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Critical Needs in Drug Discovery for Cessation of Alcohol and Nicotine Polysubstance Abuse

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Abstract

Polysubstance abuse of alcohol and nicotine has been overlooked in our understanding of the neurobiology of addiction and especially in the development of novel therapeutics for its treatment. Estimates show that as many as 92% of people with alcohol use disorders also smoke tobacco. The health risks associated with both excessive alcohol consumption and tobacco smoking create an urgent biomedical need for the discovery of effective cessation treatments, as opposed to current approaches that attempt to independently treat each abused agent. The lack of treatment approaches for alcohol and nicotine abuse/dependence mirrors a similar lack of research in the neurobiology of polysubstance abuse. This review discusses three critical needs in medications development for alcohol and nicotine co-abuse: (1) the need for a better understanding of the clinical condition (i.e. alcohol and nicotine polysubstance abuse) (2) the need to better understand how these drugs interact in order to identify new targets for therapeutic development and (3) the need for animal models that better mimic this human condition. Current and emerging treatments available for the cessation of each drug and their mechanisms of action are discussed within this context followed by what is known about the pharmacological interactions of alcohol and nicotine. Much has been and will continue to be gained from studying comorbid alcohol and nicotine exposure.

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Conflicts of Interest

The authors have no conflicts of interest to report.

Introduction: Prevalence and Onset of Alcohol, Nicotine, and their Concurrent Use

Alcohol remains the most commonly used drug of abuse in the world, accounting for nearly 6% of global deaths annually (WHO, 2014) with millions more engaging in abusive drinking that has additional health, legal and social consequences (SAMHSA, 2014). Alcohol use disorders (AUDs), or "alcoholism", are major public health problems as 13.9% of the U.S. population currently meets DSM-V diagnostic criteria for an AUD (Grant et al., 2015). Within this group, 50–92% also smoke tobacco (Miller & Gold, 1998; Falk et al., 2006; De Leon et al., 2007), resulting in alcohol and nicotine abuse as the largest group of polysubstance abusers. Despite these striking numbers, preclinical research on this comorbid condition is relatively understudied, as investigators have focused primarily on understanding the effects of each of the drugs individually. Recently, this critical oversight has begun to be remedied through new NIH funding opportunities that already have served to increase the rate of discovery in alcohol and nicotine polysubstance abuse. As the 50%–92% incidence values show, comorbid alcohol and nicotine exposure *is* the human condition for the majority of people with an AUD.

Excessive alcohol use produces a great burden to society; it accounts for 2.3 million years of potential life lost and an estimated $223.5 billion in economic costs per year (Kanny et al., 2013). Approximately 57% of Americans aged 21 and over have consumed alcohol in the last month (SAMHSA, 2014) while 18% of the adult population are binge drinkers (Kanny et al., 2013). Binge drinking is defined by the National Institute on Alcohol Abuse and Alcoholism as a pattern of drinking that results in blood alcohol concentrations above the legal limit of 0.08 g/dL, through drinking 4+ drinks for women and 5+ drinks for men within 2 hours. Although binge drinking is not necessarily synonymous with alcohol abuse, it is a risky pattern of consumption related to alcohol use problems. Tobacco use, on the other hand, is the leading cause of preventable death and accounts for approximately 20% of deaths per year (US Department of Health and Human Services, 2014). Nevertheless, 18% of adults over 18 years of age use tobacco products (Agaku et al., 2014). Tobacco smokers are more likely to binge drink, consume two times more alcohol, and are 10–14 times more likely to have an AUD than non-smokers (Carmody et al., 1985; DiFranza & Guerrera, 1990; see also McKee & Weinberger, 2013 for review). In addition, non-daily smoking (not dependent) occurs most frequently during alcohol use (McKee et al., 2004) as alcohol use dose-dependently increases smoking urges (King & Epstein, 2005). The prevalence of concurrent use is not surprising since nicotine enhances ratings of alcohol reinforcement in humans (McKee & Weinberger, 2013) and alcohol self-administration in animal models (Doyon et al., 2013a). The enhancement of alcohol's effects by nicotine may be subconsciously exploited in an *I only smoke when I drink* manner, known as "chipping," as 74% of smoking episodes occur while consuming alcohol in non-dependent smokers (McKee et al., 2004). Perhaps because of this rationalizing, non-daily smoking is associated with an even greater increase in risky drinking compared to daily smoking (McKee & Weinberger, 2013). Furthermore, concurrent use may pose significant barriers to successful alcohol cessation, as smoking is associated with increased alcohol dependence, greater symptoms of alcohol withdrawal, and decreased success in remaining abstinent from alcohol

(McKee & Weinberger, 2013; Chiappetta et al., 2014). Conversely, current or past AUDs decrease the likelihood of smoking cessation and current AUDs increase the likelihood of smoking relapse (Weinberger et al., 2013). Since alcohol and nicotine are often used concurrently, with each individual substance posing a barrier to the other substance's successful cessation, it is imperative to consider alcohol and nicotine polysubstance abuse as a singular condition and develop effective therapies that target both substances, rather than treating each condition separately.

There are several pharmacological agents that are available to treat either alcohol or nicotine dependence independently; however, as will be discussed herein, these approved medications have limited efficacy in long-term cessation. Although new pharmacotherapies are being considered in the individual conditions, a striking absence of pharmacological treatments for alcohol and nicotine polysubstance abuse remains. Indeed, the lack of research support for this specific comorbidity has hindered the development of potential therapeutic treatments for comorbid alcohol and nicotine dependence. Furthermore, for drug discovery and medications development in alcohol and nicotine cessation to succeed, there are several critical needs beyond the obvious need for new drug targets. A major difficulty in drug discovery for cessation of drug use is that substance abuse/dependence is a disease state on a continuum with normal behavior where there is little consensus on many aspects of the disorder (Roman, 2014; Litten et al., 2015). In other words, the pathology is ill defined. Therefore, a better understanding of the factors that drive alcohol and nicotine co-use and abuse is critical to the success of drug discovery. Indeed, this cannot be done without a better understanding of the pharmacological and physiological interactions of the drugs together, as well as each drugs particular effect on the other. In addition, Koob et al (2009) highlights the critical importance of having valid models that then reflect this deeper understanding of the disorder. Specifically, basic science must contribute to our understanding of the disorder, our understanding of how the drugs interact within the context of the disorder, but then, critically, must turn around and improve animal models of the disorder. In other words, a Rosetta Stone approach is necessary; one that couples the discovery of novel targets and pharmacophores with studies to better understand the disorder, and develop novel models to better mimic the disorder in which effective pharmacotherapies may be tested (Koob et al., 2009). Each of these parts of the stone will be discussed below as critical needs to the drug discovery process. After reviewing the pharmacology and current and experimental treatments available for alcohol and nicotine individually and their presumed mechanisms of action, alcohol and nicotine interactions are then discussed focusing on the role of the nicotinic receptor as the common sites of action for alcohol and nicotine. Next, we discuss the limited number of studies where alcohol and nicotine have been explored together, organized by the major neurotransmitter and signaling systems implicated in the development of alcohol and substance use disorders. Finally, the critical need for novel animal models that better mimic the human condition and in which experimental therapeutics can be tested is discussed drawing from best practices in the *in vivo* drug discovery literature.

Need: A better understanding of the co-morbid condition

As stated above, a better understanding of the co-morbid condition of alcohol and nicotine co-use and abuse is critically needed. The starting point to understanding this interaction is elucidating the pharmacology of alcohol or nicotine alone, of which there is a wealth of information. We review briefly the current state of knowledge of each individual drug's mechanism of action and discuss currently approved treatments for cessation. Experimental approaches in the drug discovery pipeline are also discussed as a way of foreshadowing potential new areas to examine for alcohol and nicotine interactions in their use and abuse.

Nicotine: Mechanism of Action

Although there are thousands of chemicals that one is exposed to during tobacco smoking, it is widely presumed that the tobacco alkaloid, nicotine, is the primary component responsible for an addiction to smoking. Nicotine acts at nicotinic acetylcholine receptors (nAChRs), ligand-gated ion channels that respond to the endogenous agonist acetylcholine, but also have a high affinity for nicotine. Nicotine acts as an agonist, initially at least, at all subtypes of nAChRs. When agonist is bound, the channel pore opens allowing for the influx of sodium (Na^+) and/or calcium (Ca^{2+}) and the efflux of potassium (K^+) cations, changing the membrane potential. Increases in intracellular Ca^{2+} concentration then augment a variety of cell-signaling mechanisms. nAChRs are located on the soma of acetylcholine interneurons where they serve as autoreceptors, as well as on terminals of numerous types of neurons where they serve as heteroreceptors. This includes axon terminals in the dorsal striatum and NAc where nAChRs modulate dopamine release into the extracellular space. nAChR modulation of striatal dopamine release is thought to be primarily responsible for the rewarding and reinforcing properties of nicotine (Di Chiara, 2000; Volkow et al., 2002; Rice & Cragg, 2004). Upon repeated nicotine exposure, nicotine binding and consequent nAChR upregulation are hypothesized to drive nicotine dependence and addiction (Wonnacott, 1990; Bardo, 1998; Sparks & Pauly, 1999; Di Chiara et al., 2004).

