mechanism of action similar to naltrexone, is currently being developed as a medication for AUD in the United States but has already received European marketing authorization [for review see (Paille and Martini, 2014)].

Novel targets are being actively explored. One such novel targets is the ghrelin receptor. Ghrelinis known to stimulate food consumption through indirect interaction with the hypothalamus; however, there is evidence that it also plays an important role in alcohol consumption [for review see (Vadnie et al., 2014)]. Additional studies suggest ghrelin might also play a role in alcohol craving (Leggio et al., 2012; Leggio et al., 2014), reward (Jerlhag et al., 2009), withdrawal and relapse (Suchankova et al., 2013), but the exact role of ghrelin in mediating the behavioral effects of alcohol remains unknown.

The endocannabinoid (EC) system and its involvement in alcohol dependence have received much attention since the identification of the cannabinoid 1 receptor (CB1) [for review see (Ciccocioppo et al., 2009; Hungund and Yaragudri, 2009; Pacher et al., 2006; Pava and Woodward, 2012)]. Due to the comorbidity of cannabis use and AUD, it has been suggested that cannabis and alcohol may act on similar targets in the CNS. Rimonabant, a cannabinoid receptor 1 blocker, appears to be effective in reducing consumption in multiple preclinical models of alcohol self-administration (Arnone et al., 1997; Cippitelli et al., 2005; Gessa et al., 2004), clinical studies conducted thus far do not support the use of rimonabant for treatment of AUD (George et al., 2010; Soyka et al., 2008).

There are a number of stress-related neuropeptides that have been implicated as important targets for alcohol such as NPY, corticotropin-releasing factor (CRF) and nociceptin/ orphanin FQ (N/OFQ) signaling [for review see (Ciccocioppo et al., 2009; Heilig and Egli, 2006)]. NPY is believed to play a role in alcohol intake, dependence and withdrawal via interruption of NPY signaling by alcohol [for review see (Thiele and Badia-Elder, 2003; Thorsell, 2007; Vadnie et al., 2014)]. NPY is an endogenous ligand shown to have anxiolytic and anti-depressant properties that might contribute to its ability to attenuate alcohol consumption. Corticotropin-releasing factor is another stress-related neuropeptide and appears to be involved in excessive alcohol consumption in post-dependent animals, stress-induced reinstatement of alcohol seeking, and anxiety associated with alcohol withdrawal [for review see (Heilig and Koob, 2007)]. Lastly, N/OFQ, an endogenous ligand for the nociception receptor (NOP), has been shown to block drug-induced increases in extracellular DA in the NAc [for review see (Heilig and Egli, 2006)].

Neurotrophic factor signaling represents an important target for medications development for AUD [for review see (Janak et al., 2006; Russo et al., 2009)]. Multiple neurotrophins such as brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3) and neurotrophin 4 (NT4) have been implicated in drug addiction [for review see (Janak et al., 2006)]. In more recent years, the neuroimmune signaling pathway has garnered attention as a probable target for alcohol action, specifically in regards to its role in intoxication, negative affect, and craving [for review see (Coller and Hutchison, 2012; Mayfield et al., 2013). Both human and animal studies provide support for the role of alcohol-induced neuroimmune signaling [for review see (Coller and Hutchison, 2012)]. Pioglitazone, a peroxisome proliferator-activated receptor agonist, has generated positive results in preclinical studies but results from clinical studies have not yet been published [for review see (Robinson et al., 2014)].

Despite the long list of implicated targets of alcohol action, demonstrations in humans are still lacking and the specific contributions of these targets are only recently beginning to be

explored (Mitchell et al., 2012b). Molecular targets such as the cys loop and glutamate superfamily of ligand-gated ion channels and the mesolimbic dopamine pathway are widely accepted as for alcohol action (Johnson, 2008). Others, such as P2X4Rs, ghrelin receptors (Vadnie et al., 2014), the EC system (Johnson, 2008), and neuroimmune signaling [for review see (Coller and Hutchison, 2012; Mayfield et al., 2013) have been clinically investigated as possible targets of alcohol action more recently. These targets have been the focus of medications development for AUD. Table 1 details medications that have previously undergone or are currently undergoing testing that were identified from clinicaltrials.gov. The primary indication and mechanism of action is listed for each. In the following sections, using the medications included in Table 1, we will discuss 3 different stages of medications development for AUD: preclinical, human laboratory and clinical research. For each stage, we will briefly discuss commonly used paradigms, limitations associated with these models, and recommendations to increase the successful translation of a drug from preclinical to clinical research. Not all medications in Table 1 have been tested in each stage of drug development and as a result, these medications are excluded from subsequent tables as no results are yet published.

Animal Paradigms

After considering the molecular targets of alcohol itself, we turn our attention to medications development for AUD at the preclinical level. Table 2 provides a detailed summary of preclinical studies using multiple animal paradigms thought to model different facets of alcoholism with the ultimate goal of testing medications that can be advanced from preclinical to clinical testing. To that end, one of the most common and important phenotypes studied using animal models is alcohol intake. There are numerous paradigms used to model social drinking, excessive alcohol consumption, and operant self-administration of alcohol in animals. The two-bottle choice paradigm is a frequently used model of social drinking because animals do not generally achieve clinically relevant blood alcohol contents [BACs; for review see (Crabbe et al., 2011; Tabakoff and Hoffman, 2000)]. In the two-bottle choice paradigm, animals have continuous access to one bottle of alcohol and one bottle of water and are able to choose freely between the two. Chronic intermittent access, scheduled high alcohol consumption, drinking in the dark, and chronic intermittent vapor exposure are some of the more commonly employed animal models of excessive alcohol consumption [for review see (Becker and Ron, 2014; Crabbe et al., 2011)]. There are numerous variations to each paradigm; however, in each case, the animals reach intoxicating BACs. Operant self-administration is unique in that it allows for evaluation of the animal's motivation to consume alcohol [for review see (Cunningham et al., 2000; Tabakoff and Hoffman, 2000)]. In this paradigm, animals are trained to press a lever to receive alcohol, however, the frequency of access to alcohol, amount of alcohol available, and number of lever presses required to gain access to alcohol can be adapted.

Although preclinical research represents a crucial step in the drug development process, several factors must be considered when using animals to model human behavior. Results from preclinical studies can vary depending upon the strain and species used. For example, the study conducted by Breslin and colleagues (2010) found that treatment with topiramate decreased alcohol consumption in alcohol-preferring (P) rats but had no effect on alcohol

consumption in Wistar rats (Breslin et al., 2010). Furthermore, studies reported differences in response to medication between alcohol dependent and non-alcohol dependent rats (Roberto et al., 2008) and high-preference and low-preference rats (Oka et al., 2013). A similar phenomenon is observed in clinical studies, whereby treatment response appears to be dependent on treatment population. Nevertheless, a deeper understanding of why a drug is effective in one strain or one species and not another is often elusive. Delving into these differences may ultimately inform precision medicine efforts. In addition to strain, alcohol intake can also fluctuate depending on the concentration of the alcohol solution and the addition of a sweetener (Yoneyama et al., 2008).

Another important issue to consider is that drugs are rarely compared against each other at a preclinical level but rather, are tested against a placebo. Using the field standard, such as naltrexone, in models where the drug has already shown efficacy, as a comparison may help to identify the animal paradigms that are predictive of human behavior through reverse translation. Perhaps equally important, reverse translation could prove informative for promising medications that do not show clinical efficacy as a means of identifying responders via animal and human laboratory studies. Unfortunately, reverse translation is uncommon as many compounds that progress to advanced stages of clinical drug development rarely endure additional testing at the preclinical level to validate the animal paradigms. Furthermore, unlike in human testing, animals are not susceptible to the “placebo effect” (van der Worp et al., 2010), which likely leads to an overestimation of the medication effects in animal models In other words, the signal-to-noise ratio is clearly higher in animal studies, yet the “signal” often fades and is no longer detectable or clinically relevant when tested in clinical samples.

It is also important to consider that FDA approved drugs that are being investigated for other indications often do not follow linear progression from preclinical to clinical stages of drug development. For example, dutasteride, approved for the treatment of benign prostatic hyperplasia, has been tested in human laboratory studies for the treatment of AUD (see Table 3), but no animal studies have been published for this indication thus far (see Table 2). In other cases such as nalmefene, topiramate and gabapentin, there are relatively fewer reported preclinical studies (see Table 2) as compared to clinical studies (see Table 4).

Although preclinical development represents an important part of the drug development pathway, there are many factors that limit the usefulness of these models in their current format. One such obstacle may be publications bias. For example, one study analyzed over 4600 published papers across disciplines in 2007 and found that 85.9% of papers reported a positive result (Fanelli, 2012). This strong bias towards positive publications makes it extremely difficult to draw conclusions between the predictive validity of animal data to clinical outcomes. Furthermore, despite the misconception that negative results are not as valuable as positive results, reporting of negative results can allow for refinement of theories or methods, encourage discussion within the field, improve quality control and ultimately help to advance science by filling gaps in knowledge (Lehrer et al., 2007; Matosin et al., 2014). Data repositories may be also be helpful in increasing access to preclinical findings and mitigating the issue of publication bias.

In summary, preclinical studies of medications development for AUD have offered important insights into the neurobiology of the disorder and alcohol's molecular targets. Current limitation of this approach include the lack of standardized methods and streamlined processes whereby animal studies can readily inform human studies, which in turn would start at the point of safety and initial efficacy (described below).

