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Preclinical Medication Development: New Targets and New Drugs

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Introduction

According to the 2013 National Survey on Drug Use and Health reported by the Substance Abuse and Mental Health Services Administration (SAMHSA) 18 million individuals in the United States aged 12 or older were reported as needing treatment for an alcohol use problem (SAMHSA, 2013). This introduction to a virtual issue for the *Alcoholism: Clinical and Experimental Research* website discusses six recent papers describing new possible treatments for alcohol use disorders and their consequences. This virtual introduction is not a comprehensive review of the current monumental efforts to find viable treatments for alcohol use disorders, but rather a focused review of these recent papers and the issues about preclinical drug development that they raise. Gubner et al. (2014) examines whether varenicline mediates ethanol conditioned place preference and locomotor sensitization, two animal models of aspects of alcohol use disorders. The role of purinergic P2X4 receptors, the neuropeptides orexin and melanocortin, and peroxisome proliferator-activated receptors (PPARs) in models of ethanol intake are investigated by Franklin et al. (2015), Olney et al. (2015), Navarro et al. (2015), and Blednov et al. (2015), respectively. Drew et al. (2015) further studies PPARs' role in neuroinflammation in a model of fetal alcohol spectrum disorders (FASD). Together, these papers prompt critical questions concerning how preclinical research may lead to better clinical outcomes for those suffering from alcohol use disorders.

Treating Alcohol Use Disorders

Currently, four treatments are approved by the FDA to treat alcohol use disorders; oral and intramuscular naltrexone antagonize μ-opioid receptors, acamprosate partially agonizes NMDA-mediated glutamatergic signaling, and disulfiram inhibits aldehyde dehydrogenase resulting in accumulation of acetaldehyde and subsequent nausea, tachycardia, and other unpleasant symptoms. All of these drugs have a treatment goal of abstinence and may present with serious side effects that range from nausea and illness to seizures. Nalmefene, which works through the opioid receptor system, is also approved in Europe to reduce drinking (Connor et al., 2015). However, these drug treatments often exhibit low success rates and their effectiveness can be dependent on self-help seeking. Moos and Moos (2006)

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followed a cohort of individuals after they first sought help for drinking problems. At each follow-up they split participants into those who had continued to seek treatment and those who had not. At the 3 year follow-up, 43% of the individuals who did not continue to seek help and 37.6% of the individuals who continued to seek help were no longer in remission. At the 16 year follow-up, 60.5% of the individuals who did not continue to seek help and 42.9% of the individuals who continued to seek help had relapsed. Although treatment-seeking was not limited to pharmacological treatment, the results of Moos and Moos (2006) indicate that current routes of treatment are not effective for all individuals suffering from alcohol use disorders even when they continue seeking help.

Other factors further complicate the pharmacological treatment of alcohol use disorders. Only 9% of individuals diagnosed with alcohol dependence actually filled a prescription for an FDA approved treatment in 2007 (Mark et al., 2009). Moreover, the rates of receiving pharmacotherapy vary greatly from place to place. Thomas et al. (2013) report that only 15.6% of individuals with private healthcare who had an alcohol dependence encounter received pharmacotherapy in 2007. That number dropped to 2.6% of those seeking treatment through the Veterans Health Administration (VHA), although the number of individuals seeking help through the VHA was more than six times greater than those with private insurance. It is important to note that all of the above rates may have increased since 2007 and do not include medications used off-label to treat alcohol use disorders. Among factors that influence low medication rates include poor insurance coverage and high cost, treatment philosophies that shun pharmacotherapy, lack of knowledge about pharmacotherapy options on the part of both treatment provider and patient, and patient resistance to a diagnosis of alcohol use disorder (see Oliva et al., 2011 for review).