nAChRs are comprised of 5 subunits and various subunit compositions make up a variety of nAChR subtypes (Changeux, 2010). However, not all nAChR subtypes are subject to upregulation following repeated nicotine exposure. Of those that are susceptible to upregulation, the α4β2 and α7 subtypes are best characterized (Fenster et al., 1997; Gotti et al., 2006; Dani & Bertrand, 2007). Positron emission tomography scanning revealed nAChR upregulation in adults who are chronic smokers (Mukhin et al., 2008; Wullner et al., 2008). Although these receptors are upregulated, chronic exposure to nicotine desensitizes α4β2 nAChRs, which leads to a decreased response to nicotine (Wonnacott, 1990). The consensus is that while more receptors are expressed following repeated nicotine exposure, these receptors are inactive, therefore an increased amount of nicotine is needed to produce the same response (Balfour, 1994; Picciotto et al., 2008). In a clinical study, Brody et al. (2006) reported that average smokers maintain nicotine levels sufficient to occupy 88–95% of α4β2 nAChRs in brain. Because smokers maintain nicotine levels that saturate at least 88% the available nAChRs, drug craving begins, theoretically, when less than 88% of the available nAChRs are occupied. In support of this idea, the extent of α4β2 nAChR upregulation correlated negatively with patients' ability to both quit smoking and maintain abstinence

after a variety of 12-week smoking cessation treatments, including nicotine-replacement therapy, pharmacotherapies or cognitive behavioral therapies (Brody et al., 2014). Thus, patients with greater α4β2 upregulation had less success overall with smoking cessation regardless of treatment regimen and tended to relapse more often after treatment completion compared to patients with lesser α4β2 upregulation. Taken together, these results suggest that 1) measuring nAChR upregulation may serve as a diagnostic tool to better assess a patient's level of dependence prior to cessation attempts, and 2) using this knowledge, physicians may be able to design more extensive treatment plans to increase success rates for patients with high levels of nAChR upregulation.

As previously mentioned, nicotine activation of nAChRs results in dopamine release from presynaptic terminals. However, as repeated exposure to nicotine desensitizes nAChRs, dopamine release decreases. For example, Rice & Cragg (2004) demonstrated through a series of electrical stimulation studies that during low frequency, tonic firing, chronic nicotine exposure desensitizes nAChRs and inhibits striatal dopamine release. However, when electrical pulses were delivered at higher, phasic (burst)-firing frequencies, associated with reward transmission, nicotine enhanced dopamine release. Taken together, these results suggest that with repeated use, nicotine may not increase dopamine release, and thereby, the initial rewarding effects may be decreased. However, nicotine activation of nAChRs enhances dopamine release during reward-driven burst firing, enhancing the rewarding effects of other primary and secondary reinforcers.

Nicotine may also decrease dopamine release via an alternate mechanism involving cholinergic interneurons. Cholinergic interneurons impinge on both dopaminergic somas as well as axon terminals (Changeux, 2010). In a recent study, Wang et al. (2014) determined that nicotine desensitizes nAChRs located on cholinergic interneurons, inhibiting transmission between the interneurons and dopaminergic neurons, and thereby eliminating the nicotine-evoked dopamine release. As a result, nicotine prevents the depletion of dopamine in releasable vesicle pools during low-frequency firing, which reduces baseline noise and allows for a cleaner higher-frequency burst firing, and consequently, nicotine-induced dopamine release during reward.

In summary, nicotine activation and desensitization of nAChRs and their net effect on dopamine release is a complex process. Effective therapeutic strategies for smoking cessation, therefore, need to consider the complex nature by which nicotine results in the modulation of dopamine release as well as the possibility that other components of tobacco smoke interact with the mesolimbic reward system to drive addiction. In addition, the majority of smokers concurrently use other drugs, particularly alcohol, which requires study of how alcohol interacts with these complicated processes and specifically within the context of the comorbid condition.

Therapeutics for Smoking Cessation

Currently, only a handful of pharmacological agents are available for smoking cessation (see Table 1), and none are available specifically for the treatment of alcohol and nicotine polysubstance abuse. Of the smoking cessation treatments that are available, few are efficacious as single-agent therapies, and relapse is common regardless of treatment type.

With or without pharmacological intervention, only about 3% of smokers are able to maintain abstinence for one year after attempting to quit (Hughes et al., 2014). Currently approved and emerging new pharmacological approaches for smoking cessation are described below.

Nicotine Replacement Therapy (NRT)—The first FDA-approved form of smoking cessation treatment was nicotine replacement therapy (NRT). NRTs are now available in five FDA approved forms, including gum, inhaler, patch, nasal spray and lozenges. NRT dosage forms are designed to administer low doses (5–20 mg daily) of nicotine, typically in a step-down approach. The goal of NRT is to make smoking cessation easier by reducing nicotine cravings and tempering the effects of nicotine withdrawal by gradually lowering circulating levels of nicotine, while forgoing the harmful effects of cigarette smoking (Stead et al., 2012). Approximately 50–70% of smokers who attempt to quit using NRTs are successful during a 12-week treatment period, but of those, 80% are smoking again by 1 year after treatment (Ferguson et al., 2006; Stead et al., 2012). The high incidence of relapse seen with NRTs is likely due, at least in part, to the fact that NRTs do not alter nicotine dependence, but rather decrease motivation to smoke by providing nicotine. In addition, there are significant sex differences in NRT efficacy, with poorer long-term abstinent rates for women (Perkins & Scott, 2008). In summary, while NRTs often help some groups of motivated smokers to quit by reducing their urge to smoke, cessation is often short lived and relapse ensues.

Bupropion—The first non-nicotine smoking cessation therapeutic approved in the U.S. is the nAChR antagonist and neurotransmitter transporter inhibitor, bupropion (Zyban®). Bupropion is an allosteric antagonist at $\alpha3\beta4$, $\alpha4\beta2$, $\alpha6\beta2$ and $\alpha7$ nAChRs (Slemmer et al., 2000; Miller et al., 2002; Rauhut et al., 2003). Bupropion-induced antagonism of nAChRs in the CNS attenuates the reinforcing properties of nicotine in rodents and humans, and attenuates nicotine withdrawal, making cessation feasible (Miller et al., 2002; Rauhut et al., 2003; Warner & Shoaib, 2005; Carroll et al., 2014). Bupropion is also a weak norepinephrine and dopamine re-uptake inhibitor and also is marketed as an antidepressant (Wellbutrin®; Dwoskin et al., 2006). Because bupropion affects nAChRs as well as norepinephrine and dopamine transporters, it is plausible that bupropion inhibition of dopamine and norepinephrine reuptake contributes to the attenuation of the reinforcing properties of nicotine (Rau et al., 2005). However, inhibition of transport would increase the concentration of extracellular transmitter, which would be predicted to increase reinforcement, rather than decrease it. Others have reported that the effect of therapeutic doses of bupropion on dopaminergic transmission is negligible, suggesting that nAChR antagonism is responsible for its efficacy as a smoking cessation agent (Damaj et al., 2004). In clinical studies, bupropion treatment increased smoking cessation rates within 7 weeks of treatment (44% vs. 19% in placebo) as well as 1 year after treatment (23% vs. 12% in placebo; Hurt et al., 1997). However, data comparing bupropion treatment to NRTs has been somewhat inconsistent. At one year, NRTs show increased cessation rates, though one study measuring cessation rates at 3 months showed bupropion was more efficacious (Wu et al., 2006). Since bupropion and NRT act via different mechanisms, these cessation therapeutics can be used in combination to obtain greater efficacy in smoking cessation. In a placebo

controlled trial, bupropion and NRT combination therapy was found to be more effective (36% were abstinent at 12 months) compared to bupropion (30%) or NRT alone (16%; Jorenby et al., 2006). Therefore, bupropion, administered either alone or in conjunction with NRT, shows significant efficacy as a long-term smoking cessation agent. Additionally, because of its utility in modulating dopamine and norepinephrine systems, bupropion could also serve as a potential therapeutic agent for comorbid alcohol and nicotine dependence.

Varenicline—In 2006, the FDA approved varenicline (Chantix®) for smoking cessation and is reported to be the most effect treatment for nicotine dependence on the market (Coe et al., 2005; Oncken et al., 2006; Reus et al., 2007; Fiore et al., 2008). Varenicline, a cytisine derivative approved for smoking cessation in Europe, is an α4β2 nAChR partial agonist that both prevents the rewarding effects of nicotine and reduces the withdrawal induced by smoking cessation (Mihalak et al., 2006; Cahill et al., 2011). Varenicline was designed to be a high affinity partial agonist at the α4β2* nicotinic receptor (nAChR) subtype; however, as concentrations are increased, varenicline selectivity is reduced with activity at α3β2*, α6β2*, and α3β4* and is a full agonist α7 nAChRs (Grady et al., 2010; Mihalak et al., 2006). Although clinical trials have shown that varenicline treatment leads to increased short-term (4 week) abstinence rates compared to bupropion and NRT and increased long-term (1 year) abstinence rates (23%) when compared to placebo (10%) or bupropion treatment (15%;), the majority of treated individuals ultimately relapse (Cahill et al, 2011; Jorenby et al., 2006; Mills et al., 2009; Volkow and Skolnick, 2012). As such, varenicline has proven to be an effective smoking cessation agent though its efficacy is limited. Additionally, varenicline has some efficacy in treating alcohol abuse, demonstrated in both animal models and human clinical trials as discussed extensively below (McKee et al., 2009; Wouda et al. 2011; Feduccia et al., 2014). Therefore, varenicline shows potential as a therapeutic for treating alcohol and nicotine polysubstance abuse.

