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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 the 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, novel therapeutics, valley of death.

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INTRODUCTION

Alcohol use disorder (AUD) has a major public health impact in the USA affecting nearly 18 million people and causing over 100,000 deaths annually (Harwood, 2000; Grant *et al.*, 2004; Bouchery *et al.*, 2011). Worldwide, alcohol abuse and misuse is the third leading risk factor for premature death and disabilities and is responsible for 4% of all deaths (World Health Organization, 2011). Although treatments for AUD have improved in the 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 this disorder (Edlund *et al.*, 2012). As such, development of effective treatments for AUD represents an important public health goal (Heilig and Egli, 2006; Johnson *et al.*, 2007; Steensland *et al.*, 2007; Johnson, 2010; Bouchery *et al.*, 2011).

Litten *et al.* (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. In order to achieve these goals, Litten *et al.* 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 a review, see Gilpin and Koob (2008), Koob and Volkow (2010), Soderpalm and Ericson (2013), Spanagel (2009), and 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 a review, see Gonzales *et al.* (2004) and 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 in the succeeding discussions do indirectly affect DA neurotransmission.

Ligand-gated ion channels are widely held to play an important role in ethanol-induced behaviors (for a review, see Dopico and Lovinger (2009), Harris *et al.* (1995), and 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 receptors (5-HT_3Rs), gamma-aminobutyric acid type A receptors (GABAARs), 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; Mitchell *et al.*, 2012c; Litten *et al.*, 2013), 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 a 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 a review, see Dodd *et al.* (2000), Moykkynen and Korpi (2012), and Tsai and Coyle (1998)). Acamprosate, one of the three FDA-approved medications for AUD, is an NMDAR antagonist and has been shown to prevent relapse in alcohol-dependent (AD) individuals acting as an anti-craving medication (for a review, see Littleton (1995) and 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 trial 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 a 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 wild-type mice using multiple models of alcohol intake but to a lesser extent in P2X4R knock-out mice (Yardley *et al.*, 2012; Wyatt *et al.*, 2014).

Another well-known target of alcohol in the CNS is the endogenous opioid system (for a review, see Gianoulakis *et al.* (1996) and Herz (1997)). There are three 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 a 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 USA but has already received European marketing authorization (for a review, see Paille and Martini (2014)).

Novel targets are being actively explored. One such novel target is the ghrelin receptor. Ghrelin is 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 a 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), and 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 a review, see Ciccocioppo *et al.* (2009), Hungund and Yaragudri (2009), Pacher *et al.* (2006), and 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; Gessa *et al.*, 2004; Cippitelli *et al.*, 2005), yet clinical studies conducted thus far do not support the use of rimonabant for treatment of AUD (Soyka *et al.*, 2008; George *et al.*, 2010).

There are a number of stress-related neuropeptides that have been implicated as important targets for alcohol such as NPY, corticotropin-releasing factor, and nociceptin/orphanin FQ (N/OFQ) signaling (for a review, see Ciccocioppo *et al.* (2009) and 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 a review, see Thiele and Badia-Elder (2003), Thorsell (2007), and 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 a 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 a review, see Heilig and Egli (2006)).

Neurotrophic factor signaling represents an important target for medications development for AUD (for a review, see Janak *et al.* (2006) and Russo *et al.* (2009)). Multiple neurotrophins such as brain-derived neurotrophic factor, neurotrophin 3, and neurotrophin 4 have been implicated in drug addiction (for a 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 regard to its role in intoxication, negative affect, and craving (for a review, see Coller and Hutchison (2012) and Mayfield *et al.* (2013)). Both human and animal studies provide support for the role of alcohol-induced neuroimmune signaling (for a 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 a 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 being important in alcohol's action (Johnson, 2008). Others, such as P2X4Rs, ghrelin receptors (Vadnie *et al.*, 2014), the EC system (Johnson, 2008), and neuroimmune signaling (for a review, see Coller and Hutchison (2012) and Mayfield *et al.* (2013)) have been clinically investigated as possible targets of alcohol action more recently. These novel targets have become 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 three 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