Human Laboratory Paradigms

Human laboratory studies offer unique opportunities to gain insight into the safety, efficacy and most importantly, the mechanism of action of the drug being tested serving as a less expensive alternative compared to full-scale clinical trials. Table 3 summarizes the results of human laboratory studies investigating the mechanism by which drugs being developed for the treatment of AUD exert their effect. As exemplified in Table 3, there are numerous laboratory paradigms used to model facets of AUD (Ray et al., 2010). Commonly used paradigms include alcohol self-administration, experimenter administered alcohol (i.e., alcohol challenge), alcohol cue-reactivity, and stress induction. For example, in one iteration of the alcohol self-administration paradigm, participants complete 2 1-h self-administration (SA) periods having the option of consuming up to 4 alcoholic drinks (0.015 g/dl each) or receiving a monetary compensation of $3 per beverage not consumed (O'Malley et al., 2007). Typically, total number of drinks consumed during the SA sessions is considered the primary outcome variable and rate of drinking (i.e., time to first drink, inter-drink interval) is often used as a secondary outcome. Regarding the ethics of alcohol administration to clinical samples, it is important to note that many studies have assessed the effect of laboratory self-administration of alcohol on future alcohol use and found that alcohol use does not increase in subjects following participation in an alcohol administration study (Pratt and Davidson, 2005; Sommer et al., 2015). Importantly, the National Advisory Council on Alcohol Abuse and Alcoholism's recommended council guidelines on ethyl alcohol administration in human experimentation encourages experiments involving alcohol administration to be conducted in non-treatment seeking subjects (Enoch et al., 2009). Yet, because of the distinct differences between non-treatment seeking and treatment seeking populations and given the lack of successful medications to treat this disorder, the benefits to society oftentimes outweigh the risks to the individual. Additional human laboratory paradigms include stress and cue-reactivity. The cue-reactivity paradigm measures alcohol craving (Bohn et al., 1995; MacKillop, 2006). In this paradigm, participants are asked to hold and smell a glass of water for 3 minutes to control for the effects of simple exposure to any potable liquid. Next, participants hold and smell a glass of their preferred alcoholic beverage for three 3-minute trials (Monti et al., 1987; Monti et al., 2001). After every 3 minutes of exposure, craving for alcohol is assessed. Given the number of studies that suggest an association between stress and alcohol use, stress-induction in the laboratory has been used to understand the relationship between stress- and cue-induced craving in relation to alcohol use (Plebani et al., 2012). Two paradigms are often used to induce stress in the laboratory: 1) the Trier Social Stress Test [TSST; (Kirschbaum et al., 1993)] and 2) guided imagery exposure to a stressful event (Sinha et al., 1999).

In addition to behavioral assessments, brain imaging techniques can provide additional insight into the mechanism of the pharmacotherapies being tested. Although beyond the

scope of this review, brain imaging studies have become increasingly popular in clinical and therapeutic developments in addictive disorders (Fowler et al., 2007), with a particular focus on the neural bases of cue-reactivity (Jasinska et al., 2014). A review by Borsook and colleagues (2011) highlights the importance of brain imagining in bridging preclinical and clinical CNS drug discovery (Borsook et al., 2011). Specifically, they emphasize that this technique may be able to help better identify pharmacodynamics markers, improve paradigms to predict efficacy, evaluate safety, elucidate dose-response relationships, and more accurately define symptom response. As noted in a recent review by our group, neural markers, in particular those during cue reactivity, appear to be promising predictors of relapse in clinical contexts (Courtney et al., 2015). Taken together these paradigms and techniques used in behavioral pharmacology studies provide insight into the mechanism of action of the drug; however, certain precautions, such as sample size and consideration of inclusion and exclusion criteria due to known variations in response associated with certain clinical characteristics, need to be taken to ensure the conclusions reached are valid.

As discussed for animal studies, different populations respond differently to each drug therefore, Table 3 is organized according to the lab paradigm and sample tested. In the study by Drobes and colleagues (2003), naltrexone decreased alcohol self-administration in a naturalistic setting in non-treatment seeking AD individuals but had no effect on social drinkers in the same study (Drobes et al., 2003), non-treatment seeking AD individuals (Anton et al., 2004a; O'Malley et al., 2002) or heavy beer drinkers (Davidson et al., 1999) suggesting that the results of each study should be interpreted carefully and the population tested must be taken into consideration. Interestingly, human laboratory studies are more often conducted in non-treatment seeking AD individuals whereas clinical trials employ treatment seeking AD individuals, which likely accounts for the at least part of the discrepancy between results from human laboratory studies and clinical trials. It remains unclear what variables differentiate treatment seekers from non-treatment seekers for alcoholism, whether it be severity of the disorder or the act of treatment seeking itself. Importantly, epidemiological data suggest that there is an average lag of 8 years between AUD onset and treatment seeking (Hasin et al., 2007). Ongoing studies in our laboratory suggest that treatment-seekers are older and have a more severe AD presentation, as compared to non-treatment seekers. Additional attention to discrepancies in sample characteristics between human laboratory and clinical trials is likely to promote greater consilience across approaches.

In addition to the variance regarding drinking status and treatment-seeking efforts, sample size is another significant factor contributing to the lack of predictability between human laboratory studies and clinical trials. Human laboratory studies tend to have a much smaller sample size compared to clinical trials and therefore, may affect the reliability of the estimates. The average samples size for the human laboratory studies included in Table 3 is 47 ± 48 participants whereas the average sample size for the clinical trials listed in Table 4 is 207 ± 235 participants. Unlike the *p*-value, effect size is independent of sample size and indicates the magnitude of the effect (Sullivan and Feinn, 2012). Therefore, both effect size and *p*-value should be considered when interpreting and comparing results from human laboratory studies and clinical trials.

Similar to the preclinical models, human laboratory studies could be strengthened if the drugs of interest were tested against a field standard pharmacotherapy instead of, or in addition to, a placebo treatment (Rothman and Michels, 1994). Arguments can be made that placebos offer a more suitable reference for determining efficacy, provide a more straightforward comparison, and increase the likelihood of achieving statistical significance; however, the use of active medication as a comparison can be beneficial to establish whether the new treatment is superior to the currently available/approved treatment. It is important to acknowledge that comparison to a placebo may be important in earlier stages of development to establish initial efficacy. However, in the later in development, it might be more informative to include both a placebo arm and a gold standard arm although this introduces additional challenges as it requires a larger sample. Comparing multiple doses of the drug could also provide a strategic method for conducting dose-finding studies prior to proceeding to relatively expensive clinical trials.

Another important issue to consider is the monetary compensation of research subjects, which provides an incentive for non-treatment seeking subjects and can strongly influence participation in the research study (Grady, 2005). As these subjects are not seeking medical benefit from the treatment, their primary motivation to participate in the research study is the monetary compensation, investigators should guard against the compensation becoming coercive or an excessive inducement. Further, there are concerns that the motivation for monetary compensation itself could lead to a general disinterest in the study and low level of concern about data accuracy. A recent commentary by Resnik and McCann (2015) highlights this complex issue (Resnik and McCann, 2015). The authors cite a recent study reporting that a quarter of respondents admitted to exaggerating their symptoms and 14% pretended to have a health problem to qualify for a study. While these concerns are often mitigated by an effective consent process and by forming a strong alliance with research participants as they are helping others with similar conditions through their participation in research studies, Resnik and McCann suggest that additional strategies can be used to address this concern including the use of laboratory tests to confirm self-reported information, the use of reinforcements to promote truthfulness, and increased utilization of available clinical trial registries (Resnik and McCann, 2015).

In sum, considering clinical costs associated with drug development are estimated to be more than $500 million, it is crucial to find novel ways to improve the translational predictability between relatively less expensive human laboratory studies and clinical trials (Paul et al., 2010). Specifically, phase I studies can provide a less expensive and extremely valuable opportunity to assess the feasibility of an approach prior to initiating larger scale clinical trials such as identifying a specific population more likely to respond to the medication and issues concerning retention, analyses, assessments, etc. (Leon et al., 2011). These studies can be then be used to establish standardized procedures in regards to environment, treatment goals and drinking severity of the population as well as sample size. Limitations not with standing, before the FDA will approve a drug, clinical trials must be conducted.

Clinical Trials

A relatively small percentage of drugs successfully make the transition from preclinical studies to clinical development and even fewer make it all the way through phase 3 clinical trials (Paul et al., 2010). Table 4 summarizes the results from clinical trials on drugs being developed as treatments for AUD. As evident in Table 4, clinical trials usually employ multiple primary efficacy outcomes such as time to first heavy drinking day (HDD), time to first lapse, days abstinent, maintenance of abstinence, drinks per drinking day, and percent drinking days. In addition to the outcomes measured, duration of trial, time abstinent prior to the clinical trial and dosing regimen are also variable across trials of different drugs and different trials of the same drug, as illustrated in Table 4. Once again, the lack of standardized methods among clinical trials and between human laboratory studies and clinical trials hinders the translation from human laboratory findings to clinical outcomes. First, although there tends to be less heterogeneity regarding drinking status and treatment seeking status in clinical trial participants, there are marked differences in AD phenotype and treatment goals that have been shown to alter the effect of medication (Bujarski et al., 2013; DeMartini et al., 2014). For instance, analyses of the COMBINE Study found that a goal of complete abstinence was associated with an increase in percent days abstinent, days to relapse to heavy drinking and global clinical outcome compared to a goal of conditional abstinence or controlled drinking (Bujarski et al., 2013). Therefore, it is important to acknowledge the known, clinically significant differences between human laboratory and clinical trial participants when drawing associations between human laboratory results to clinical trial outcomes. Similarly, it is important to recognize there are differences not only between but within each population as well and these should be considered when interpreting data.