Naltrexone—Naltrexone is an opioid receptor antagonist that is typically used in the treatment of opioid abuse/dependence, but also AUDs. However, naltrexone has been investigated more recently as a treatment for nicotine dependence. Naltrexone acts by inhibiting mesolimbic dopamine release in the NAc, which is modulated also by nicotine too. While preclinical evidence has not supported a role for endogenous opioids in nicotine self-administration (Corrigall & Coen, 1991), one clinical trial found that daily naltrexone increased smoking cessation rates in males, but not females (30% in men and 20% in women compared to placebo rates of 17% and 28%, respectively; King et al., 2012). Although cessation was maintained for the entirety of the 12-week treatment period, differences in abstinence rates between naltrexone treatment and control groups were no longer apparent at either the 26- or 52-week follow up assessments. Therefore, while naltrexone is somewhat effective for alcohol abuse (as discussed below), it does not appear to be more efficacious than other treatment options (NRTs, bupropion and varenicline) for smoking cessation. However, naltrexone does appear to reduce weight gain that often accompanies smoking cessation (Toll et al., 2008; Parsons et al., 2009; King et al., 2012), and therefore may hold promise as an augmentative treatment option.

Mecamylamine—Mecamylamine is a nonselective, noncompetitive inhibitor of all subtypes of nAChRs (Nickell et al., 2013). While originally marketed as an antihypertensive agent, mecamylamine readily crosses the blood-brain barrier, making it a candidate for CNS-based therapeutics, including smoking cessation. Neuropharmacological studies have shown that mecamylamine dose-dependently decreases nicotine-evoked dopamine release from superfused rat striatal slices (Nickell et al., 2013). Additionally, mecamylamine deceases nicotine self-administration in animal models (DeNoble & Mele, 2006). In one clinical trial, mecamylamine increased cessation rates when combined with NRT compared to patients who used NRT alone (Rose et al., 1994); however clinical trials of mecamylamine have not been successful. Although the effective dose of mecamylamine is 3-fold lower than the antihypertensive dose (Shytle et al., 2002), the nonselective effects of mecamylamine at these low doses include peripheral side effects (autonomic ganglionic blockade) such as constipation, dry mouth, and urinary retention that limit its utility as a smoking cessation agent. Nevertheless, the usefulness of a nAChR antagonist as a cessation therapy may be promising if the peripheral effects were eliminated. Therefore, mecamylamine analogs and other more selective nAChR antagonists may provide an avenue for future development of smoking cessation agents (Crooks et al., 2014).

GSK598809—Selective dopamine receptor (D3) antagonists have been proposed to prevent drug-seeking behavior by reducing the rewarding effects of drugs such as nicotine. In rats, the D3 antagonist GSK598809 reduced nicotine self-administration as well as nicotine-induced conditioned place preference (Mugnaini et al., 2013). These results suggest that D3 blockade can attenuate drug craving independent of nicotinic mechanisms. GSK598809 has progressed into Phase II clinical trials for smoking cessation as a singular agent and in combination with both cognitive behavior therapy and NRT (clinicaltrails.gov, 2009a).

NicVAX—A novel approach to smoking cessation treatment is the anti-nicotine vaccines, for example, NicVAX. NicVAX is designed to specifically prevent and treat relapse of tobacco use by stimulating the production of anti-nicotine antibodies, which bind to nicotine as it enters the blood stream, thus preventing it from reaching the brain. While bound to anti-nicotine antibodies in the plasma, nicotine cannot cross the blood-brain barrier to elicit its rewarding effects (Kosten & Owens, 2005). Interference with nicotine entry into the brain may attenuate nicotine dependence and prevent the rewarding properties of tobacco smoking; however, this therapeutic approach does not reduce nicotine craving (Maurer & Bachmann, 2007). NicVAX entered clinical trials in 2005, but failed to show efficacy over placebo in two rounds of Phase III trials (clinicaltrials.gov, 2009b). Subsequent data analysis revealed that a subgroup of individuals with high titers had success in demonstrating smoking cessation.

In summary, there are several pharmacotherapeutic treatment options for nicotine dependence that capitalize on different mechanisms to reduce aspects of nicotine addiction - reward, craving, and withdrawal symptoms - that promote abstinence. However, many of these medications do not show high rates of long-term success with respect to tobacco smoking cessation. As alcohol use negatively impacts smoking cessation (Weinberger et al.,

2013), it is important to assess the contribution of alcohol use to the high relapse rates found with these therapies. Nevertheless, new nicotine therapies are being developed, and likely would be improved by treating alcohol and nicotine use as one condition.

Alcohol: Mechanisms of Action

The mechanisms of alcohol's actions are complex, as it has widespread pharmacologic targets and effects that change as alcohol use progresses from first-time or acute use to chronic use and abuse. As describing alcohol's mechanism of action results in a lengthy review in and of itself, we highlight alcohol's major effects briefly and direct the reader to more thorough reviews (Lawrence et al., 2008; Vengeliene et al., 2008; Dopico & Lovinger, 2009; Cui et al., 2013; Tabakoff & Hoffman, 2013; Most et al., 2014; Zhou & Kreek, 2014). Acute alcohol in a non-tolerant individual alters receptor and ion channel function both directly and indirectly. Directly, acute alcohol alters the function of multiple ligand-gated ion channels including $GABA_A$ receptors (Grobin et al., 1998), NMDA receptors (Lovinger et al., 1989) serotonin receptors (Lovinger, 1991), glycine receptors (Murail et al., 2011), nAChRs (Gessa et al., 1985) and norepinephrine receptors (Vengeliene et al., 2008). Acute alcohol also inhibits dihydropyridine-sensitive L-type voltage-gated calcium channels (Mah et al., 2011) and opens G-protein activated inwardly rectifying K^+ channels (Ericson et al., 1998; Lewohl et al., 1999). Neuroadaptations occur as alcohol use transitions to abuse and dependence, which contributes to alcohol craving and the maintenance of alcohol use (Vengeliene et al., 2008; Cui et al., 2013; Zhou & Kreek, 2014). Chronic alcohol consumption alters neurotransmitter systems including GABAergic (Grobin et al., 1998), glutamatergic (Grant et al., 1990), serotonergic (Kelai et al., 2008), dopaminergic (Liljequist et al., 1977; Karkhanis et al., 2015), adenosine (Butler & Prendergast, 2012), and cholinergic systems (Nordberg et al., 1982). Neuropeptide systems are also altered and include opioids (Gianoulakis, 1996), endocannabinoids (Basavarajappa & Hungund, 1999; Pava & Woodward, 2012), corticotropin-releasing factor (Dave et al., 1986; Phillips et al., 2015), and neuropeptide Y (Thiele et al., 1998). Additionally, L-type voltage-gated calcium channels are modulated (Mah et al., 2011); and neuroinflammatory pathways are activated (Lippai et al., 2013), among other neuroadaptations (see also the following in depth reviews: Lawrence et al., 2008; Vengeliene et al., 2008; Cui et al., 2013; Tabakoff & Hoffman, 2013; Most et al., 2014; Zhou & Kreek, 2014). Thus, alcohol alters behavior and neural functioning through numerous mechanisms. Due to its widespread pharmacologic targets, alcohol is considered a "promiscuous" drug.

Especially relevant to comorbid alcohol and nicotine use, is the role of nAChRs in alcohol use. As discussed in greater detail below, the cholinergic system is involved in alcohol dependence and is therefore a viable target for novel pharmacotherapies (Rahman & Prendergast, 2012; Rahman et al., 2014). As described in the nicotine section above, nAChRs are located in the mesocorticolimbic pathway, where they contribute to reinforcement through activation of dopaminergic neurons in the ventral tegmental area (VTA; Okamoto et al., 2006; Tsai et al., 2009). Through actions at nAChRs, alcohol increases dopamine overflow in the NAc (Ericson et al., 1998), increases extracellular acetylcholine levels in the VTA (Larsson et al., 2005), and stimulates VTA dopaminergic transmission *in vitro* (Brodie et al., 1999) and *in vivo* (Gessa et al., 1985). Additionally, the

nAChR antagonist, mecamylamine, inhibits dopamine overflow in the NAc and reduces voluntary alcohol consumption in rats (Ericson et al., 1998). Interestingly, overexpression of α5, α3 and β4 subunits in transgenic mice reduces alcohol intake in a 2-bottle choice procedure (Gallego et al., 2012), which suggests a reduction in the rewarding effect of alcohol. In any case, these data highlight the role of the cholinergic system in alcohol reinforcement and drinking maintenance, as well as the therapeutic potential of nAChR ligands. More about the interaction of alcohol and nicotine at this common site of action is discussed below.

Pharmacological Treatment of Alcohol Use Disorders

Currently, there are only four medications approved by the FDA for the treatment of alcohol dependence: the competitive opioid receptor antagonist, naltrexone, extended release naltrexone, the acetaldehyde dehydrogenase inhibitor, disulfiram, and acamprosate, a modulator of glutamatergic tone (see Table 2). The limited number of pharmacotherapeutic approaches to AUDs is due, in part, to the promiscuous action of alcohol in the nervous system coupled with the poorly defined disease state and/or the presence of multiple – and also poorly defined - subpopulations of alcoholics (Roman, 2014). Indeed these drugs act on multiple neurotransmitter systems implicated in reward and addiction (e.g., dopamine, glutamate, and GABA) but have shown only moderate efficacy in the treatment of AUDs. While total abstinence (i.e., relapse prevention) is typically the main objective for pharmacological treatment of AUDs, recent research efforts are aimed at putative pharmacotherapies that reduce rates of consumption in alcohol-dependent individuals. Below, we will discuss approved drugs then emerging targets in drug discovery for the treatment of AUDs according to their general mechanism of action.