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[a]
Nalmefene	Opioid dependence	Opioid receptor antagonist
Ondansetron	Antiemetic	5-HT_3 receptor antagonist
LY686017	Antiemetic[b]	Neurokinin-1 antagonist
Topiramate	Anticonvulsant	Glutamate and $GABA_A$ receptor modulator
Zonisamide	Anticonvulsant	Sodium channel blocker and calcium channel modulator[a]
Levetiracetam	Anticonvulsant	Interaction with synaptic vesicle protein SV2A[a]
Gabapentin	Analgesic/anticonvulsant	Modulation of GABA synthesis and glutamate synthesis[a]
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[b]	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; post-synaptic alpha-adrenoceptors blocker[a]
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[a]
Rimonabant	Obesity[b]	CB1 endocannabinoid antagonist

Note: Not all ongoing/ completed trials on medications for the treatment of AUD are registered to clinicaltrials.gov. [a]Current beliefs presented as the exact mechanism remains unknown. [b]Not FDA -approved for this indication.

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 concentrations (BACs; for a review, see Crabbe *et al.* (2011) and 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 a review, see Becker and Ron (2014) and 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 a review, see Cunningham *et al.* (2000) and 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 AD and non-AD rats (Roberto *et al.*, 2008) and high-preference and

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 with 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; Walker and Koob, 2008)
	Fluid deprivation + limited access two-bottle choice voluntary intake	Decreased alcohol intake	(Hubbell *et al.*, 1991)

(Continues)

Table 2 (Continued)

Medication	*Model*	*Effect*	*References*
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)
	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)

(Continues)

Table 2 (Continued)

Medication	*Model*	*Effect*	*References*
	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 Decreased operant self-administration of alcohol	(Piasecki *et al.*, 1998) (Sabino *et al.*, 2013)
	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)

(Continues)

Table 2 (Continued)

Medication	*Model*	*Effect*	*References*
	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)
			(Ford *et al.*, 2008; Kuzmin *et al.*, 2009;
	Operant self-administration	Decreased operant self-administration of alcohol	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; 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)

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 a 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 (Table 3), but no animal studies have been published for this indication thus far (Table 2). In other cases, such as nalmefene and varenicline, there are relatively fewer reported preclinical studies (Table 2) as compared with clinical studies (Table 3 and 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 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 limitations 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 in the succeeding discussions).

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 with 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 two 1-h self-administration (SA) periods having the option of consuming up to four alcoholic drinks (0.015 g/dl each) or receiving a monetary compensation of $3 per beverage not consumed (O'Malley *et al.*, 2007). Typically, the 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 and 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 min 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-min trials (Monti *et al.*, 1987; Monti *et al.*, 2001). After every 3 min of exposure, craving for alcohol is assessed. Given the number of studies that

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 number of drinks per drinking day	(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 accessgroup; 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 libitum* 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)
		Non-treament-seeking AD	No effect during delayed access	(Anton *et al.*, 2004a)

(Continues)

Table 3 (Continued)

Medication	*Model*	*Population*	*Effect*	*References*
		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 measure	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)

(Continues)

Table 3 (Continued)

Medication	*Model*	*Population*	*Effect*	*References*
Nalmefene	Self-administration in a naturalistic setting	AD	Decreased number of drinks consumed	(Drobes *et al.*, 2003)
		Social drinkers	No effect	(Drobes *et al.*, 2003)
	Self-administration 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)
	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 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)

(Continues)

Table 3 (Continued)

Medication	*Model*	*Population*	*Effect*	*References*
	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)
	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 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)

(Continues)

Table 3 (Continued)