In clinical trials, the FDA requires investigators to commit to an a priori hypothesis as stated in the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims making the selection of an appropriate endpoint imperative (2009). This guidance requires investigators to thoroughly consider the aims of the clinical trial prior to execution by having them declare the hypothesis and primary outcomes ahead of time allowing investigators to test for statistical significance (Furberg and Furberg, 2007). The analyses are focused specifically on the predetermined outcome(s) and represent an important safeguard to eliminate coincidental findings. Therefore, selection of an appropriate hypothesis and outcome measures becomes extremely vital for the proper evaluation of a drug in clinical trials.

The FDA recommends that percent subjects with no heavy drinking days (PSNHDDs) be the primary endpoint measure for phase III clinical trials evaluating pharmacotherapy for AUD (FDA, 2006). Further examination of the utility and validity of this particular outcome measure was pursued by Falk and colleagues (2010) (Falk et al., 2010) who concluded that not only was this endpoint clinically relevant and as sensitive as other endpoints such as percent subjects abstinent, percent days abstinent, drinks per day, drinks per drinking day or drinks per drinking week, but that a grace period should be used where appropriate. For example, studies involving medications that require titration to reach the target dose should allow a grace period to ensure subjects are receiving the full effect of the medication prior to

evaluation. Additionally, studies might include a grace period to confirm that participation in the clinical trial, itself, is not the only factor affecting changes in drinking habits. Allowing the novelty of participating in a clinical trial to diminish prior to evaluation could be especially important in preventing false negatives that can arise with the use of a placebo.

Importantly, as many clinical trials compare the treatment under investigation to placebo, there are ethical issues that arise from administering placebo to a treatment seeking population of individuals with AUD when there is a known, effective treatment. Furthermore, given that Weiss and colleagues (2008) found that administration of placebo medication in the COMBINE study lead to a significant "placebo effect" (Weiss et al., 2008), it is important to consider that the use of a placebo could potentially lead to false negatives. A possible avenue to addressing the placebo effect in AUD is to provide less robust behavioral interventions within the treatment protocol and to provide longer duration of trial and follow-up, which could unmask "real" medication versus placebo differences emerging over time.

In brief, clinical development (phase I-III studies) represents the most expensive part of drug development, making up just over 60% of the total cost, highlighting the need for a streamlined process (Paul et al., 2010) and utilization of alternative methods to reduce costs. One possible solution for alleviating the financial burden associated with clinical trials is through the use of interim analyses as it allows for the investigator to halt the study when there is enough data available to reach a conclusion (Todd et al., 2001). Not only is this beneficial in terms of financial obligations but it also carries significant ethical implications.

Moving from the Human Laboratory to the Clinic

The potential translational value of animal, human laboratory and clinical studies can be better achieved through refinements of the drug development process to ensure the successful development of novel therapeutics for AUD (Litten et al., 2012). To more fully appreciate the predictive value of preclinical and human laboratory results to clinical outcomes, we have classified each study, including drugs with at least 3 or more reported clinical trials, as either positive or negative (Figure 1; Supplementary Table 1). For the purposes of this summary figure, if the human laboratory study or clinical trial showed a statistically significant positive effect for any one of the outcomes tested, it was considered positive. As previously stated, there appears to be a bias towards positive findings in the studies reported, particularly with the animal and human laboratory studies. Interestingly, with the exception of naltrexone, there have been more clinical trials, compared to human laboratory studies, conducted on all the drugs included in Figure 1 and Supplementary Table 1. This suggests that there is less information being obtained concerning mechanism of action and dosing and more of an emphasis on efficacy outcomes. Understanding the mechanism of action can provide insight that can be advantageous when designing a clinical trial such as by helping to determine the patient population most likely to respond to the drug, identifying the most suitable drinking endpoint, establishing a more accurate dosing regimen, or predicting common side effects associated with the drug (2010). The central questions remaining are: what specific animal paradigms are predictive of human laboratory and clinical trial success and which human laboratory paradigms are predictive of clinical

trial success. Further, it remains crucial to identify which experimental paradigms (in animal and in humans) can meaningfully inform our understanding of mechanisms of action of AUD pharmacotherapies and can in turn help target medications to patient populations on the basis of these mechanisms.

Conclusions

While only four pharmacotherapies are currently approved for the indication of AUD and their efficacy is small-to-moderate, the past two decades has seen extensive research on medications development for AUD. The neuropharmacology of alcohol is such that it targets multiple brain systems, thus offering unique challenges and opportunities. Research to date has focused primarily on medications targeting endogenous opioids and associated dopamine release in the ventral striatum, a brain region often implicated in the rewarding properties of alcohol and drugs. More recently however, increased attention has been paid to novel targets, such as CRF, ligand-gated ion channels, and the neuroimmune system. Medications in these novel drug classes are still early in their development and their potential efficacy remains unclear. The primary goal of this manuscript was to provide a perspective on medications development for AUD along with an illustrative review of the literature encompassing preclinical, human laboratory, and clinical trials. In order to provide an up-to-date survey of the field, medications undergoing testing were identified from clinicaltrials.gov and extensive literature searches were conducted. Tables were developed to characterize the medications and their purported mechanisms of action (Table 1), preclinical studies including animal models selected and results obtained (Table 2), human laboratory studies including experimental paradigms, population studied, and results (Table 3), and clinical trials, including abstinence period at study entry, treatment and dosing protocol, and results from primary outcomes (Table 4). Finally, a comparison across animal, human laboratory, and clinical trial findings was provided for pharmacotherapies for which three or more clinical trials were completed to date (Figure 1; Supplementary Table 1).

This extensive effort towards covering a large body of research has allowed us to derive some important conclusions and recommendations for the field. While a critical interpretation of the studies summarized in the tables is provided at each level of analysis (i.e., preclinical, human lab, and clinical trials), some general conclusions can also be drawn. Specifically, there is a marked need for standardization of testing procedures at each level of medications development, including standard protocols for experimental paradigms, population characteristics (in both animal and human studies), and analyses of predefined primary and secondary outcomes. Such standardization would allow us to more effectively integrate results from various studies using both critical reviews of the literature as well as quantitative studies (i.e., meta-analysis). In addition, opportunities for studies that can more effectively detect ideal dosing and mechanisms of action were highlighted throughout the review. Finally, it is important to recognize that this review ends at the efficacy testing stage, namely clinical trials. The dissemination of these findings at the level of effectiveness studies and public health efforts represents an important next frontier from the development of efficacious medications. In the current health care context, only a very small minority of patients ever receive a medication for the treatment of AUD (Bates, 2005) and that dissemination of research findings to the clinical community represents a crucial step

towards the ultimate goal of alleviating suffering from this prevalent and debilitating disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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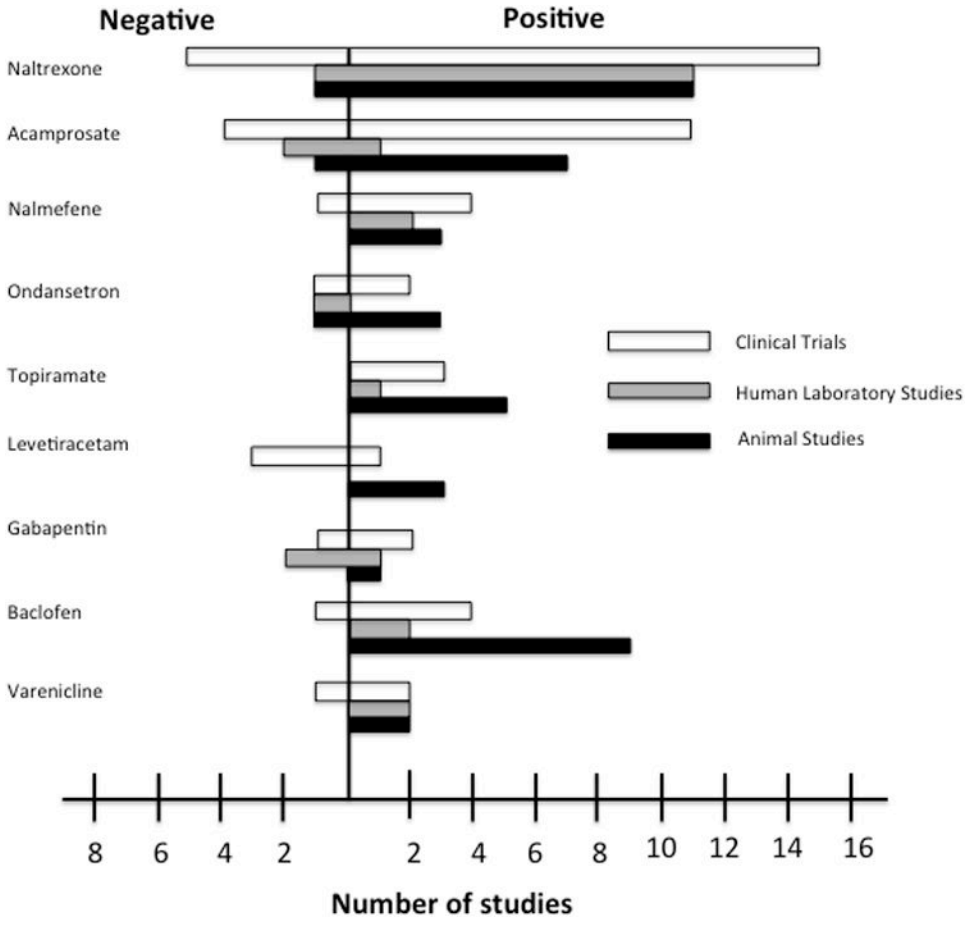

Figure 1.