Disulfiram—Discovered in the 1920s and in use since the late 1940s, disulfiram (Anatabuse®) blocks the metabolism of alcohol by inhibiting the liver enzyme, acetaldehyde dehydrogenase. Alcohol intake therefore results in the accumulation of the primary metabolite, acetaldehyde, producing the disulfiram-alcohol reaction characterized by severe nausea, vomiting, headache, tachycardia, sweating, and flushing (reviewed in Franck & Jayaram-Lindstrom, 2013). Theoretically, the production of these aversive symptoms upon ingestion of alcohol deters the individual from drinking. This approach can work to prevent relapse in individuals who are motivated to remain abstinent, but, if an individual is highly motivated to obtain alcohol, they simply can discontinue the medication. Thus, compliance rates are low. In addition, consuming ethanol while taking disulfiram results in the accumulation of acetaldehyde in the blood, which can have dangerous medical risks. In a well-known trial employing 605 alcohol-dependent male veterans in the United States, disulfiram (250mg) was shown to reduce the number of drinking days by 35 - 43% compared to a lower dose of disulfiram (1mg) and placebo, respectively, but only in those individuals (20%) who were compliant with the treatment (Fuller et al., 1986). Overall, there were no significant differences between the groups in abstinence or other outcome measures. Recent efforts with “supervised Disulfiram” therapy have increased abstinence days (Krampe et al., 2011). Unfortunately, many drinking-related outcomes are not different, statistically, from placebo, and long-term effects have not been evaluated (Jorgensen et al.,

2011). In sum, the clinical utility of disulfiram remains limited (Franck & Jayaram-Lindstrom, 2013).

Naltrexone—Naltrexone (Revia® or Depade®), as described above, is a non-specific opiate receptor antagonist with an active metabolite, 6β-naltrexol that was first approved for use in alcohol dependence in 1994. Naltrexone is currently marketed in both oral and extended release injectable (Vivitrol®) forms. Early studies on naltrexone reported moderate success with reduced craving, blunted alcohol-induced euphoria and lower relapse rates in naltrexone versus controls (e.g. O'Brien et al., 1996). Similar to other therapeutics, higher efficacy was found in fully compliant patients. Subsequent studies have show that it is most effective in reducing the extent of "heavy" drinking (Pettinati et al., 2006), rather than in maintenance of abstinence (Garbutt, 2010). Importantly, there may be sex differences in naltrexone's efficacy (Garbutt et al., 2005), again highlighting that no single drug has been widely successful in all individuals with an AUD. As previously reviewed, the effect size has been only modest, 0.15 – 0.2, which has impacted its use as a therapeutic (Garbutt, 2010). Furthermore, the clinical utility of oral naltrexone is limited as indicated by the black box warning for the risk of liver damage (Franck & Jayaram-Lindstrom, 2013). Liver damage is a significant concern as long-term chronic alcoholics often have liver problems. The extended release naltrexone formulation lowers the risk of additional hepatotoxicity by bypassing first pass metabolism in the liver.

Acamprosate—Acamprosate (*N*-acetylhomotaurine) was first approved for use in the treatment of alcohol dependence in Europe in 1989, after significant efficacy was demonstrated for promoting abstinence in a large clinical trial (reviewed in Kranzler & Gage, 2008). In 2004, the FDA approved Campral® for this same indication in the U.S. Although acamprosate's mechanism of action is not particularly well understood, its presumptive mechanism(s) of action are enhancement of $GABA_A$ receptor function (Williams, 2005) and indirect modulation of NMDA receptors via antagonist actions at group I metabotropic glutamate receptors (Harris et al., 2002). Both of the later effects are theorized to attenuate the hyperglutamtergic state that occurs during alcohol withdrawal. Various meta-analyses, based mostly on European trials, report moderate efficacy of acamprosate. For example, one meta-analysis of 17 trials that encompassed over 4000 alcohol-dependent individuals confirmed that acamprosate increased 6-month abstinence rates by around 50% (from 23.4% to 36.1%; Mann et al., 2004). However, two large clinical trials completed in the United States failed to demonstrate significant efficacy of acamprosate (Anton et al., 2006; Mason et al., 2006). The reason for these disparate results is an active debate, focused on the differences between European and American studies in patient characteristics and abstinence requirements prior to study inclusion (see Franck & Jayaram-Lindstrom, 2013; Zindel & Kranzler, 2014 for discussion). Patient characteristics and/or subpopulations could be the critical reason for the difference in efficacy, as acamprosate may provide a particular benefit in promoting abstinence in highly motivated and abstinent drinkers (Maisel et al., 2013) or in females with a late age-of-onset of drinking and negative family history (Verheul et al., 2005). Once again, particular subgroups may respond better to one pharmacotherapy versus another and no single treatment has proven effective for producing abstinence in all drinkers.

Anticonvulsants/GABAeric agents—Recent research efforts have been focused on assessing the efficacy of anticonvulsant medications for the treatment of AUDs. Several studies have examined topiramate, an anticonvulsant with several mechanisms of action including facilitation of GABAergic neurotransmission, inhibition of L-type calcium channels, and antagonism of the excitatory AMPA and kainate glutamate receptors (Kuzniecky et al., 1998; Matsumura & Nakaki, 2014). A double-blind, randomized clinical trial demonstrates that oral administration of topiramate reduced the number of 'heavy drinking days' in alcohol-dependent individuals (Johnson et al., 2007). These findings are consistent with others showing efficacy of topiramate in the treatment of alcohol dependence (Johnson et al., 2003; Johnson et al., 2004; Ma et al., 2006; Fernandez Miranda et al., 2007; Baltieri et al., 2008; Rubio et al., 2009). Topiramate is more efficacious in promoting abstinence than acamprosate (Narayana et al., 2008), and as good or better than naltrexone for treating alcohol dependence (Belcheva et al., 1991; Florez et al., 2008; 2011). In contrast, rates of abstinence were higher for disulfiram (Koppaka et al., 2012) than for topiramate in a 9-month randomized trial (De Sousa et al., 2008).

Gabapentin, an inhibitor of voltage-gated calcium channels (Sills, 2006), is another anticonvulsant medication assessed for treatment of alcohol dependence. Results from a recent randomized clinical trial indicate that oral administration of gabapentin dose-dependently increases rates of abstinence in recently detoxified alcohol-dependent individuals (Mason et al., 2014). In contrast, findings from a 4-week randomized trial indicate that gabapentin did not promote abstinence in alcohol-dependent males (Furieri & Nakamura-Palacios, 2007). These results are consistent with another trial that suggested that higher doses of gabapentin are not effective in increasing rates of abstinence (Anton et al., 2009). Zonisamide, a sodium channel blocker (Leppik, 2004), resulted in significantly fewer self-reports of craving in a 12-week trial (Rubio et al., 2010), but did not promote abstinence in another 12-week trial (Arias et al., 2010). Other anticonvulsant medications, such as oxcarbazepine, a calcium channel blocker (Croissant et al., 2006; Stefani et al., 1995), and tiagabine, an inhibitor of the GABA transporter, GAT-1 (Meldrum & Chapman, 1999; Paparrigopoulos et al., 2011) have shown limited therapeutic potential for the treatment of alcohol dependence.

Baclofen, a $GABA_B$ receptor agonist used to treat skeletal muscle spasms (Browning & Travagli, 2001), has been assessed for promoting abstinence in alcohol-dependent individuals, spurred by the popular press surrounding a book describing one doctor's detailed self-report of the efficacy of high dose baclofen for alcoholism (Ameisen, 2005). One randomized, double-blind 12-week trial demonstrated that baclofen administration resulted in significant rates of abstinence compared to placebo. These findings were consistent with prior work indicating that baclofen administration is efficacious in promoting abstinence in dependent individuals (Addolorato et al., 2002; Addolorato et al., 2011). However, other randomized trials suggest that baclofen did not promote abstinence at 12 months (Garbutt et al., 2010). A recent meta-analysis found only weak support for its abstinence promoting effects (Lesouef et al., 2014). In sum, these studies collectively show that the relationship between anticonvulsants and abstinence remains unclear in regards to treatment of AUDs.

Serotonergic Agents—Selective serotonin reuptake inhibitors (SSRIs) also have been assessed as potential candidates for treatment of AUDs as comorbidity rates of alcohol dependence and mood disorders are high. Results from a 14-week double-blind trial indicate that the SSRI, sertraline (did not affect percentage of “drinking days” but did increase relapse rates (Nutt et al., 1999; Pettinati et al., 2001). In one double blind, randomized trial, administration of sertraline produced significant decreases in alcohol consumption in late-onset alcohol-dependent individuals, but significant increases in consumption were observed in early-onset alcoholics treated with sertraline (Kranzler et al., 2011). Further, sertraline administration produced significant decreases in ‘heavy drinking days’ in late-onset alcohol-dependent individuals at 3-months post treatment (Kranzler et al., 2012). In contrast, administration of the SSRI, fluvoxamine did not produce significant increases in abstinence rates as compared to placebo in early onset alcohol-dependent individuals (Chick et al., 2004; Stahl, 1998). Similarly, escitalopram, a newer SSRI, was not effective in relapse prevention when administered alone, but was shown to be effective when administered in combination with other drugs, such as gabapentin and naltrexone (Braestrup & Sanchez, 2004; Stella et al., 2008).