Although many drugs are currently in clinical trials to treat alcohol use disorders, it has been quite some time since any new treatment has become available. Indeed, the last treatment approved by the FDA was extended-release naltrexone in April, 2006 (Pettinati & Rabinowitz, 2006). Further, few interventions exist to treat other consequences of alcohol use, such as fetal alcohol spectrum disorders (FASD), which are a leading cause of mental retardation. FASD is difficult to identify early and may present with a large range of symptoms that are similar to other disorders, such as ADHD, but do not respond similarly to treatment (Murawski et al., 2015). It is necessary to investigate other non-traditional pharmacological treatment options to curb the damage of alcohol use disorders. Because clinical trials are long, expensive, and risk harm to humans, preclinical animal models are necessary to gather preliminary data on potential treatments and to guide decisions concerning when clinical trials are warranted.

Preclinical Models

The DSM-5 (APA, 2013) places alcohol use disorders on a spectrum of severity. Diagnosis is based on self-report of 11 various symptoms such as: “Has drinking recently interfered with your every-day responsibilities?” “Do you blindly crave alcohol?” “Have attempts to cut down on drinking been unsuccessful?” “Do you feel withdrawal symptoms when you go without alcohol?” Researchers are unable to literally ask these questions of preclinical animal models, leaving them to find other ways of modeling aspects of, and testing possible

treatments for, alcohol use disorders. Egli (2005) outlines the following aspects of alcohol use disorders that can be characterized in preclinical models: Consumption, alcohol deprivation, reinstatement, conditioned place preference (CPP), and locomotor activity/ sensitization. For potential pharmacological treatments the ideal place to start is ethanol consumption. Multiple preclinical models of ethanol exist, such as 24-hour free-choice drinking that models chronic intake, binge-like limited-access drinking that may be likened to “party” drinking, and operant response paradigms that are able to characterize intake as well as motivation to consume ethanol. Although some of these models produce low levels of drinking, the oft-employed Drinking-in-the-Dark or chronic intermittent access protocols achieve relatively high levels of consumption that correspond to pharmacologically relevant alcohol intake (see Crabbe et al., 2011 for review). This is primarily where the selected papers start as a means of identifying potential treatments. Surely, a treatment is not viable if it is unable to alter the hallmark feature of alcohol use disorders, that being high alcohol drinking.

Once a drug has successfully been shown to reduce ethanol intake, often in more than one study using more than one model of consumption, it may be tested under the other conditions outlined by Egli (2005). A number of other alcohol behaviors beyond intake can be modeled. Alcohol deprivation following chronic intermittent ethanol vapor or ethanol liquid diet exposure (see Crabbe et al., 2011) results in withdrawal symptomology, and treatments may be tested for their efficacy at reducing these withdrawal effects. Extinction, wherein ethanol is no longer available following completion of a contingent operant response, allows for quantifying craving and motivational drive to receive ethanol. Reinstatement of ethanol following extinction in operant paradigms allows researchers to investigate whether drugs minimize cues associated with ethanol intake and alcohol seeking. The development of a conditioned place preference for ethanol, in which the animal spends more time in an area that has been paired with ethanol, is considered a demonstration of “liking” the drug. Locomotor stimulation to an acute ethanol injection and sensitization, which is increased locomotor response over repeated ethanol injections, may be decreased by drugs that reduce ethanol intake. Not mentioned by Egli (2005) is alcohol tolerance, which is a critical aspect of alcohol use disorders. Alcohol tolerance can be modeled many ways in animals by observing functional and metabolic tolerance, which refer to the reduction in behavioral efficacy or the blood ethanol concentration achieved following repeated ethanol exposure (see Crabbe et al., 2013 for review).

Gubner et al. (2014) investigated whether varenicline, which successfully reduces ethanol intake in humans and preclinical models, also weakens ethanol-induced CPP expression or acquisition and expression of locomotor sensitization. Varenicline was unable to block expression of CPP or locomotor sensitization, although it did show a trend towards reducing sensitization. Acquisition of locomotor sensitization was initially reduced by varenicline but recovered over time, indicating no effect of varenicline on locomotor response to ethanol.