Translational research outcomes figure with depicting the number of positive (right side) and negative (left side) outcomes for each clinical trial (white bars), human laboratory study (gray bar) and animal study (black bar).

Note: Only pharmacotherapies with three or more reported clinical trials were included.

Table 1

Identified from actively studied medications and completed trials for the treatment of AUD (registered to Clinicaltrials.gov)

Name	Primary Indication	Primary Mechanism of Action
Disulfiram	Alcohol dependence	Blocks ethanol metabolism
Naltrexone	Alcohol dependence	Opioid antagonist
Acamprosate	Alcohol dependence	Glutamatergic activity modulator *
Nalmefene	Opioid dependence	Opioid receptor antagonist
Ondansetron	Antiemetic	5-HT_3 receptor antagonist
LY686017	Antiemetic **	Neurokinin-1 (NK-1) antagonist
Topiramate	Anticonvulsant	Glutamate & $GABA_A$ receptor modulator
Zonisamide	Anticonvulsant	Sodium channel blocker and calcium channel modulator *
Levetiracetam	Anticonvulsant	Interaction with synaptic vesicle protein SV2A *
Gabapentin	Analgesic/ anticonvulsant	Modulation of GABA synthesis and glutamate synthesis *
Pregabalin	Neuropathic pain/ anticonvulsant	Binds with high affinity to the α2-delta site on voltage-gated calcium channels
Baclofen	Anti-spasmodic	$GABA_B$ receptor agonist
Ivermectin	Antiparasitic	Glutamate-gated chloride channels
Minocycline	Antibiotic – acne/ infections	Inhibition of protein synthesis
Ibudilast	Bronchodilator/ vasodilator	Phosphodiesterase inhibitor
Varenicline	Smoking cessation	nACH receptor partial agonist
Mifepristone	Antiprogestational activity	Progesterone receptor antagonist
Oxytocin	Labor induction	Oxytocin receptors
ABT-436	Anxiety/ Major depressive disorder **	HPA axis normalization via pituitary V1B antagonism
Memantine	Moderate- severe dementia	NMDA receptor antagonist
Pioglitazone	Antidiabetic	PPARγ agonist
Mecamylamine	Antihypertensive	Non competitive nACh receptor antagonist
Prazosin	Antihypertensive	Relaxant action on vascular smooth muscle; Postsynaptic alpha-adrenoceptors blocker *
Psilocybin	Psychomimetic	$5HT_{2A}$ serotonin receptor
Olanzapine	Antipsychotic	D_2 receptor antagonist and $5HT_2$ receptor antagonist
Doxazosin	Benign prostatic hyperplasia	Selective inhibitor of the α1-subtype of α adrenergic receptors
Dutasteride	Benign prostatic hyperplasia	5α-reductase inhibitor
Mirtazapine	Antidepressant	α2 adrenergic receptor antagonist *
Rimonabant	Obesity **	CB1 endocannabinoid antagonist

Note:

* Current beliefs presented as the exact mechanism remains unknown;

** Not FDA approved for this indication; Not all trials are registered to Clinicaltrials.gov

Table 2

Effect of drugs on animal models of AUD.

Medication	Model	Effect	References
Naltrexone	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Froehlich et al., 1990)
		Decreased alcohol intake in h/mOPRM1-118GG mice only (no effect in 118AA mice)	(Bilbao et al., 2015)
	Operant self-administration	Decreased operant self-administration of alcohol	(Bilbao et al., 2015; Gonzales and Weiss, 1998; Le et al., 1999; Steensland et al., 2007; Tanchuck et al., 2011; Walker and Koob, 2008)
	Scheduled high alcohol consumption	Decreased alcohol intake	(Tanchuck et al., 2011)
	Drinking in the dark	Decreased alcohol intake	(Kamdar et al., 2007)
	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Ji et al., 2008)
	Operant binge drinking	Decreased alcohol intake	(Ji et al., 2008)
	Alcohol- induced locomotion	Suppressed alcohol-induced locomotion (higher dose needed for C57BL/6 mice compared to BALB/c and DBA/2 mice	(Kiianmaa et al., 1983)
	Alcohol discrimination	Failed to alter discrimination of alcohol	(Middaugh et al., 1999)
	Alcohol-induced mesolimbic dopamine release	Prevented alcohol-induced mesolimbic dopamine release	(Gonzales and Weiss, 1998)
	Alcohol deprivation effect	Diminished alcohol deprivation effect (naltrexone + acamprosate also reduced ADE)	(Heyser et al., 2003)
	Alcohol-induced reinstatement of alcohol-seeking behavior	Diminished alcohol-induced reinstatement	(Le et al., 1999)
	Stress-induced reinstatement of alcohol-seeking behavior	No effect	(Le et al., 1999)
	Intravenous self-administration	Dose dependently decrease self-administration in rhesus monkeys	(Altshuler et al., 1980)
Acamprosate	24-h access two-bottle choice voluntary intake	Decreased alcohol intake in high-preference rats; No effect on low-preference rats	(Oka et al., 2013)
	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Olive et al., 2002)
	Alcohol-induced mesolimbic dopamine release	Suppressed alcohol-induced mesolimbic dopamine release	(Olive et al., 2002)
	Drinking in the dark	Decreased alcohol intake	(Gupta et al., 2008)
	Alcohol discrimination	Failed to alter discrimination of alcohol	(Spanagel et al., 1996c)
	Operant self-administration	No effect in alcohol preferring rats	(Spanagel et al., 2014)
	Alcohol deprivation effect	Diminished alcohol deprivation effect	(Heyser et al., 1998; Oka et al., 2013; Spanagel et al., 1996a)
		No effect	(Spanagel et al., 2014)
	Alcohol withdrawal	Reduced some withdrawal signs	(Spanagel et al., 1996b)
	Cue-induced reinstatement of alcohol-seeking behavior	Reduced ethanol-paired cue effects	(Bachteler et al., 2005)
		No effect	(Spanagel et al., 2014)
Nalmefene	Operant self-administration	Decreased operant self-administration of alcohol	(Bilbao et al., 2015; Nealey et al., 2011;

Medication	Model	Effect	References
			Walker and Koob, 2008)
	Fluid deprivation + Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Hubbell et al., 1991)
Ondansetron	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Tomkins et al., 1995)
	Alcohol withdrawal	Reduced withdrawal signs	(Costall et al., 1990)
	Operant self-administration	No effect	(Beardsley et al., 1994)
	Stress-induced reinstatement of alcohol-seeking behavior	Diminished stress-induced reinstatement	(Le et al., 2006)
LY686017	Insufficient affinity for the mouse or rat NK1R		(George et al., 2008)
Topiramate	24-h access two-bottle choice voluntary intake	Decreased alcohol intake at 2-h time point (50 mg/kg dose) and increased alcohol intake at 23-h time point (25 mg/kg dose) in C57BL/6J	(Gabriel and Cunningham, 2005)
		Decreased alcohol intake at 2-h time point but not at 21-h time point in C57BL/6J	(Ngyuen et al., 2007)
		Decreased alcohol intake in P rats; No effect in Wistar rats	(Breslin et al., 2010)
	Three-bottle choice voluntary intake	No effect	(Breslin et al., 2010)
	Limited access alcohol only	Decreased alcohol intake	(Knapp et al., 2007a)
	Alcohol-induced motor locomotion	No effect	(Ngyuen et al., 2007)
	Alcohol withdrawal	Reduced alcohol withdrawal signs	(Farook et al., 2007)
Zonisamide	Limited access alcohol only	Decreased alcohol intake	(Knapp et al., 2007a)
Levetiracetam	24-h access two-bottle choice voluntary intake	Decreased in alcohol intake	(Zalewska-Kaszubska et al., 2011)
	Alcohol-induced motor locomotion	Decreased alcohol-induced motor locomotion	(Robinson et al., 2013)
	Drinking in the dark	Increased alcohol intake	(Fish et al., 2014)
	Intermittent access two-bottle choice	Decreased alcohol intake	(Fish et al., 2014)
Gabapentin	Operant self-administration	Decreased operant self-administration of alcohol in dependent rats; No effect in non-dependent rats	(Roberto et al., 2008)
	Alcohol-induced anxiety	Increased % time spent in open arms in plus-maze in ethanol-injected rats only	(Roberto et al., 2008)
Pregabalin	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Stopponi et al., 2012)
	Operant self-administration	Decreased operant self-administration of alcohol; No effect on operant responding for food	(Stopponi et al., 2012)
	Stress-induced reinstatement of alcohol-seeking behavior	Inhibited reinstatement	(Stopponi et al., 2012)
	Cue-induced reinstatement of alcohols-seeking behavior	Diminished cue-induced reinstatement	(Stopponi et al., 2012)
Baclofen	Alcohol withdrawal	Decrease in total score of intensity of ethanol withdrawal in dependent rats	(Colombo et al., 2000)
		Reduced withdrawal signs in ethanol-withdrawn rats	(Knapp et al., 2007b)