Ondansetron, a serotonin 5-HT3 receptor antagonist, α7 nAChR antagonist and antiemetic, produced significant decreases in alcohol consumption in early onset alcohol-dependent individuals compared to late-onset alcoholics in an open-label 8-week study (Arcioni et al., 2002; Kranzler et al., 2003). These findings were consistent with others who found that ondansetron dose-dependently promoted abstinence in early-onset patients, but not in late-onset patients (Roache et al., 2008). In a randomized 11-week trial, ondansetron promoted abstinence in individuals with functional polymorphisms of the serotonin transporter gene (Johnson et al., 2011). Also, metadoxine, a 5HT2B antagonist (Daniely et al., 2011) was found to promote abstinence in alcohol-dependent individuals (Guerrini et al., 2006). Collectively, these findings suggest that there are individual differences (e.g., early versus late onset and polymorphisms in serotonin transporter gene) that underlie the differing efficacies of serotonergic agents for the treatment of AUDs. Drug combination therapy also should be considered when assessing effects of serotonergic agents on abstinence.

Dopaminergic Modulators—Antipsychotic medications have been assessed previously as potential candidates for the treatment of AUDs. Aripiprazole, an atypical antipsychotic medication, partial agonist at D2 and 5HT1A receptors, and 5HT2A antagonist, was assessed in a double blind clinical trial for treatment of alcohol dependence (Anton et al., 2008; Potkin et al., 2003). Aripiprazole did not promote abstinence in alcohol-dependent individuals compared to placebo. Flupenthixol, an antagonist at D2 and 5HT2A receptors, resulted in significant increases in relapse rates compared to placebo at both 6 and 12 months (Reimold et al., 2007; Wiesbeck et al., 2001; Wiesbeck et al., 2003). Consistent with these results, other studies have shown that antipsychotics, such as olanzapine, a D2 and 5HT2A receptor antagonist (Bymaster et al., 1996; Guardia et al., 2004), tiapride, a selective D2 antagonist (Bender et al., 2007; Navarro & Manzaneque, 1997), lisuride, a dopamine agonist (Rinne, 1989; Schmidt et al., 2002), and amisulpride, an antagonist at D2 and D3 receptors (Marra et al., 2002; Perrault et al., 1997) do not effectively promote abstinence in

alcohol-dependent individuals. These findings suggest that administration of dopaminergic agents alone is not efficacious in the treatment of AUDs.

Opioid Receptor Antagonists—Nalmefene is a kappa opioid receptor antagonist derived from naloxone (Faden et al., 1988) and currently approved in European countries for the treatment of alcohol dependence in patients who do not seek abstinence as a realistic goal. Results from large-scale randomized clinical trials indicate that as-needed oral administration of nalmefene, in combination with cognitive therapy, significantly reduces alcohol consumption in detoxified alcohol-dependent individuals (Gual et al., 2013; Mann et al., 2013; van den Brink et al., 2013). Future studies are needed to compare the efficacy of nalmefene to naltrexone for the treatment of AUDs.

In summary, these clinical studies demonstrate that several novel putative pharmacotherapies may offer hope to reduce rates of alcohol consumption in individuals with an AUD. Furthermore, an area of opportunity that has emerged in medications development is in human genetics, i.e. pharmacogenetics, which has led to the identification of specific genotypes that respond best (or worse) to particular pharmacotherapies (Zindel & Kranzler, 2014). Utilizing pharmacogenetic approaches, or personalized/precision medicine, along with defining successful treatment as a reduction in intake (and not what may be an unrealistic goal of abstinence), should broaden the options available for the treatment of AUDs. However, much remains to be learned and there are no drugs approved for cessation of alcohol and nicotine intake. As is discussed in the next section, nicotine changes many aspects of the addicted individual, from neurobiology to treatment response.

Alcohol and Nicotine: Mechanisms of interaction

The high rate of comorbid alcohol and nicotine dependence suggests the likelihood of a pharmacological interaction between alcohol and nicotine in the central nervous system. This interaction is especially clear in human studies where drinking alcohol increases various measures related to smoking, including amount of cigarettes smoked (Mitchell et al., 1995), ratings of how pleasurable smoking is (Rose et al., 2004; Harrison et al., 2009), and craving to smoke (King & Epstein, 2005; for review see McKee & Weinberger, 2013). Conversely, smoking appears to increase alcohol drinking, most likely through enhancing the reinforcing effects of alcohol while reducing its perceived sedative effects (Batel et al., 1995; Perkins et al., 1995; McKee et al., 2004; 2007; 2010; Harrison & McKee, 2008; McKee & Weinberger, 2013). Animal models have provided compelling evidence of this interaction in humans as nicotine enhances alcohol consumption in a variety of models (Blomqvist et al., 1993; Smith et al., 1999; Le et al., 2000; 2003; 2014; Doyon et al., 2013a; Sharma et al., 2014). Indeed, nicotine may drive the transition to compulsive drinking (Leao et al., 2015). However, the neurobiological and/or pharmacological mechanism behind this interaction is not yet clear, but likely arises from neural substrates that are common to both drugs. Although alcohol and nicotine have pharmacological actions in similar receptor systems, the effects of concurrent administration are not always additive, and in some cases are opposing (Lajtha & Sershen, 2010). This section of the review will describe the little that is known about the effects of concurrent alcohol and nicotine administration on major neurotransmitter and signaling systems implicated in the development of alcohol and

substance use disorders. Currently approved and experimental therapeutic agents that target these particular systems are discussed within each section to help illustrate the neurobiological mechanisms underlying the interaction of alcohol and nicotine.

Nicotinic Acetylcholine Receptors—Much attention has focused on one common site of action of both alcohol and nicotine, nAChRs (Larsson & Engel, 2004; Drews & Zimmer, 2010; Cui et al., 2012; Doyon et al., 2013b). A large body of evidence, derived from human and animal subjects, suggests that pharmacological blockade of nAChRs reduces alcohol seeking and alcohol self-administration (Rahman & Prendergast, 2012). For example, administration of the non-selective nAChR antagonist, mecamylamine, reduces alcohol drinking in a host of animal models, as well as reduces the effects of alcohol on NAc dopamine release (Ericson et al., 1998; Le et al., 2000; Soderpalm et al., 2000; Farook et al., 2009). As detailed above, however, results with mecamylamine in human smokers, have been mixed. Considering its adverse, peripheral effects on autonomic ganglia, the use of mecamylamine for the cessation of alcohol drinking is limited (Rahman & Prendergast, 2012; Rahman et al., 2014).

Although the effect of alcohol on nAChRs appears to be nicotinic subtype dependent and region specific (Yoshida et al., 1982; Booker & Collins, 1997; Jerlhag et al., 2006; see also Larsson & Engel, 2004; Doyon et al., 2013b for review), the alcohol and nicotine addiction literature converge on α4β2-containing nAChRs, which are expressed on cell bodies of dopaminergic neurons in the VTA and on axon terminals in the striatum. Activation of these receptors elicits extracellular dopamine release in the NAc, which is believed to produce the rewarding effects of both drugs (Wonnacott, 1997; Soderpalm et al., 2000; Zoli et al., 2002; Champtiaux et al., 2003; Steensland et al., 2007; Chatterjee & Bartlett, 2010). Although the high affinity nAChRs, in particular, are implicated in mediating the rewarding effects of alcohol, there may well be roles for both high and low affinity nAChRs in mediating the rewarding effects of alcohol. Specifically, neuronal nAChRs containing α3/β2*, β3*, and/or α6* subunits also appear to mediate rewarding effects of alcohol (Kuzmin et al., 2009). Recent work implicates a role for α6-containing nAChRs for both drugs (Schilaty et al., 2014), though their interaction may be indirect, through amplifying AMPA receptor function in the VTA (Engle et al., 2015). Although alcohol enhances nAChR-mediated currents *in vitro*, an effect not blocked by nAChR α7 antagonist α-bungarotoxin (Aistrup et al., 1999), mice lacking the α7 subunit consumed less alcohol than did wild-type mice (Kamens et al., 2010). Thus, the homomeric α7 receptors have a role in alcohol and nicotine action. Nicotine may mitigate alcohol-induced neurotoxicity in adults, likely through α7-mediated effects on inflammation and/or activation of the cholinergic anti-inflammatory pathway (Han, 2014).

Whereas dihydro-β-erythroidine, a selective α4β2 antagonist, failed to reduce alcohol drinking in male mice (Larsson et al., 2002), there has been success in both alcohol and nicotine drinking cessation with nAChR partial agonists. Cytisine, a partial agonist at β2-containing nAChRs (but also a full agonist at α3β4 and α7*; Carbonnelle et al., 2003), reduced alcohol intake in a variety of rodent models (e.g. Bell et al., 2009; Sajja & Rahman, 2011, 2013a;b Sotomayor-Zarate et al., 2013). Despite the success of cytisine in animal

models and its approval for smoking cessation in Europe, its limited commercial appeal decreases the likelihood of its broad use.