While these results are predominately null they still beg important considerations. Is it truly necessary for potential treatments to mitigate all aspects of preclinical models? Egli (2005) states that alcohol consumption measured in animal models alone is a poorly valid model, yet a recent multi-site clinical trial revealed that varenicline reduced number of heavy

drinking days, drinks per day, and alcohol craving in individuals meeting alcohol dependence criteria (Litten et al., 2013). Egli's predominant concern is that of false positives; many treatments may reduce ethanol intake in animal models without necessarily exhibiting clinical effectiveness. This argues for additional preclinical criteria for examining drug efficacy. But is it possible that aspects of preclinical models, outside of consumption, are currently focusing on the wrong criteria for successful treatments? And how do we determine which aspects of the current preclinical models signal clinical success? FDA drug approval does not follow a sequential preclinical-to-human laboratory-to-clinical trial order. In some cases, such as with dutasteride and baclofen, drugs previously approved for use by humans to treat other disorders can be tested in human laboratory or medical office settings for off-label use, and preclinical tests occur as supplements to off-label testing (Yardley & Ray, 2016). There are also issues in surveying preclinical and human laboratory literature to predict clinical trial outcome. These issues include lack of standardization across studies, bias towards publishing positive results, and treatment-seeking status of participants (Litten et al., 2012a; Yardley & Ray, 2016). One approach to identify predictively valid preclinical models may be to test compounds approved by the FDA for alcohol use disorders against those that have failed clinical trials and those that are currently in clinical trials across a wide array of alcohol-related phenotypes. Results could be compiled in an open-source database to circumvent issues with access to publications and publication bias (Litten et al., 2012a).

Classical Circuitry

The neurobiological systems involved in disorders can be identified via systemic or site-specific injections of various pharmacological agents. Brain regions of interest vary by their classically perceived role in substance abuse behavior. Some of these regions include the nucleus accumbens shell and core and ventral striatum for their collective role in reinforcement, the dorsal striatum for its role in habit formation, the hippocampus for its role in processing drug and alcohol contexts, and the prefrontal cortex for its role in exerting executive control over these regions. Considerable research has focused on GABA, glutamate, and dopamine receptors as pharmacological targets, as the above brain regions are predominately connected by GABAergic, glutamatergic, and dopaminergic projections. Focus has also been on compounds that target opioid receptors and, more recently, nicotinic acetylcholine receptors due to their prevalence in these regions (see Koob et al., 1998; Everitt & Robbins, 2005; Hendrickson et al., 2013 for review of these regions and circuitries). Pharmacological manipulation of these targets has been met with moderate success. As discussed, naltrexone and nalmefene target the opioid receptor system, whereas acamprosate mediates the glutamatergic system (Connor et al., 2015). Drugs targeting classical systems currently or recently in clinical trials include the nicotinic receptor partial agonist varenicline, the GABAergic drug baclofen, the a2δ voltage-gated calcium channel ligand and GABAergic modulator gabapentin, the GABAergic and glutamatergic modulator topiramate, and the atypical antipsychotic quetiapine, which acts via dopaminergic, serotonergic, and adrenergic mechanisms ((See clinicaltrials.gov for current clinical trial information). Of these, all but quetiapine have been shown to be effective in reducing ethanol drinking days and number of drinks consumed (Garbutt et al., 2010; Leggio et al., 2010; Litten et al., 2012b; Litten et al., 2013; Mason et al., 2014; Falk et al., 2015;

Guglielmo et al., 2015). However, they often require meetings to monitor compliance, may produce significant side effects such as sedation or cognitive impairment, and may be dependent on genetic factors for their efficacy (i.e., baclofen's effects on drinking appear to depend on both D4 dopamine receptors and polymorphisms in the serotonin transporter gene) (Knapp et al., 2015; Leggio et al., 2013). As researchers make great strides in brain discovery, and the classical treatment targets do not hold up to the standards we hope to set, the field has started to look for more innovative pharmacological interventions.