Medication	Model	Effect	References
	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Colombo et al., 2000)
	Scheduled high alcohol consumption	Decreased alcohol intake	(Tanchuck et al., 2011)
	Operant self-administration	No effect	(Tanchuck et al., 2011)
		Decreased operant self-administration of alcohol in dependent and non-dependent rats	(Walker and Koob, 2007)
		Decreased alcohol-reinforced responding	(Besheer et al., 2004)
	Alcohol-induced locomotion	Suppressed alcohol-induced locomotion	(Besheer et al., 2004; Broadbent and Harless, 1999; Chester and Cunningham, 1999)
	Alcohol deprivation effect	Diminished alcohol deprivation effect	(Colombo et al., 2003)
	Cue-induced reinstatement of alcohol-seeking behavior	Diminished cue-induced reinstatement	(Maccioni et al., 2008)
Ivermectin	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Asatryan et al., 2014; Yardley et al., 2012; Yardley et al., 2014)
	Intermittent limited access	Decreased alcohol intake	(Yardley et al., 2012)
Minocycline	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Agrawal et al., 2011)
Ibudilast	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Bell et al., 2013)
Varenicline	Operant self-administration	Decreased operant self-administration of alcohol	(Steensland et al., 2007; Wouda et al., 2011)
	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Steensland et al., 2007)
	Intermittent access two-bottle choice	Decreased alcohol intake	(Steensland et al., 2007)
	Cue-induced reinstatement of alcohol-seeking behavior	Diminished cue-induced reinstatement	(Wouda et al., 2011)
Mifepristone	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Koenig and Olive, 2004)
	Alcohol withdrawal	Reduced withdrawal signs	(Jacquot et al., 2008; Sharrett-Field et al., 2013)
	Operant self-administration	Decreased operant self-administration of alcohol in dependent rats	(Vendruscolo et al., 2012)
	Stress-induced reinstatement of alcohol-seeking behavior	Diminished stress-induced reinstatement	(Simms et al., 2012)
Oxytocin	Alcohol withdrawal	Reduced withdrawal signs	(Szabo et al., 1987)
	Operant self-administration	Decreased preference for alcohol relative to sucrose	(McGregor and Bowen, 2012)
Memantine	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Piasecki et al., 1998)
	Operant self-administration	No effect	(Piasecki et al., 1998)
		Decreased operant self-administration of alcohol	(Sabino et al., 2013)

Medication	Model	Effect	References
	Alcohol withdrawal	Reduced withdrawal signs	(Lukoyanov and Paula-Barbosa, 2001)
	Alcohol deprivation effect	Diminished alcohol deprivation effect	(Holter et al., 1996)
Pioglitazone	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Stopponi et al., 2011)
	Operant self-administration	Decreased operant self-administration of alcohol	(Stopponi et al., 2011)
	Stress-induced reinstatement of alcohol-seeking behavior	Diminished stress-induced reinstatement	(Stopponi et al., 2011)
	Cue-induced reinstatement of alcohol-seeking behavior	No effect	(Stopponi et al., 2011)
	Alcohol withdrawal	Reduced withdrawal signs	(Stopponi et al., 2011)
Mecamylamine	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Farook et al., 2009)
	Alcohol-induced dopamine release	Prevented alcohol-induced dopamine release	(Blomqvist et al., 1997; Ericson et al., 1998; Larsson et al., 2002)
	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Ericson et al., 1998; Ford et al., 2009; Le et al., 2000)
	Alcohol-induced locomotion	Suppressed alcohol-induced locomotion	(Bhutada et al., 2010; Blomqvist et al., 1992; Kamens and Phillips, 2008; Larsson et al., 2002)
	Conditioned place preference (CPP)	Prevented development, expression, and reinstatement of ethanol-induced CPP	(Bhutada et al., 2012)
	Stress-induced reinstatement of CPP	Blocked stress-induced reinstatement of ethanol-induced CPP	(Bhutada et al., 2012)
	Operant self-administration	Decreased operant self-administration of alcohol	(Ford et al., 2008; Kuzmin et al., 2009; Nadal et al., 1998)
	Alcohol deprivation effect	Diminished alcohol deprivation effect	(Kuzmin et al., 2009)
	Drinking in the dark	Decreased alcohol intake	(Hendrickson et al., 2009)
Prazosin	Intermittent access two-bottle choice	Decreased alcohol intake	(Skelly and Weiner, 2014)
	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Froehlich et al., 2013; Rasmussen et al., 2009)
	Operant self-administration	Decreased operant self-administration of alcohol	(Verplaetse et al., 2012)
	Stress-induced reinstatement of alcohol-seeking behavior	Diminished stress-induced reinstatement	(Le et al., 2011)
Olanzapine	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Ingman and Korpi, 2006)
	Alcohol withdrawal	Reduced some withdrawal signs	(Unsalan et al., 2008)
Doxazosin	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(O'Neil et al., 2013)
Rimonabant	Limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Arnone et al., 1997; Colombo et al., 1998;

Medication	Model	Effect	References
			Dyr et al., 2008; Gessa et al., 2004)
	Operant self-administration	Decreased operant self-administration of alcohol	(Cippitelli et al., 2005; Economidou et al., 2005; Freeland et al., 2001; Maccioni et al., 2009)
		Decreased extinction responding	(Colombo et al., 2004)
	Stress-induced reinstatement of alcohol-seeking behavior	No effect	(Economidou et al., 2005)
	Cue-induced reinstatement of alcohol-seeking behavior	Diminished cue-induced reinstatement	(Cippitelli et al., 2005; Economidou et al., 2005)
	Alcohol deprivation effect	Diminished alcohol deprivation effect	(Gessa et al., 2004; Serra et al., 2002)
	24-h access two-bottle choice voluntary intake	Decreased alcohol intake	(Gessa et al., 2004; Lallemand et al., 2001)

Table 3

Effect of drugs on human laboratory models of AUD.

Medication	Model	Population	Effect	References
Naltrexone	Self-administration in a naturalistic setting	AD	Decreased number of drinks consumed	(Drobes et al., 2003)
		Social drinkers	No effect	(Drobes et al., 2003)
		Non-treatment seeking AD	No effect	(Anton et al., 2004a; Krishnan-Sarin et al., 2007; O'Malley et al., 2002)
		Heavy beer drinkers	No effect on number of drinking days or amount of drinks per drinking days	(Davidson et al., 1999)
	Self-administration alcohol in a bar-lab setting	AD	Decreased number of drinks consumed (priming dose)	(Drobes et al., 2003)
		Social drinkers	No effect (priming dose)	(Drobes et al., 2003)
		Non-treatment seeking AD	Decreased number of drinks consumed (delayed access group; priming dose); No effect on immediate access group	(Anton et al., 2004a)
		Heavy beer drinkers	Decreased number of beers consumed and subjective positive affect; No effect on subjective negative affect	(Davidson et al., 1999)
	Alcohol self-administration following priming drink	Non-treatment seeking AD	Decreased number drinks consumed in FH+ only	(Krishnan-Sarin et al., 2007)
		Non-treatment seeking AD	Decreased number of drinks consumed	(O'Malley et al., 2002)
	Alcohol-induced craving	AD	Decreased craving	(Drobes et al., 2004)
		Non-treatment seeking AD	No effect during delayed access	(Anton et al., 2004a)
		Non-treatment seeking AD	Decreased craving during ad lib drinking period; No effect during the priming dose	(O'Malley et al., 2002)
		Heavy beer drinkers	Decreased craving before and after alcohol consumption	(Davidson et al., 1999)
	Alcohol-induced stimulation	AD	Decreased stimulation (in alcoholics only)	(Drobes et al., 2004)
		Non-treatment seeking AD	No effect during delayed access	(Anton et al., 2004a)
		Heavy beer drinkers	Decreased stimulation	(Davidson et al., 1999)
		Non AD male social high risk drinkers	Decreased stimulation	(King et al., 1997)
		Non AD male social low risk drinkers	No effect	(King et al., 1997)
		Non AD social drinking African Americans	No effect	(Plebani et al., 2011)
	Alcohol-induced sedation	AD	No effect	(Drobes et al., 2004)

Medication	Model	Population	Effect	References
		Non-treatment seeking AD	No effect during delayed access	(Anton et al., 2004a)
		Heavy beer drinkers	No effect	(Davidson et al., 1999)
		Non AD male social high and low risk drinkers	No effect	(King et al., 1997)
		Non AD social drinking African Americans	No effect	(Plebani et al., 2011)
		Moderate-heavy drinkers	Increased alcohol-induced sedation	(McCaul et al., 2000)
	Alcohol-induced intoxication	Non-treatment seeking AD	No effect during delayed access	(Anton et al., 2004a)
		Non AD social drinking African Americans	No effect	(Plebani et al., 2011)
		Moderate-heavy drinkers	No effect	(McCaul et al., 2000)
	Alcohol cue exposure	Non-treatment seeking AD	Naltrexone alone: Decreased alcohol cue-induced activation of the ventral striatum; No effect in self-reported craving	(Myrick et al., 2008)
			Naltrexone + Ondansetron: Decreased alcohol cue-induced activation of the ventral striatum and self-reported craving	(Myrick et al., 2008)
		Treatment seeking AD	Decreased percent reporting urge to drink; No effect on degree of urge to drink	(Monti et al., 1999)
	Experimenter administered alcohol (IV)	Non treatment seeking heavy drinkers of East Asian ethnicity	Compared to Asn40 homozygotes: Increased alcohol-induced sedation and subjective intoxication in Asp40 carriers; Decreased alcohol-induced craving in Asp40 carriers; No effect on alcohol-induced stimulation	(Ray et al., 2012)
	Subjective measures	Moderate-heavy drinkers	Post alcohol challenge session: Decreased baseline desire to drink, alcohol-induced desire to drink, best and like effects; Increased sick/ unpleasant effects	(McCaul et al., 2000)
Acamprosate	Challenge-induced craving: yohimbine and mCPP	Treatment seeking AD in early abstinence	No effect on PACS scores or anxiety during the challenge treatments	(Umhau et al., 2011)
	Alcohol cue exposure	Treatment seeking AD	No effect	(Hammarberg et al., 2009)
	Alcohol-induced craving	Treatment seeking AD	Prevented increase in short-DAQ score	(Hammarberg et al., 2009)
	Alcohol choice paradigm after priming dose	Treatment seeking AD	No effect on alcohol consumed, positive or negative subscale	(Hammarberg et al., 2009)
	Self-administration in a naturalistic setting	Treatment seeking AD	No effect on number of drinking days or HDD	(Hammarberg et al., 2009)
	Alcohol-induced stimulation	Heavy social drinkers	No effect	(Brasser et al., 2004)
	Alcohol-induced sedation	Heavy social drinkers	No effect	(Brasser et al., 2004)
	Alcohol-induced intoxication	Heavy social drinkers	No effect	(Brasser et al., 2004)
Nalmefene	Self-administration in a naturalistic setting	AD	Decreased number of drinks consumed	(Drobes et al., 2003)