The cytisine derivative and α4β2 nAChR partial agonist, varenicline however, shows some promise. Varenicline reduced voluntary alcohol intake in both animal models and human subjects (Steensland et al., 2007; McKee et al., 2009; 2013; Hendrickson et al., 2010; Kamens et al., 2010; Bito-Onon et al., 2011; Chatterjee et al, 2011; Saija and Rahman, 2013, Wouda et al., 2011; Mitchell et al., 2012; Litten et al, 2013; Sotomayor-Zarate et al., 2013; Kaminski and Weerts, 2014; de Bejczy et al, 2015; see also Chatterjee & Bartlett, 2010; Nocente et al., 2013; and Erwin & Slaton, 2014 for review). Preclinical studies demonstrated that the α4-containing receptor is necessary and sufficient for varenicline to decrease alcohol consumption (Hendrickson et al., 2011), whereas other nAChR subtypes do not appear to play as critical of a role (Hendrickson et al., 2010; Kamens et al., 2010; Liu et al., 2013; Santos et al., 2012). One of the first studies to evaluate varenicline's effects on alcohol intake and alcohol craving was a double-blind, placebo-controlled, human laboratory study employing non-alcohol dependent, heavy drinking smokers (n=20). Varenicline reduced alcohol self- administration (voluntary alcohol intake during a 2 hr period) and reduced alcohol craving and its subjective reinforcing effects (McKee et al 2009). In a small trial employing non-dependent, heavy drinking smokers treated with varenicline for 4 weeks, a reduction in alcohol craving and a non-significant reduction in the number of heavy drinking days were reported; however, no difference in the number of drinks consumed was found with varenicline (Fucito et al., 2011). In a randomized, double-blind 16 week trial, varenicline reduced alcohol consumption in non-treatment seeking, also non-alcohol dependent, heavy-drinking smokers; although the effect on drinking was independent of the effect on smoking (Mitchell et al., 2012). Using an epidemiological sample of smokers surveyed by phone from four countries, varenicline was associated with a reduced likelihood of drinking alcohol, which was also independent of smoking cessation (McKee et al., 2013). In a multi-site double-blind clinical trial evaluating 13 weeks of varenicline in a larger group (n=400) of subjects, who importantly were alcohol dependent and were stratified to treatment condition on baseline smoking status upon randomization, varenicline reduced both alcohol consumption and alcohol craving, which was independent of smoking status (Litten et al., 2013). A recent secondary analysis of the data from the Litten et al (2013) data revealed that varenicline had greater efficacy to decrease alcohol consumption in subjects who reduced their smoking and in those subjects who had "less severe" alcohol-dependence (Falk et al., 2015). Some recent small but placebo-controlled clinical trials have found that varenicline does not always reduce alcohol drinking or smoking, though it appears to effectively reduce alcohol craving (Plebani et al., 2013; Schacht et al., 2014). Importantly, in the subgroup of baseline smokers in the Plebani study, varenicline decreased self-reported tobacco smoking and had a lower rate of heaving drinking (Plebani et al., 2013). The reduction in alcohol craving may be the result of varenicline reducing the rewarding properties of alcohol or due to it's enhancing the aversive effects of alcohol. These studies in particular, suggest that varenicline might be most effective among treatment-seeking individuals who are motivated to decrease alcohol and/or nicotine consumption. Therefore, like the majority of treatments for either substance alone, no single drug has been widely successful in alcohol or nicotine cessation.

There are several limitations that should be taken into account in the interpretation of these clinical studies. First, the number of subjects in most studies was relatively small and the length of varenicline treatment varied from 1 to 16 weeks. Further, only one dose of varenicline was used when evaluating efficacy as a treatment for alcohol dependence, i.e., the dose used for tobacco cessation. Higher varenicline doses or longer treatment periods may be required to reduce alcohol intake than to reduce nicotine intake since varenicline acts directly at nicotinic receptors, whereas alcohol only modulates nicotinic receptor function. Also, the efficacy of varenicline may be dependent on the amount of alcohol consumed, which is difficult to determine considering the categorization of the subjects as not heavy drinkers, heavy drinkers or very heavy drinkers. Also, only two of the studies reported data for alcohol dependent non-smokers, as most of the subjects in these studies had concurrent nicotine dependence, as has been reported in the literature. Nevertheless, the majority of the studies indicate that the effects of varenicline were independent of tobacco smoking, and the most consistent finding was a varenicline-induced reduction in alcohol craving.

Dopamine signaling—Intertwined in the nAChR story, is another major neural substrate common to both drugs and their abuse/addiction, the mesolimbic dopamine reward system (Wise and Bozarth, 1987; Wise and Rompre, 1989; Di Chiara, 2000; Gonzales et al., 2004; Koob and Vokow, 2010; De Biasi and Dani, 2011). The mesolimbic dopamine system consists of dopamine projections from the VTA to limbic structures including NAc, amygdala and prefrontal cortex. The rewarding and reinforcing properties of nicotine and alcohol are associated with an increase in dopamine release in NAc (Di Chiara and Imperato, 1986, 1988; Benwell and Balfour, 1992; Samson et al., 1992; Diana et al, 1993; Weiss et al., 1993). A number of interconnected brain circuits regulate VTA activity and function and provide potential targets for both nicotine and alcohol effects that underlie their complex interaction (Fields et al., 2007; Hendrikson et al., 2013). For example, excitatory cholinergic input to the VTA from the pedunculopontine tegmental and laterodorsal tegmental areas have an important modulatory role on the VTA activity (Larsson and Engel, 2004; Laviolette and van der Kooy, 2004), and are likely involved in the associations between nicotine and alcohol use. A number of nicotinic receptor subtypes are expressed on VTA dopamine neurons including α4β2*, α4α5β2*, α4α6β2*, α6β2* and α7, and mediate dopamine release (Picciotto et al, 1998; Champtiaux et al., 2002; Grady et al, 2007; Gotti et al., 2010). Excitatory afferents to the VTA also arise from the dorsal raphe serotonergic neurons (Herve et al., 1987) and inhibitory afferents come from GABAergic neurons in the rostromedial tegmental nucleus, ventral pallidum, LDTg, and NAc (Geisler and Zahm, 2005; Xia et al., 2011; Jhou et al., 2009).

The interaction of nicotine and alcohol on the complex regulation of VTA function has only recently been evaluated. Through different mechanisms, nicotine and alcohol each increase the firing rate and phasic bursting activity of VTA dopamine neurons projecting to NAc facilitating dopamine release (Gessa et al., 1985; Mameli-Engvall et al., 2006; Schilstrom et al, 2003; Foddai et al, 2004; Exley et al, 2011). Nicotine directly activates nicotinic receptors in VTA (Mameli-Engvall et al., 2006; Exley et al, 2011) and activates cholinergic inputs from LDTg and PPTg (Omelchenko and Sesack, 2005; Floresco et al, 2003; Lodge

and Grace, 2006; Maskos, 2008), as well as a number of other afferents that converge on the VTA dopamine system (Doyon et al., 2013a,b). Alcohol acts less specifically relative to nicotine, but also directly and indirectly activates VTA dopamine neurons (Brodie et al., 1990, 1999; Okamoto et al, 2006; Hendrickson et al., 2013). Nicotinic receptors have been suggested to be targets of alcohol potentiation as a result of stabilization of the open channel state of the receptor (Wu et al., 1994; Nagata et al., 1996; Forman and Zhou, 1999; Zuo et al., 2004). Nicotine and alcohol each increase dopamine release in NAc in microdialysis studies (Di Chiara and Imperato, 1986, 1988; Ericson et al, 1998; Doyon et al, 2003; Larsson et al., 2005). Interestingly, alcohol-induced NAc dopamine release involves nicotinic receptors in VTA and locally in NAc (Blomqvist et al, 1993; Ericson et al, 1998; Le et al., 2000; Soderpalm et al., 2000; Farook et al, 2009a; Hendrickson et al., 2013). Alcohol-induced NAc dopamine release is blocked by mecamylamine, a nonselective nicotinic receptor antagonist in VTA, but not NAc (Blomqvist et al, 1993, 1997; Ericson et al., 2008; Larsson and Engel, 2004; Larsson et al, 2005), alpha-conotoxin MII, a selective antagonist for alpha6-containing nicotinic receptors (Larsson et al, 2004; Kuzmin et al., 2009), and varenicline, an alpha4beta2 partial agonist (Ericson et al., 2009).

Although nicotine and alcohol reward and abuse clearly involve the mesolimbic dopamine system, mechanistic information has been obtained only recently to help explain the complex and multifaceted interactions between nicotine and alcohol on the mesolimbic dopamine system. The timing and order of presentation of nicotine and alcohol has a profound influence on the overall outcome. That is, simultaneous co-administration of nicotine and alcohol produces an *additive* increase in NAc dopamine release relative to the response of each drug (Tizabi et al., 2002; Doyon et al., 2013a,b). Perhaps surprisingly, pretreatment with nicotine *diminishes* the sensitivity of the mesolimbic dopamine system to alcohol (Lopez-Moreno et al., 2008; Doyon et al., 2013a,b; Ostroumov et al., 2015). An acute 3, 15 or 40 hr pretreatment with nicotine (0.4 mg/kg, ip) significantly blunted the alcohol (1.5 g/kg, iv)-induced increase in dopamine release in rat NAc (Doyon et al., 2013a,b). This prolonged inhibitory effect of nicotine on alcohol-induced dopamine release was blocked by dihydroxy-beta-erythroidine (DHBE) pretreatment, but not by methyllycaconitine (MLA), indicating specific involvement of β2-containing, but not α7-containing nicotinic receptors. Importantly, pretreatment with nicotine did not inhibit nicotine-induced dopamine release, suggesting that the nicotine-induced attenuation of the alcohol effects on dopamine release could not be explained simply by changes in nicotinic receptor function. Rather, the prolonged (15–40 hr) effect of acute nicotine pretreatment on dopamine release induced by alcohol was suggested to be due to an enhancement of GABAergic inhibition of dopamine neuron firing in VTA and required stress hormone signaling (glucocorticoid and/or progesterone) specifically in the VTA (Doyon et al., 2013a,b; Ostroumov et al., 2015). The observation that acute pretreatment with nicotine blunts the mesolimbic dopaminergic response to alcohol seems counter to the greater alcohol intake in smokers. However, as suggested previously (Martinez et al., 2005), a reduction in dopamine system functioning likely leads to compensatory increases in alcohol intake to augment dopamine release and further promote reward. These findings are certainly intriguing. Important follow-up questions to this research include determining the nicotine dose relationship, the impact of chronic intermittent administration of nicotine on

the effect of alcohol on the mesolimbic dopamine system, the duration and dose (binge) of alcohol presentation and questions regarding experimenter administered versus self-administered drug.