New Horizons

The five remaining papers highlighted in this issue focus on several new horizons in alcohol and substance abuse research. The papers discussed herein only scratch the surface of efforts to find new, alternative, and exciting treatments for alcohol use disorders. Each of the targets discussed are vitally linked to the "classical circuitry" described above and have been shown to be effective in some preclinical models of ethanol intake. Franklin et al. (2015) investigated the role of purinergic P2X4 receptors across the CNS and specifically in the posterior VTA (pVTA), which has long been implicated as an important component of the reinforcement circuitry (Rodd-Henricks et al., 2000; Moore & Boehm, 2009). Purinergic receptors mediate neuronal activity and the function of many other neurotransmitter systems, including those of "classical" interest, and are sensitive to intoxicating levels of ethanol (Asatryan et al., 2011). Using selectively bred high alcohol drinking (HAD) rats, Franklin et al. (2015) demonstrated that both non-specific agonism using the drug ivermectin and pVTA-targeted knockdown of P2X4 receptors reduces ethanol intake. The authors suggested that the seemingly contradictory effect of both agonism and knockdown to reduce ethanol intake may have been due to ivermectin's ability to reduce ethanol effects at P2X4 receptors, the virus reducing the number of receptors for ethanol to interact with, and ivermectin's effects on non-purinergic systems. Interestingly, HAD-1 males displayed an extended reduction of drinking following systemic ivermectin compared to the HAD-2 males, which may reflect genetic differences in the selectively bred lines (Franklin et al., 2015; McBride et al., 2012).

Work by Olney et al. (2015) and Navarro et al. (2015) sought to further elucidate the role of neuropeptides that originate in the hypothalamus in ethanol drinking. Long known to be involved in the reinforcement pathway, the hypothalamus gives rise to various neurotransmitters and shares connections with many other brain regions, including the amygdala, nucleus accumbens, prefrontal cortex, and VTA. It has been implicated in mood and anxiety disorders, addiction, and drug effects (Noori et al., 2012). The neuropeptide orexin, as well as a group of peptide hormones known as the melanocortins, are involved in the various roles of the hypothalamus (Chen et al., 2015; Caruso et al., 2014). Olney et al. (2015) pursued two questions; Are there changes in hypothalamic orexin levels following binge-like ethanol consumption, and can antagonizing orexin-1 receptors reduce binge-like ethanol intake? Both short and extended ethanol and sucrose binge cycles lead to decreased orexin-A positive neurons in the lateral hypothalamus, an area specifically associated with reinforcement-motivated behavior (Harris et al., 2005). Systemic antagonism of orexin-1 receptors reduced both ethanol and saccharin intake without affecting locomotion, suggesting a non-caloric-specific effect on reinforcers. Navarro et al. (2015) investigated the

role of the melanocortin agonist melanotan-II, a synthetic analogue of α-melanocyte-stimulating hormone that is produced in the arcuate nucleus of the hypothalamus, in ethanol drinking. Melanocortin peptides arise from POMC along with beta-endorphins, leading to interactions between melanocortin and opioid receptors (Hadley & Haskell-Luevano, 1999). Considering the role of opioid receptors in ethanol intake, Navarro et al. (2015) sought to establish whether melanotan-II could reduce ethanol intake alone, and whether it could produce a synergistic effect with naltrexone, an FDA-approved treatment for alcohol use disorders. Using a binge-like intake paradigm, melanotan-II was shown to effectively reduce ethanol intake on its own, as well as to significantly shift the potency of naltrexone.

Drew et al. (2015) and Blednov et al. (2015) investigated the role of PPARs in inflammatory responses in a model of FASD and two preclinical models of ethanol consumption, respectively. PPARs are nuclear receptor proteins that regulate target gene expression. There are three distinct isoforms (α, γ, and δ) with diverse patterns of distribution throughout the peripheral and central nervous systems, as well as isoform-specific ligands. Fatty acids act as their natural ligands and many synthetic ligands have also been identified. PPARs play a key role in metabolism and have been researched as treatments for dyslipidemia, diabetes, inflammatory disorders, and cancer (Berger & Moller, 2002; Lee & Kim, 2015). PPARs became the focus of interest in alcohol research for their involvement in the cannabinoid and dopamine systems, and much research has demonstrated their efficacy at reducing ethanol intake (see Le Foll et al., 2013 for review). Drew et al. (2015) demonstrated that hippocampal, cerebellar, and cortical pro-inflammatory responses are increased and dendritic morphology is altered following PND4-9 ethanol administration, and that concurrent administration of the PPARγ agonist pioglitazone with ethanol rescued these effects. Drew et al. (2015) suggest that, as these brain regions are critical in later deficits seen in FASD, future research should focus on whether pioglitazone can be used as a post-ethanol exposure intervention, and whether the effects of pioglitazone will persist long-term.