Medication	*Model*	*Population*	*Effect*	*References*
	Subjective measures	Moderate-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)
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 with control medication (cyproheptadine, 4 mg): No effect	(Hutchison *et al.*, 2003)
	Alcohol-induced stimulation	Heavy social drinkers	No effect	(Hutchison *et al.*, 2001)
	Alcohol-induced sedation	Heavy social drinkers	Compared with control medication (cyproheptadine, 4 mg): No effect	(Hutchison *et al.*, 2003)

(Continues)

Table 3 (Continued)

Medication	*Model*	*Population*	*Effect*	*References*
	Alcohol-induced craving	Heavy social drinkers	In alcohol group only: Decreased alcohol-induced craving and subjective want	(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.*, 2003)
Dutasteride	Alcohol-induced stimulation	Male light and heavy drinkers	No effect	(Covault *et al.*, 2014)
	Alcohol-induced sedation	Male light and heavy drinkers	Decreased alcohol-induced sedation	(Covault *et al.*, 2014)
	Self-administration in a naturalistic setting	Male light drinkers	No effect	(Covault *et al.*, 2014)
		Male heavy drinkers	Decreased HDD and total number of drinks consumed	(Covault *et al.*, 2014)
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)

suggest an association between stress and alcohol use, stress induction in the laboratory has been used to understand the relationship between stress-induced 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 *et al.* (2011) highlights the importance of brain imaging in bridging preclinical and clinical CNS drug discovery. Specifically, they emphasize that this technique may be able to help better identify pharmacodynamic 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 *et al.* (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, non-treatment-seeking AD individuals (O'Malley *et al.*, 2002; Anton *et al.*, 2004a) 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

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 with 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 with TPM (50 mg t.i.d.): Increased days to first relapse; No effect on days abstinent, discontinuation of treatment, or dropout 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 X 333 mg acamprosate t.i.d.	Increased time to first relapse and time to first drink (compared with 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 with 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)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
	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)
	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 with pre-treatment measures: Decreased number of standard drinks consumed, HDD, and drinks per drinking day; 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 with 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 with 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 days 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)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
	3 days	12 weeks/ 50 mg b.i.d. (in addition to a one week placebo lead-in)	Decreased number of HDD	(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 with 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 x 333 mg per day); 1998 mg per day (6 x 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 continuous abstinence at 12 months	(Paille *et al.*, 1995)
	5 days	24 weeks/ 2 X 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 X 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 X 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 X 333 mg t.i.d.	No effect on continuous abstinence or cumulative abstinence duration	(Chick *et al.*, 2000b)
	5 days	24 weeks/ 2 X 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 abstinence duration, time to first relapse, % abstinent on assessment day 135	(Geerlings *et al.*, 1997)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
	0 days	180 days/ 2 X 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 X 333 mg t.i.d.	Increased cumulative abstinence duration; Decreased relapse rate	(Pelc *et al.*, 1997)
	5 days	24 weeks/ 2 X 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 months 1, 6, and 12; No effect on abstinence at months 3 and 9	(Poldrugo, 1997)
	5 days	360 days/ 2 X 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 weeks 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.*, 1999)
	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 with 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 with placebo: Decreased change in number of drinks per drinking day from single-blind placebo phase	(Mason *et al.*, 1994)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
			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 days 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 with 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 with 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 with DSF (250 mg q.d.): Decreased days to first relapse; No effect on days of abstinence, discontinuation of treatment, or dropout 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 with baseline: Decreased number of drinks per week, craving severity and GGT levels	(Rubio *et al.*, 2010)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
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)
	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 weeks 5–14 followed by a 2-week taper (in addition to a follow-up interview week 19)	No effect on % HDD or % subjects with no HDD	(Fertig *et al.*, 2012)
Gabapentin	3 days	12 weeks/ 2 X 150 mg t.i.d.; 2 X 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 with both tiapride and lorazepam: Increased abstinence; Decreased CIWA-Ar scores on items regarding headache and orientation Compared with 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 with baseline: Decreased number of drinks per day	(Addolorato *et al.*, 2011)

(Continues)

Table 4. (Continued)

Medication	Time abstinent	Treatment duration/target dose	Primary outcome	References
	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 with 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 two follow-up visits at weeks 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)
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	(Kenna *et al.*, 2015)
			In AD patients with low FHDA: Increased drinks per week, No effect on HDD per week, time to first drink or time to first HDD	
Rimonabant	7–28 days	12 weeks/20 mg q.d.		(Soyka *et al.*, 2008)

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

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 with 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 with 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, later in the 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. 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.