Medication	Model	Population	Effect	References
		Social drinkers	No effect	(Drobes et al., 2003)
	Self-administration in a bar-lab alcohol setting	AD	Decreased number of drinks consumed (priming dose)	(Drobes et al., 2003)
		Social drinkers	No effect (priming dose)	(Drobes et al., 2003)
	Alcohol-induced craving	AD	Decreased craving	(Drobes et al., 2004)
	Alcohol-induced stimulation	AD	Decreased stimulation (in alcoholics only)	(Drobes et al., 2004)
	Alcohol-induced sedation	AD	No effect	(Drobes et al., 2004)
Ondansetron	Alcohol cue exposure	Non-treatment seeking AD	No effect on alcohol cue-induced activation of the ventral striatum or self-reported craving	(Myrick et al., 2008)
Topiramate	Self-administration in a naturalistic setting	Heavy drinkers	During titration period: Reduced % HDD and drinks/week	(Miranda Jr. et al., 2008)
	Alcohol cue exposure	Heavy drinkers	No effect	(Miranda Jr. et al., 2008)
	Subjective measures	Heavy drinkers	No effect on positive or negative affect post alcohol challenge session	(Miranda Jr. et al., 2008)
	Alcohol-induced sedation	Heavy drinkers	No effect	(Miranda Jr. et al., 2008)
	Alcohol-induced stimulation	Heavy drinkers	Decreased alcohol-induced stimulation	(Miranda Jr. et al., 2008)
	Alcohol-induced craving	Heavy drinkers	No effect	(Miranda Jr. et al., 2008)
Zonisamide	Alcohol self-administration following priming drink	Non treatment seeking risky drinkers	Decreased number of drinks consumed in second SA session only	(Sarid-Segal et al., 2009)
	Alcohol-induced craving	Non treatment seeking risky drinkers	Decreased alcohol-induced craving	(Sarid-Segal et al., 2009)
	Alcohol-induced stimulation	Non treatment seeking risky drinkers	No effect	(Sarid-Segal et al., 2009)
	Alcohol-induced sedation	Non treatment seeking risky drinkers	No effect	(Sarid-Segal et al., 2009)
Gabapentin	Self-administration in a bar-lab alcohol setting	Non-treatment seeking AD	No effect (after priming dose)	(Myrick et al., 2007)
	Self-administration in a naturalistic setting	Non-treatment seeking AD	No effect	(Myrick et al., 2007)
	Alcohol-induced craving	Non-treatment seeking AD	No effect on craving after initial drink and during free-choice drinking period	(Myrick et al., 2007)
		Non AD heavy drinkers	No effect	(Bisaga and Evans, 2006)
	Alcohol-induced stimulation	Non-treatment seeking AD	No effect (after priming dose)	(Myrick et al., 2007)
		Non AD heavy drinkers	No effect	(Bisaga and Evans, 2006)
	Alcohol-induced sedation	Non-treatment seeking AD	No effect (after priming dose)	(Myrick et al., 2007)
		Non AD heavy drinkers	No effect	(Bisaga and Evans, 2006)

Medication	Model	Population	Effect	References
	Alcohol-induced intoxication	Non-treatment seeking AD	No effect (after priming dose)	(Myrick et al., 2007)
	Alcohol cue exposure	Non-treatment seeking, cue-reactive AD	Decreased alcohol cue-induced craving	(Mason et al., 2009)
	Affective cue reactivity	Non-treatment seeking, cue-reactive AD	Decreased affectively-evoked craving	(Mason et al., 2009)
	Subjective measures	Non AD heavy drinkers	Post alcohol challenge session: No effect on BVAS measures, ratings of drink taste, CADSS scores or DEQ ratings	(Bisaga and Evans, 2006)
Baclofen	Self-administration in a naturalistic setting	Non-treatment seeking AD heavy drinkers	No effect	(Leggio et al., 2013)
	Self-administration in a bar-lab alcohol setting	Non-treatment seeking AD heavy drinkers	No statistically significant effect (robust medication effect d=0.76)	(Leggio et al., 2013)
	Alcohol cue exposure	Non-treatment seeking AD heavy drinkers	No effect	(Leggio et al., 2013)
	Alcohol-induced stimulation	Non-treatment seeking AD heavy drinkers	Increased stimulation during pre ad-libitum period	(Leggio et al., 2013)
		Non treatment seeking heavy social drinkers	No effect	(Evans and Bisaga, 2009)
	Alcohol-induced sedation	Non-treatment seeking AD heavy drinkers	Increased sedation during ad-libitum period	(Leggio et al., 2013)
		Non treatment seeking heavy social drinkers	No effect	(Evans and Bisaga, 2009)
	Alcohol-induced craving	Non treatment seeking heavy social drinkers	No effect	(Evans and Bisaga, 2009)
	Subjective measures	Non treatment seeking heavy social drinkers	Post alcohol challenge session: No effect on VAS score, DEQ score; Increased ratings of High on BVAS scale	(Evans and Bisaga, 2009)
Varenicline	Alcohol-induced craving	Non AD heavy drinkers and daily smokers	Decreased craving following priming drink; No effect during SA period	(McKee et al., 2009)
	Alcohol self-administration following priming drink	Non AD heavy drinkers and daily smokers	Decreased number of drinks consumed and subjective effects of alcohol; Increased likelihood of remaining abstinent during SA period	(McKee et al., 2009)
	Subjective measures	Moderate-to-heavy social drinkers	Increased ratings of dysphoria; Decreased ratings of drug liking	(Childs et al., 2012)
Memantine	Alcohol-induced craving	Non AD moderate drinkers	No effect (decreased craving prior to alcohol administration)	(Bisaga and Evans, 2004)
	Alcohol-induced stimulation	Non AD moderate drinkers	No effect	(Bisaga and Evans, 2004)
	Alcohol-induced sedation	Non AD moderate drinkers	No effect	(Bisaga and Evans, 2004)
	Subjective measures	Non AD moderate drinkers	Post alcohol challenge session: No effect on BVAS measures, POMS scores or performance tasks; Increased CADSS score; Decreased DEQ ratings of “drug strength”	(Bisaga and Evans, 2004)
	Alcohol cue exposure	AD males	Decreased alcohol cue-induced craving; No effect on craving prior to alcohol exposure	(Krupitsky et al., 2007)

Medication	Model	Population	Effect	References
Mecamylamine	Subjective measures	Healthy volunteers	Decreased DEQ and Alcohol Sensation Scale stimulant subscale scores	(Blomqvist et al., 2002)
	Alcohol-induced stimulation	Social drinkers	Decreased alcohol-induced stimulation	(Chi and de Wit, 2003; Young et al., 2005)
	Alcohol-induced sedation	Social drinkers	No effect	(Chi and de Wit, 2003)
	Subjective effects	Social drinkers	Decreased ratings of 'want more' and euphoric effects	(Chi and de Wit, 2003)
	Alcohol choice paradigm	Social drinkers	No effect	(Young et al., 2005)
Prazosin	Stress imagery exposure	Early abstinent, treatment seeking AD	Decreased stress-induced craving	(Fox et al., 2012)
	Alcohol cue exposure	Early abstinent, treatment seeking AD	Blocked increase in alcohol cue-induced craving	(Fox et al., 2012)
Olanzapine	Alcohol cue exposure	Heavy social drinkers	Decreased urge to drink and positive affect after exposure to water and alcohol; No effect on negative affect	(Hutchison et al., 2001)
			Compared to control medication (cyproheptadine, 4 mg): Decreased craving in DRD4-L patients; No effect in DRD4-S patients	(Hutchison et al., 2003)
		AD	In DRD4-L Patients: Decreased alcohol cue-induced craving and alcohol cue-induced increases in depression and anxiety	(Hutchison et al., 2006)
	Alcohol-induced intoxication	Heavy social drinkers	No effect	(Hutchison et al., 2001)
			Compared to control medication (cyproheptadine, 4 mg): No effect	(Hutchison et al., 2003)
	Alcohol-induced stimulation	Heavy social drinkers	No effect	(Hutchison et al., 2001)
			Compared to control medication (cyproheptadine, 4 mg): No effect	(Hutchison et al., 2003)
	Alcohol-induced sedation	Heavy social drinkers	Compared to control medication (cyproheptadine, 4 mg): No effect	(Hutchison et al., 2003)
	Alcohol-induced craving	Heavy social drinkers	In alcohol group only: Decreased alcohol-induced craving and subjective want	(Hutchison et al., 2001)
			Compared to control medication (cyproheptadine, 4 mg): Decreased alcohol-induced craving in DRD4-L patients; No effect in DRD4-S patients	(Hutchison et al., 2003)
	Subjective measures	Heavy social drinkers	Post alcohol challenge session: No effect on subjective liking	(Hutchison et al., 2001)
	Self-administration in a naturalistic setting	AD	In DRD4-L Patients: Decreased drinks per drinking day and total number of drinks; No effect on % days abstinent	(Hutchison et al., 2006)
Dutasteride	Alcohol-induced stimulation	Male light and heavy drinkers	No effect	(Covault et al.)
	Alcohol-induced sedation	Male light and heavy drinkers	Decreased alcohol-induced sedation	(Covault et al.)
	Self-administration in a naturalistic setting	Male light drinkers	No effect	(Covault et al.)