PPARs may also be effective treatments to reduce ethanol consumption. Blednov et al. (2015) demonstrated both a model- and isoform-specific effect of PPARs. Fenofibrate and tesaglitazar, PPARα and PPARα,γ agonists, respectively, reduced chronic and limited ethanol intake and preference. The PPARγ and pan agonists were less effective, while the PPARδ agonist was completely ineffective. Similar to Blednov et al. (2015), Stopponi et al. (2011) demonstrated that the PPARγ-specific agonist pioglitazone reduces 24-hour two-bottle choice ethanol intake. However, rosiglitazone, which is also a PPARγ-specific agonist, does not reduce ethanol intake. Fenofibrate, tesaglitazar, and pioglitazone also significantly altered multiple behaviors associated with alcohol consumption. Blednov et al. (2016a) demonstrated decreased novelty-induced locomotion, reduced ethanol-induced loss of righting reflex, reduced ethanol withdrawal symptoms, and enhanced ethanol metabolism with some sex differences. Neither fenofibrate nor tesaglitazar reduced ethanol-induced CPP. Fenofibrate and tesaglitazar also altered the genomic profile of GABAergic interneurons in the amygdala compared to a PPAR agonist that did not alter ethanol intake (Ferguson et al., 2014). Pioglitazone reduced operant responses for ethanol, but not saccharin, reduced yohimbine-induced (but not cue-induced) ethanol reinstatement, and reduced ethanol withdrawal scores independent of PPARα activation (Stopponi et al., 2011). Although the ability of PPAR agonists to reduce drinking appears to be dependent on presence of the α

subunit, the γ subunit may be critical for enhancing the effects of PPARα agonists on alcohol-related behaviors (Stopponi et al., 2011; Blednov et al., 2016a; 2016b).

Non-invasive human research can also be incorporated into preclinical studies. Blednov et al. (2015) associated human PPAR single-nucleotide polymorphisms (SNPs) with DMS-IV criteria alcohol dependence and withdrawal. Both α and γ were primarily associated with withdrawal, whereas the transcriptional coactivator for the PPARG gene, PPARC1A, was associated with dependence. *PPARD* SNPs showed no association. The methodology and results of Blednov et al. (2015) highlight some important considerations for preclinical research; multiple models should be used, isoform-specific drugs ought to be considered when possible, and preclinical researchers may non-invasively link their results to human populations.

Conclusions

Research on alcohol use disorders paints a picture of a varied disease that is difficult to treat. Few medical interventions exist, and those that do are not taken advantage of at a high rate (Mark et al., 2009). Developing successful treatments requires the use of preclinical animal models. However, there is no specific battery of tests that are accepted as sufficient making it difficult to determine when a drug has been successful enough in animal models to move it forward to clinical testing. The papers highlighted within this virtual issue touch on various points of concern and raise questions and directions for the future of the field (see Box 1 for summary points). Gubner et al. (2014) demonstrate that varenicline, a drug shown to be effective in both preclinical and clinical trials of ethanol consumption, is unable to reduce ethanol CPP or locomotor sensitization. But are those constructs directly relevant to the human disorder, and should failure of effectiveness in tests outside of ethanol intake stop drugs from moving into clinical trials? Further, how much of a concern are non-specific effects of drugs? Olney et al. (2015) demonstrated orexin-1 agonism-induced reduction of saccharin intake. Considering the entwined nature of food and drug reinforcement pathways, such results are not surprising. However, may they be indicative of concerns over general effects on motivation and potentially ill-tolerated side-effects in clinical populations? Clearly, it is necessary to test for amotivational and anhedonic effects of drugs of interest. Navarro et al.'s (2015) results may advise a path when side effects are of concern; combining subthreshold doses of two drugs reduced ethanol intake further than either effective dose alone. This synergistic effect of subthreshold doses is also seen with naltrexone and the PPARγ-specific agonist pioglitazone (Stopponi et al., 2013). Therefore, combination of lower drug doses may effectively reduce ethanol intake without ill-tolerated side effects. Also of consideration is repeated dosing, which is not always used in preclinical testing. Blednov et al. (2015) and Franklin et al., (2015) employed repeated dosing procedures and found effects of lower drug doses that were not evident on the first day of drug administration. Considering that approved medications are designed for use over a repeated course, employing repeated testing of a drug dose-range may be useful.