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, and so on (Leon *et al.*, 2011). These studies can then be used to establish standardized procedures in regard to environment, treatment goals, and drinking severity of the population as well as sample size. Limitations notwithstanding, 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 III 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 with 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 and clinical trial outcomes. Similarly, it is important to recognize there are differences not only between but also 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 *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 also 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 with 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 *et al.* (2008) found that administration of placebo medication in the COMBINE study leads to a significant 'placebo effect', 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 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 three or more reported clinical trials, as either positive or negative (Fig. 1; Supporting Information 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, there have been more clinical trials, compared with human laboratory studies, conducted on all drugs included in Fig. 1 and Supporting Information 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. The

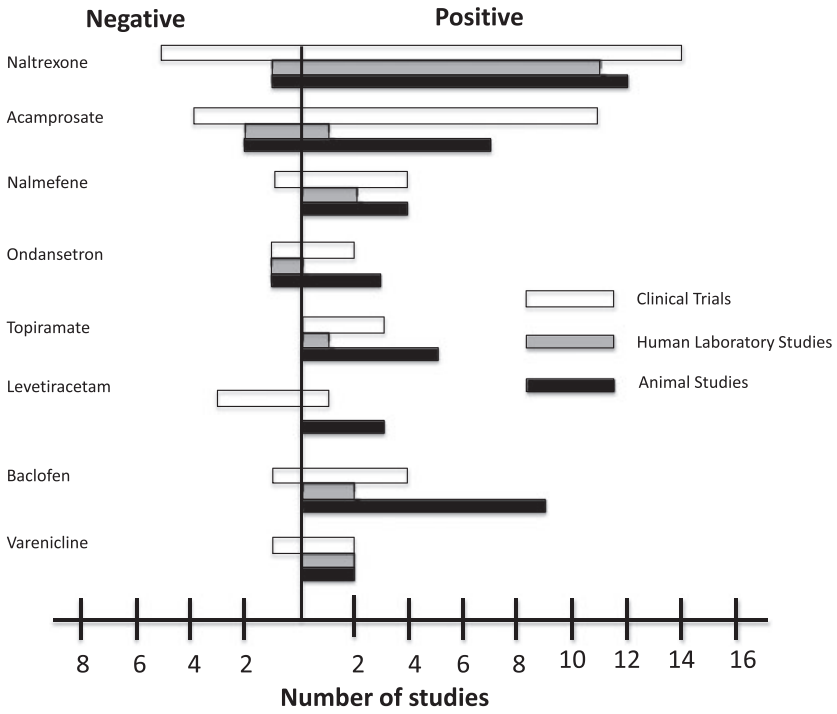

Figure 1 Translational research outcomes figure with depicting the number of positive (right side) and negative (left side) outcomes for each clinical trial (white bars), human laboratory study (gray bar) and animal study (black bar). Note: Only pharmacotherapies with three or more reported clinical trials were included

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 (Editorial, 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 DA 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 corticotropin-releasing factor, P2X4Rs, 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 paper 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 (Fig. 1; Supporting Information 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 healthcare context, only a very small minority of patients ever receive a medication for the treatment of AUD (Bates, 2005) and 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.

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Conflict of Interest

Lara Ray is a paid consultant for GSK and has received medication from Pfizer and Medicinova.

Authors Contribution

MMY wrote the first draft of the manuscript. LAR provided critical revisions of the manuscript. Both authors critically reviewed content and approved final version for publication.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 Translational research outcomes table.