Medication	Model	Population	Effect	References
		Male heavy drinkers	Decreased HDD and total number of drinks consumed	(Covault et al.)
Rimonabant	Self-administration in a naturalistic setting	Heavy drinkers	No effect	(George et al., 2010)
	Alcohol self-administration following priming drink	Heavy drinkers	No effect	(George et al., 2010)

Table 4

Primary outcomes of clinical trials testing drugs for the treatment of AUD.

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
Disulfiram	0 days	119 weeks (12 week supervised medication, up to 52 week targeted medication, 67 week follow-up period); 100-200 mg q.d. or 2 × 400 mg twice a week	Compared to naltrexone (50 mg q.d.) and acamprosate (2 × 333 mg t.i.d. for people ≥ 60 kg body weight; 1332 mg for people < 60 kg body weight): Increased time to first HDD and time to first drink during the first 12 weeks	(Laaksonen et al., 2008)
	Men; abstinent 19 ± 5 days on average for DSF group; 20 ± 11 for TPM group	9 months/ 250 mg q.d.	Compared to TPM (50 mg t.i.d.): Increased days to first relapse; No effect on days of abstinence, discontinuation of treatment, or drop out rate; Decreased craving severity and GGT	(De Sousa et al., 2008)
Naltrexone	5 days	12 weeks/ 50 mg q.d.	Decreased drinks per drinking day; Increased time to first relapse, and % days abstinent	(Anton et al., 1999)
	AD or Alcohol abusers, 5-30 days abstinent	12 weeks/ 50 mg q.d.	No effect on time to first episode of heavy drinking	(Chick et al., 2000a)
	0 days	24 weeks/ 380 mg or 190 mg long-acting injectable naltrexone administered monthly	380 mg dose decreased event rate of HDD; Treatment effects were greater in subpopulation that were abstinent for 7 days prior to treatment	(Garbutt et al., 2005)
	5- 30 days (19.5 ± 9.4 days on average)	12 weeks/ 50 mg q.d.	No effect on time to first heavy drinking episode	(Gastpar et al., 2002)
	12-15 days	12 weeks/ 50 mg q.d.	Increased time to first relapse and time to first drink	(Kiefer et al., 2003)
	12-15 days	12 weeks/ 50 mg naltrexone q.d.+ 2 × 333 mg t.i.d.	Increased time to first relapse and time to first drink (compared to both placebo and acamprosate alone)	(Kiefer et al., 2003)
	Predominantly male, 5 days abstinent	12 months/ 50 mg q.d. for 12 months; 50 mg q.d. for 3 months + placebo for 9 months	No effect on time to relapse during the first 3 months, % drinking days over the 12 month period or number of drinks per drinking day over the 12 month period	(Krystal et al., 2001)
	3-21 days	12 weeks/ 50 mg q.d.	Compared to both placebo and acamprosate: No effect on number of days to first lapse, days to first relapse, cumulative days abstinent, or drinks per drinking day	(Morley et al., 2006)
	Males; 3-30 days abstinent (8 ± 5 days on average for NTX group; 9 ± 6 for placebo)	12 weeks/ 50 mg q.d.	Decreased relapse to drinking; No effect on maintenance of abstinence	(Morris et al., 2001)
	Non treatment seeking heavy drinkers (63% AD); 0 days abstinent	3 weeks/ 50 mg q.d. (in addition to a 1-week placebo lead-in)	Decreased % drinking days; No effect on drinks per day, drinks per drinking day, % HDD or any subjective effects of alcohol	(Tidey et al., 2008)

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
	4-21 days	16 weeks/ 50 mg b.i.d.	Increased % days abstinent; Decreased risk of HDD	(Anton et al., 2006)
	Males; 3-30 days abstinent	12 weeks/ 50 mg q.d.	Decreased relapse to heavy drinking	(Ahmadi and Ahmadi, 2002)
	14-28 days	12 weeks/ 50 mg q.d. (in addition to a 1 week placebo run-in and therapy every 4th week from week 12-24)	Decreased HDD	(Balldin et al., 2003)
	Non AD heavy drinkers; 0 days	6 weeks/ 25 mg q.d.; 50 mg q.d. (in addition to a one month post treatment follow-up)	Compared to pre-treatment measures: Decreased number of standard drinks consumed, HDD, and drinks per drinking days; increased number of days abstinent	(Bohn et al., 1994)
	5-30 days	12 weeks/ 50 mg q.d.	Decreased relapse to heavy drinking	(Guardia et al., 2002)
	0 days	12 weeks/ 50 mg q.d. (in addition to a 1 week placebo run-in and 20 week post treatment targeted medication)	Naltrexone + cognitive coping skills decreased relapse to heavy drinking	(Heinala et al., 2001)
	0 days	12 weeks/ 50 mg q.d.	Compared to placebo + treatment as usual and treatment as usual alone: No effect on % days drinking, average drinks per day, average drinks per drinking day, HDD, or time to first heavy drink	(Killeen et al., 2004)
	3 days	8 weeks/ 50 mg PO daily for 2 weeks, followed by a 2-week, no-medication wash out period, a 4-week 206 mg injection (single) period, and a 4-week follow-up period	Compared to placebo injection: Decreased % HDD during injection period; No effect on average drinks per drinking day during injection period; Decreased % HDD and average drinks per day during follow-up period	(Kranzler et al., 1998)
	7-51 days (11.7 day on average)	12 weeks/ 50 mg q.d.	Decreased relapse rate; Increased time to first relapse; No effect on reported side effects	(Latt et al., 2002)
	3 days	12 weeks/ 50 mg b.i.d. (in addition to a one week placebo lead-in)	Decreased number of heavy drinking days	(Monterosso et al., 2001)
Acamprosate	12-15 days	12 weeks/ 2 × 333 mg t.i.d.	Increased time to first relapse and time to first drink	(Kiefer et al., 2003)
	<10 days (must have reduced drinking to no more than 2 (F) or 3 (M) drinks in the 2-10 days pre randomization)	24 weeks/ 2 × 500 mg b.i.d.; 3 × 500 mg b.i.d.	No effect on % days abstinent	(Mason et al., 2006)
	3-21 days	12 weeks/ 2 × 333 mg t.i.d.	Compared to both placebo and NTX: No effect on number of days to first lapse, days to first relapse, cumulative days abstinent, or drinks per drinking day	(Morley et al., 2006)
	Predominantly male; 1 day abstinent	8 weeks/ 1998 mg for people ≥ 60 kg body weight or 1332 mg for people < 60 kg body weight (dosing schedule not specified)	No effect on time to first drink, time to relapse, or % days abstinent	(Namkoong et al., 2003)
	7-28 days (18 days on average)	12 months/ 1332 mg per day (4 × 333 mg per day); 1998 mg per day (6 × 333 mg per day) (in addition to a single-blind 6 month follow-up on placebo)	Dose dependently increased continuous abstinence at 6 months; No effect on	(Paille et al., 1995)

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
			continuous abstinence at 12 months	
	5 days	24 weeks/ 2 × 333 mg t.i.d. (in addition to a 12 week medication-free follow-up)	Increased abstinence rate, cumulative abstinence duration, period of continued abstinence	(Tempesta et al., 2000)
	4-21 days	16 weeks/ 2 × 500 mg t.i.d.	No effect on mean % days abstinent or time to first HDD	(Anton et al., 2006)
	5 days	360 days/ 2 × 333 mg t.i.d. for people ≥ 60 kg body weight; 1332 mg (2+1+1) for people < 60 kg body weight (in addition to a 360 day follow up period)	Increased cumulative abstinence duration; Decreased relapse rate through assessment day 270	(Besson et al., 1998)
	5 days	24 weeks/ 2 × 333 mg t.i.d.	No effect on continuous abstinence or cumulative abstinence duration	(Chick et al., 2000b)
	5 days	24 weeks/ 2 × 333 mg t.i.d. for people ≥ 60 kg body weight; 1332 mg (333 mg, 2+1+1) for people < 60 kg body weight (in addition to a medication free 6-month follow-up period)	Increased cumulative duration of abstinence, time to first relapse, % abstinent on assessment day 135	(Geerlings et al., 1997)
	0 days	180 days/ 2 × 333 mg t.i.d.	Increased cumulative abstinence duration	(Gual and Lehert, 2001)
	Within 48 h following hospitalization for alcohol withdrawal; 5-30 days abstinent	90 days; 1332 mg (333 mg, 2+1+1)	Decreased GGT	(Lhuintre et al., 1990)
	14 day inpatient detoxification program	90 days/ 1332 mg (333 mg, 2+1+1); 2 × 333 mg t.i.d.	Increased cumulative abstinence duration; Decreased relapse rate	(Pelc et al., 1997)
	5 days	24 weeks/ 2 × 333 mg t.i.d. for people ≥ 60 kg body weight; 1332 mg (333 mg, 2+1+1) for people < 60 kg body weight (in addition to a 24 week follow-up period)	Increased abstinence at month 1, 6, and 12; No effect on abstinence at month 3 and 9	(Poldrugo, 1997)
	5 days	360 days/ 2 × 333 mg t.i.d. for people > 60 kg body weight; 1332 mg (333 mg, 2+1+1) for people ≤ 60 kg body weight (in addition to a 360 day follow-up period)	Increased time to first treatment failure	(Whitworth et al., 1996)
Nalmefene	3 days	12 weeks/ 2 × 2.5 mg q.d.; 2 × 10 mg q.d.; 2 × 20 mg q.d.	No effect of treatment on number of HDD per month	(Anton et al., 2004b)
	0 days	24 weeks/ up to 18 mg per day prn (in addition to a 1-2 week screening period and 4-week double-blind run-out period)	Decreased HDD; No effect on monthly total alcohol consumption	(Gual et al., 2013)
	0 days	24 weeks/ up to 18 mg per day prn (in addition to a 1-2 week screening period and 4-week double-blind run-out period)	Decreased number of HDD and total alcohol consumption	(Mann et al., 2013)
	2 weeks on average	12 weeks/ 10 mg b.i.d.; 40 mg b.i.d. (in addition to a 2-week single-blind placebo period)	Decreased relapse to heavy drinking; No effect on drinks per drinking day or % days abstinent	(Mason et al.)
	0 days	12 weeks/ 20 mg b.i.d; 5 mg b.i.d. (in addition to a 2-week single-blind placebo lead-in)	40 mg dose compared to 10 mg and placebo: Decreased relapse to heavy drinking; Increased change mean abstinence days/week from single-blind placebo phase to treatment phase	(Mason et al., 1994)
			Both doses compared to placebo: Decreased change in number of drinks per drinking	(Mason et al., 1994)