Another question concerns how we effectively consider genetics in potential drug efficacy? Multiple studies have shown clear genetic associations with drug effectiveness in clinical populations (e.g. Leggio et al., 2013; Kranzler et al., 2011; 2014), which can be reflected in

preclinical populations, such as the differences in P2X4 expression and agonist efficacy in HAD-1 versus HAD-2 rats (Franklin et al., 2015). Genetic association studies may also indicate success of drugs with certain receptor selectivity. Blednov et al. (2015) found that PPARα and γ, but not δ, agonists effectively reduced ethanol intake in two different models. In the COGA analysis, the *PPARA* and *PPARG* genes, but not *PPARD* gene, were associated with alcohol withdrawal, indicating that non-invasive human studies may be able to guide preclinical testing targets. These findings support the drive for personalized medicine based on genetic predisposition for alcohol use disorders, comorbid disorders, features of the alcohol use disorder, and other criteria that may be of concern. One major advantage of preclinical models is the ability to manipulate genetic predisposition toward high alcohol intake and other associated phenotypes. Animal lines identified as having high or low ethanol consumption, such as P rats or the High Alcohol Preferring (HAP) mice, may be analyzed for unique genes that contribute to intake (Mulligan et al., 2006). Genetic targets may also be pulled from open source databases, such as the Integrative Neuroscience Initiative on Alcoholism (INIA) Texas Gene Expression Database (http://inia.icmb.utexas.edu/). These genes can then be conditionally or permanently altered via methods such as receptor knockout or designer receptors exclusively activated by designer drugs (DREADDs) (see Roth, 2016) to further understand the relationship between alcohol consumption, alcohol-related phenotypes, and specialized treatment in animal models of alcohol use and comorbid disorders.

Alcohol use disorders pose a major threat to individuals and society. They result in loss of friends and family, increased rates of illness, loss of life of the individual or bystanders, and individual economic instability as well as increased economic costs to support those suffering. The current rates of those seeking medical treatment are low, existing treatment outcomes are bleak, and current pharmacological treatments come with contraindications and warnings that may exacerbate existing health issues (SAMHSA, 2015). New drug interventions cannot be identified fast enough. Fortunately the preclinical field is rapidly advancing new targets to treat alcohol use disorders. Rigorous criteria will need to be identified for when a drug is ready to move into clinical trials. These considerations include examining behavior across an expanse of testing paradigms, whether a failure under certain behavioral testing paradigms excludes a drug from moving forward, side effect profiles, repeated-dosing and using low or combined drug doses, and genetic contribution to efficacy.

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Box 1

Key Considerations

- How should the preclinical research community determine which preclinical models may signal treatments that would successfully make it through clinical trials?
- Should failure of treatment effectiveness in preclinical behavioral tests related to ethanol consumption stop a drug from moving to preclinical trials?
- Considering the similar underlying pathways of food, drug, and other natural reinforcements, when do non-specific drug effects become a red flag?
- How do we effectively consider aspects of personalized medicine, such as genetic contributions?

Suggestions

- Test drugs that have and have not passed FDA clinical trials for alcohol use disorders in a large range of behavioral tests in an attempt to find critical aspects that may suggest success.
- Maintain open source preclinical, human laboratory, and clinical trial databases with positive and negative results that can easily be cross-referenced.
- Consider combined subthreshold doses of efficacious drugs that display anhedonic or amotivational effects.
- Cross-reference human findings to identify genetic targets which can be manipulated in preclinical models.