GABAergic signaling—Given that GABAergic neurotransmission has received extensive attention regarding alcohol's intoxicating effects; it follows that this neurotransmitter system would be implicated in concurrent nicotine and alcohol abuse. GABA is the primary inhibitory neurotransmitter in the brain and regulates the mesolimbic dopamine system (Kalivas, 1993). Alcohol-induced adaptations of the ionotropic $GABA_A$ subtype of receptors (Kumar et al., 2009) are ultimately responsible for alcohol tolerance (Liang et al., 2007) and physical dependence (Liang et al., 2004). Less research has been done on metabotropic $GABA_B$ receptors, however positive allosteric modulators of $GABA_B$ receptors have recently become a target for drug development in the treatment of AUDs and other drugs of abuse (Agabio et al., 2012; Phillips & Reed, 2014). As discussed above, concurrent alcohol and nicotine use modulates GABAergic signaling within the mesolimbic dopamine system. Alone, both drugs produce dose dependent increases in NAc dopamine levels and when applied concurrently, they additively increase dopamine release at low, but not high, doses (Doyon et al., 2013a; Tizabi et al., 2002). However, GABAergic interneurons in the NAc express nAChR subtypes that are desensitized by nicotine (Pidoplichko et al., 2004). The net effect is that nicotine pretreatment and receptor desensitization decreases alcohol induced dopamine release in the NAc by enhancing GABAergic transmission in the VTA (Doyon et al., 2013a). Additionally, nAChRs modulation reduces $GABA_AR$ sensitivity to $GABA_AR$ agonists, including alcohol (Lof et al., 2007). Behaviorally, this could lead to decreased sedative and increased activating properties of alcohol (Lof et al., 2007), which is consistent with reports from human studies (Perkins et al., 1995).

Additionally, nAChRs are important modulators of GABAergic and glutamatergic neurotransmission in the hippocampus. Specifically, $\alpha7$ and $\alpha4\beta2$ nAChRs are highly concentrated on inhibitory hippocampal interneurons and mediate nicotine potentiation of GABAergic transmission within the hippocampus (Proctor et al, 2011). Therefore, nicotine indirectly increases GABAergic neurotransmission through the $\alpha7$ and $\alpha4\beta2$ nAChRs, and alcohol potentiates this effect (Proctor et al., 2011).

The $GABA_A$ receptor complex is also directly affected by simultaneous nicotine and alcohol addiction and withdrawal. For instance, tobacco smokers had a decreased availability of benzodiazepine sensitive $GABA_A$ receptors compared to non-smokers during recovery from alcohol dependence (Staley et al., 2005). Given that the upregulation of benzodiazepine sensitive $GABA_A$ receptors correlates with alcohol withdrawal severity, the nicotine-induced suppression of receptor availability found in tobacco smokers may attenuate some of the symptoms of alcohol withdrawal (Cosgrove et al., 2011). Although nicotine may reduce some of the GABA-mediated symptoms of alcohol withdrawal, as mentioned earlier, smoking reduces overall alcohol abstinence rates (McKee & Weinberger, 2013). Indeed, during protracted withdrawal, $GABA_A$ receptor upregulation remains only in alcohol dependent individuals who smoke, but return to normal in alcohol dependent non-smokers, and the level of $GABA_A$ receptor upregulation correlates with craving for alcohol and cigarettes (Cosgrove et al., 2014). Interestingly, in non-human primates dependent on

nicotine instead of cigarettes, $GABA_A$ receptors return to baseline after one month of abstinence in both nicotine and control groups during alcohol abstinence (Cosgrove et al., 2014). These results indicate that it may be the constituents in tobacco smoke, rather than nicotine, which prevent the normalization of GABAergic signaling. Nevertheless, tobacco smoking has a powerful modulatory effect on alcohol-induced $GABA_A$ receptor changes during alcohol withdrawal and abstinence.

Glutamatergic signaling—Excitatory neurotransmission is a common target for alcohol and nicotine (for review see Prendergast & Mullholland, 2012) and modulatory interactions between alcohol and nicotine are mediated, in part, via modulation of glutamatergic neurotransmission. Glutamatergic systems include ionotropic (N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and kainate receptors) and metabotropic glutamate (mGlu) receptors (e.g., group 1 mGlu-family proteins). Overstimulation of these amino acid receptor complexes is known to produce cell death following exposure to ethanol and other excitotoxins (Olney et al., 1986). The NMDA receptor is a likely candidate for producing these excitotoxic effects *in vitro*; through an excessive influx of extracellular calcium and the subsequent activation of phospholipases, endonucleases, and proteases (Choi, 1992). Indeed, chronic alcohol exposure increases calcium influx through NMDA receptors, confers the sensitivity of NMDA receptors (Lovinger et al., 1993), increases expression of NMDA-receptor complexes (Floyd et al., 2003), and increases aggregation of NMDA receptors at the synapse (Carpenter-Hyland et al., 2004). Neuroadaptive effects of NMDA receptors and group 1 mGlu-family protein following binge-like alcohol exposure contributes functionally to cytotoxicity of hippocampal cell layers neurotoxic effects of alcohol *in vitro* and *in vivo* (Reynolds et al., 2015a; b).

Recent research efforts have delineated the influence of glutamatergic signaling on the interactive effects of alcohol and nicotine. For example, co-administration of alcohol and nicotine for 10 consecutive weeks produced long-lasting increases in basal extracellular glutamate within the medial prefrontal cortex whereas neither alcohol nor nicotine produced these effects alone (Deehan et al., 2015). Leão et al. (2015) suggest a role for glutamatergic pyramidal neurons in the dorsomedial prefrontal cortex in acceleration of compulsive alcohol drinking in alcohol-dependent rats following chronic nicotine administration (8 mg/kg/day). These synergistic effects of alcohol and nicotine on glutamate release likely reflect neuroadaptative changes in glutamate receptor function. For example, Ford et al. (2012) demonstrated that NMDA receptor activity mediates the discriminative-stimulus effects of alcohol and nicotine co-administration in inbred C57BL/6J trained to discriminate alcohol-nicotine mixtures (0.8 mg/kg nicotine+0.5–2.0 g/kg alcohol). In vitro, the combined application of alcohol (5 mM) and nicotine (100 nM) increases AMPA receptor function in VTA dopaminergic neurons whereas neither alcohol nor nicotine altered the function of these receptors alone (Engle et al., 2015). Other prior studies employing electrophysiological techniques demonstrate that alcohol application (80 mM) attenuates nicotine-induced increase in hippocampal NMDA and AMPA excitatory postsynaptic currents (EPSPs) (Proctor et al., 2011). In addition, microarray and western blot analyses reveal that tobacco smoking produced marked increases in vesicular glutamate transporters

SLC17A6 and SLC17A7 in the human VTA whereas co-exposure to alcohol reversed these effects (Flatscher-Bader et al., 2008). Collectively, these studies demonstrate that alcohol and nicotine interactions produce neuroadaptative changes in glutamatergic neurotransmission and signaling that likely contribute to their abuse potential via alterations in synaptic plasticity.

Endogenous opioids—The endogenous opioid systems in brain are widely distributed and consist of at least three major receptor subtypes, i.e., μ, δ and κ. Each of these subtypes has preference for endogenous opioid, with μ being selective for β-endorphin, δ being selective for met- and leu-enkephalin and κ being selective for the dynorphins A and B. The strongest evidence for an involvement of endogenous opioid peptides in concurrent alcohol and nicotine use comes from clinical trials using naltrexone (Revia® or Depade®), which is a non-specific opioid receptor antagonist with an active metabolite 6β-naltrexol. Although not specifically evaluated as a potential therapeutic for comorbid alcohol and nicotine dependence, it has been tested against each substance separately as discussed above. While naltrexone does not differentiate among μ, δ and κ opioid receptors, κ receptors may play a prominent role based on work with nalmefene. Nalmefene is a κ opioid receptor antagonist derived from naloxone (Faden et al., 1988) and results from large-scale randomized clinical trials in Europe indicate that oral administration of nalmefene, in combination with cognitive therapy, significantly reduces alcohol consumption in detoxified alcohol-dependent individuals as discussed above (Mann et al., 2013; van den Brink et al., 2013). Despite these findings, there is little work specifically assessing the role of opioid peptides on concurrent alcohol and nicotine dependence. One preclinical study assessed the effects of naltrexone using a multiple schedule of reinforcement in which rats received either alcohol or nicotine in alternating 5-min intervals each day (Le et al., 2014). Naltrexone reduced alcohol intake, but not nicotine intake. In contrast, other preclinical studies examining antinociception have shown an additive effect of alcohol and nicotine that is reduced by naloxone (Campbell et al., 2006), as well as by μ, δ and κ selective antagonists (Campbell et al., 2007). Together, these findings suggest a dissociation between the role of opioid peptides in regulation of combined alcohol and nicotine reward from the regulation of combined alcohol and nicotine antinociceptive activity, which is likely due to differences in limbic and brainstem systems controlling these behaviors.