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
			day from single-blind placebo phase to treatment phase; No effect on craving or retention in treatment	
Ondansetron	0 days	11 weeks/ 1 μg/kg b.i.d.; 4 μg/kg b.i.d.; 16 μg/kg b.i.d. (in addition to a 1 week placebo lead-in)	All doses in early onset alcoholics: Decreased drinks per day and drinks per drinking day	(Johnson et al., 2000)
			4 μg/kg b.i.d. in early onset alcoholics: Increased % days abstinent and total day abstinent per study week	(Johnson et al., 2000)
	0 days	8 weeks/ 4 μg/kg/ml b.i.d.	In early onset alcoholics: Decreased drinks per day and drinks per drinking day compared to late onset alcoholics; No effect on % days abstinent or number of HDD between groups	(Kranzler et al., 2003)
	Non severely AD males; 0 days	6 weeks/ 0.25 mg b.i.d.; 2 mg b.i.d. (in addition to a 2 week baseline period)	In all patients: No effects on number of standard drinks per drinking day between baseline and treatment	(Sellers et al., 1994)
			In light drinkers: Decreased number of drinks per drinking day compared to baseline	(Sellers et al., 1994)
Topiramate	0 days	12 weeks/ escalating dose of 25-300 mg per day (weeks 8-12 100 mg + 2 × 25 mg b.i.d.)	Decreased drinks per day, drinks per drinking day, % HDD and plasma GGT; Increased % days abstinent	(Johnson et al., 2003)
	0 days	14 weeks/ 300 mg per day (100 q.a.m. + 2 × 100 mg q.p.m.)	Decreased % HDD	(Johnson et al., 2007)
	Men; abstinent 19 ± 5 days on average for DSF group; 20 ± 11 for TPM group	9 months/ 50 mg t.i.d.	Compared to DSF (250 mg q.d.): Decreased days to first relapse; No effect on days of abstinence, discontinuation of treatment, or drop out rate; Increased craving severity and GGT	(De Sousa et al., 2008)
Zonisamide	0 days	12 weeks/ 100-500 mg q.d. (increased 100 mg every 2 weeks for 8 weeks)	Medications × Treatment week interaction: Decreased HDD per week and drinks per week; No effect on abstinent days per week	(Arias et al., 2010)
	Detoxified or present mild symptoms of abstinence (scores on the CIWA for Alcohol-Revised of <6)	12 weeks/ 50-300 mg per day (flexible-dose schedule with average of 220 mg per day ± 50)	Compared to baseline: Decreased number of drinks per week, craving severity and GGT levels	(Rubio et al., 2010)
Levetiracetam	Heavy social drinkers; 0 days abstinent	2, 14 day treatment periods (one cycle with placebo and the other with low or high dose Levetiracetam)/ 250-500 g b.i.d.; 500-1000 g b.i.d. (in addition to a 3-day drug taper and 7 day washout period)	No effect on number of drinks consumed	(Mitchell et al., 2012a)
	0 days	6 days/ fixed dose schedule (days: 1-3: 1000-0-1000 mg; 4: 500-0-1000 mg; 5: 500-0-500 mg; 6: 0-0-500 mg)	No effect on dose of diazepam as a rescue medication or the severity of withdrawal symptoms	(Richter et al., 2010)

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
	0 days	10 weeks/ titrated up to 1000 mg b.i.d. over the first 3 weeks to a total of 2000 mg (in addition to 1 week of screening and 2 weeks taper)	Decreased standard drinks per day	(Sarid-Segal et al., 2008)
	0 days	16 weeks/ titrated for the first 4 weeks from 500 to 2000 mg/day week 5-14 followed by a 2 week taper (in addition to a follow-up interview week 19)	No effect on percent HDD and percent subjects with no HDD	(Fertig et al., 2012)
Gabapentin	3 days	12 weeks/ 2 × 150 mg t.i.d.; 2 × 300 mg t.i.d.	Dose dependently increased rates of complete abstinence and no heavy drinking	(Mason et al., 2014)
	Patients with moderate-severe AWS; 0 days	2 days/ 400 mg q.i.d. (data on safety and tolerability continued to be measured until day 7)	No effect on amount of CLO required in the first 24 hours (no psychosocial component specified)	(Bonnet et al., 2003)
Pregabalin	5-10 days	16 weeks/ flexible dose of 150-450 mg per day (mean 262.5 mg per day ± 117.9)	Half (n=10) were completely abstinent for duration of the study; One quarter (n=5) relapsed	(Martinotti et al., 2008)
	0 days	14 days; up to 450 mg per day	Compared to both tiapride and lorazepam: Increased abstinence; Decreased CIWA-Ar scores on items regarding headache and orientation Compared to tiapride only: Increased time to dropout	(Martinotti et al., 2010)
Baclofen	12-24 h	30 days/ 10 mg t.i.d.	Increased % abstinent and number of cumulative abstinent days	(Addolorato et al., 2002)
	3 days	12 weeks/ 10 mg t.i.d.; 20 mg t.i.d.	Compared to baseline: Decreased number of drinks per day	(Addolorato et al., 2011)
	AD with liver cirrhosis, 3-4 days abstinent	12 weeks/ 10 mg t.i.d.	Increased % abstinent and cumulative abstinent duration	(Addolorato et al., 2007)
	3 days	12 weeks/ 30 mg per day (dosing schedule not specified)	No effect on % HDD	(Garbutt et al., 2010)
	3 days	12 weeks/ 10 mg t.i.d.	Compared to baseline measures: Decreased number of drinks per drinking day and HDD; Increased number of abstinent days	(Flannery et al., 2004)
Varenicline	0 days	13 weeks/ 1 mg b.i.d.	Decreased weekly % HDD	(Litten et al., 2013)
	Heavy drinking smokers seeking treatment for smoking only; 0 days abstinent	12 weeks/ 1 mg b.i.d. (in addition to 2 follow-up visits at week 14 and 16)	Decreased drinks and cigarettes per week from weeks 3-11; No effect on craving per week	(Mitchell et al., 2012c)
	0 days	12 weeks/ 1 mg b.i.d.	No effect on alcohol use	(Plebani et al., 2013)
Oxytocin	0 days	3 days/ 24 IU/dose b.i.d.	Required less total lorazepam to complete detoxification	(Pedersen et al., 2013)
Memantine	0 days	12 weeks/ 20 mg b.i.d. (in addition to a 2 week placebo lead-in and a 2 week placebo lead-out)	Increased % HDD; Decreased % days abstinent; No effect on average drinks per day or drinks per drinking day	(Evans et al., 2007)

Medication	Time Abstinent	Treatment Duration/Target Dose	Primary Outcome	References
Prazosin	0 days	6 weeks/ 4 mg q.a.m. + 4 mg q.p.m. + 8 mg q.h.s.	No effect on mean drinks per week or mean drinking days per week; Decreased drinking days per week in the final 3 weeks	(Simpson et al., 2009)
			In men only in the final 3 weeks: Decreased drinking days per week, average total number of drinking days, drinks per week, average number of total drinks	(Simpson et al., 2009)
Doxazosin	0 days	10 weeks/ titrated during the first 4 weeks up to 16 mg per day and a 1-week downward titration at week 10 (in addition to a follow-up week 12)	In AD patients with high family history density of alcoholism (FHDA): Reduced drinks per week and HDD per week In AD patients with low FHDA: Increased drinks per week, No effect on HDD per week	(Kenna et al., 2015)
Rimonabant	7-28 days	12 weeks/ 20 mg q.d.	No effect on time to first drink or time to first HDD	(Soyka et al., 2008)

Note: All results are compared to placebo unless otherwise stated; Population was AD males and females unless otherwise stated. All treatment included a psychosocial/medical management component.