Serotonin—Serotonin systems are known to play a prominent role in emotional processing, aggressivity and other mood-based traits (Lin et al., 2014; Cools et al., 2011). From serotonin-synthesizing cell bodies in the midbrain raphe system, serotonin neurons project rostrally to innervate various limbic and cortical structures. The serotonin pathway emanating from the dorsal raphe consists of primarily fine axons that are highly susceptible to neurotoxic damage following drug treatment (Wilson et al., 1989), which may underlie some of the mood disturbances that accompany drug abuse. However, as for the specific role of serotonin in concurrent alcohol and nicotine dependence, the evidence is largely circumstantial. For example, at least one report has speculated that serotonin may mediate the ability of nicotine to enhance dopamine VTA activity and alcohol reward (Soderpalm et al., 2000). Circumstantial evidence also indicates that serotonin systems are involved in comorbid depression and polydrug abuse. SSRIs can ameliorate the comorbid occurrence of

depression with addiction to various drugs of abuse, including alcohol and nicotine (Torrens et al., 2005). Further, variants of the repeat length polymorphisms of the serotonin transporter gene are associated with both depression and polydrug abuse (Homberg & Lesch, 2011; Murphy et al., 2003). Thus, although more direct evidence is needed, it appears that affective disorders involving serotonin dysfunction may be a common pathway for multiple addictive disorders, and thus treating the underlying depression may reduce alcohol and nicotine polydrug abuse.

Endocannabinoid—One area particularly ripe for discovery is in the endocannabinoid system. The endocannabinoid signaling system, though originally identified as the endogenous site of action for Δ9-tetrahydrocannabinol (THC) from Cannabis sativa (Matsuda et al., 1990), is now known for its roles in modifying synaptic efficacy (Freund & Hajos, 2003). The endocannabinoid signaling system consists of two main types of G-protein coupled receptors, the cannabinoid 1 (CB1) and 2 (CB2) receptors and their endogenous ligands, the endocannabinoids, such as anandamide and 2-arachidonoylglycerol which remain the best characterized (Devane et al., 1992; Herkenham et al., 1990; Sugiura et al., 1995); see also (Hillard et al., 2012; Piomelli, 2003) for review). The breadth of the roles the endocannabinoid system plays in brain and behavior is highlighted by the fact that the CB1 receptor is considered the most abundant G-protein coupled receptor and accounts for the majority of cannabinoid action in brain (Herkenham et al., 1990). CB1 receptors are expressed at high levels in many of the brain regions implicated in addiction such as basal ganglia, cingulate cortex, frontal cortices and hippocampus, while moderate levels are found in many other addiction-relevant regions such as amygdala, basal forebrain and NAc (Mackie, 2005). Indeed, others have noticed the remarkable overlap in the expression of nAChRs and CB1 receptors in the mesolimbic dopamine system, amygdala, and hippocampus (Gamaleddin et al., 2015), which may underlie the interaction between endocannabinoid and cholinergic systems, especially in nicotine abuse/dependence (Narushima et al., 2007). Similarly for alcoholism, many groups have explored the relationship between alcohol exposure, alcohol addiction and the endocannabinoid system (e.g. (Hansson et al., 2007; Hungund & Basavarajappa, 2004; Naassila et al., 2004); see also (Pava & Woodward, 2012). It seems that many studies have implicated the endocannabinoid system for their on demand presynaptic action in modulating dopamine release in both drug and natural rewards (Cheer et al., 2007). And, as has been reviewed for alcohol (Pava & Woodward, 2012) or nicotine (Gamaleddin et al., 2015) elsewhere, low CB1 levels are associated with a greater likelihood of developing an AUD (e.g. (Ortiz et al., 2004) while CB1 antagonism or deletion has been effective in reducing both alcohol and nicotine self-administration and other addiction relevant behaviors (e.g. (Castane et al., 2002; Cippitelli et al., 2005; Cohen et al., 2002; Freedland et al., 2001; Hungund & Basavarajappa, 2004; Hungund et al., 2003; Rodriguez de Fonseca et al., 1999; Simonnet et al., 2013); see also (Gamaleddin et al., 2015; Pava & Woodward, 2012) for more detailed review). Although there appear to be some similarities in how alcohol or nicotine alone affect the endocannabinoid system (e.g. Gonzalez et al., 2002), there are only a handful of studies that have investigated the combination of alcohol and nicotine on the endocannabinoid system and these have focused solely on manipulating CB1 receptors. For example, rimonabant, the CB1 receptor antagonist pulled from clinical trials for its psychiatric adverse drug reactions,

dose-dependently reversed nicotine-induced relapse to alcohol (Lopez-Moreno et al., 2007) as well as alcohol-induced nicotine conditioned place preference reinstatement (Biala & Budzynska, 2010). Thus, the role of the endocannabinoid system in drug abuse coupled with the common effects alcohol and nicotine have on the structure and function of the endocannabinoid system support that this system is ripe for discovery.

Need: Neurobehavioral methods for assessing potential medications

Animal models of voluntary drug taking behavior can provide good translational models for drug addiction behaviors in humans. However, it is important to identify which paradigms create successful animal models of addiction in order to efficiently and effectively test new treatments for addiction. Ideal behavioral paradigms for studying addiction treatment in animals are those that accurately predict the effectiveness of a clinical candidate in human trials. Previous research has primarily focused on animal models of either voluntary alcohol consumption or nicotine self-administration separately, with relatively few studies examining voluntary co-administration of alcohol and nicotine in the same animal (Funk et al., 2015; Hauser et al., 2012; Le et al., 2014; Marshall et al., 2003; see also McBride et al., 2014 for review). Finding a suitable model for alcohol drinking and nicotine self-administration is imperative in identifying and testing new compounds for this common polysubstance dependence.

Although there are many aspects of comorbid alcohol and nicotine dependence that merit examination during preclinical evaluation, including craving and relapse, the initial focus should be on establishing a reliable and high-throughput animal model that is based on voluntary alcohol and nicotine intake. However, rodents typically do not readily consume alcohol in quantities that are representative of binge drinking in humans. For this reason, it is common to use selective breeding techniques to increase the frequency and amount of alcohol consumed. Several selectively bred lines of mice have been generated for alcohol drinking (Crabbe et al., 2009; Matson & Grahame, 2013). However, since it is difficult to perform long-term studies on intravenous nicotine self-administration in mice, rats offer a distinct advantage. Among the various selective rat lines available, the alcohol-preferring (P) rat developed and maintained at Indiana University has been among the most widely used (Bell et al., 2006). P rats voluntarily consume not only intoxicating amounts of alcohol, but also avidly self-administer intravenous nicotine (Le et al., 2006). Thus, P rats may be especially advantageous for drug discovery for concurrent alcohol and nicotine use.

In outbred rats, various procedures have been designed to increase voluntary oral alcohol consumption, and include sucrose fading (Tolliver et al., 1988; Maldonado et al., 2008), food and water deprivation (Macenski & Meisch, 1992), and limited access to alcohol (Sinclair et al., 1992). Recently, sucrose and saccharin have been shown to be addictive in and of themselves (Morgan & Sizemore, 2011), acting as a more potent reinforcer than cocaine (Augier et al., 2012), while also potentially altering blood alcohol concentrations (Matthews et al., 2001). Therefore, the use of sweetened alcohol solutions adds a potential confounding variable in models of addiction. More recently, paradigms of intermittent access to alcohol have been shown to successfully induce high voluntary oral alcohol consumption (Simms et al., 2008; Hwa et al., 2011).

In terms of drug discovery to treat combined alcohol and nicotine dependence, preclinical investigational studies should include procedures that model concomitant use of both alcohol and nicotine. For *in vivo* model systems, viable procedures might include conditioned place preference, self-administration, and reward via intracranial brain stimulation. Among these, measuring medication-induced decreases in concomitant alcohol and nicotine intake would be modeled most closely using self-administration, with alcohol available orally and nicotine administered intravenously. Despite the importance and prevalence of comorbid alcohol and nicotine use, however, there is surprisingly little literature available on combined alcohol plus nicotine administration in animal models. In one relevant study in P rats, the nicotinic receptor desensitizer sazetidine-A was found to decrease alcohol and nicotine intake independently (Rezvani et al., 2010). While this research provides a potential therapeutic compound that is efficacious in reducing the intake of both drugs independently, a model needs to be developed that includes simultaneous availability of both alcohol and nicotine that typifies human smokers who drink heavily.

Little is known about the concurrent administration of alcohol and nicotine in animal models. In one study (Hauser et al., 2102), P rats were shown to readily self-administer alcohol plus nicotine solutions to attain pharmacologically relevant levels of both drugs. Although subjects were given access to the combination of alcohol and nicotine in solution, subjects were never given the choice between concurrently available alcohol and nicotine. Nonetheless, these findings, in combination with findings from animal addiction models for alcohol and nicotine individually, provide the foundation for exploring choice procedures with concurrent access to alcohol and nicotine to construct a useful animal model of alcohol and nicotine polysubstance addiction, which could be used to evaluate novel compounds as treatments.

One way to evaluate potential candidates as treatments for combined alcohol and nicotine polysubstance use is to use a concurrent schedule of reinforcement in animal models. With a concurrent schedule, alcohol and nicotine are available simultaneously, each presented under a simple schedule (e.g., fixed ratio); animals are able to switch back-and-forth freely between alcohol and nicotine. Concurrent schedules have been used frequently to study alcohol intake provided by two or more bottles that vary in alcohol concentration (Rodd-Henricks et al., 2001; Rodd et al., 2009). In addition, concurrent schedules have been used with access to either alcohol or food (Ginsburg & Lamb, 2006) and with access to either nicotine or food (Mello et al., 2013). In more recent studies, male Wistar rats were trained to self-administer alcohol alone, nicotine alone, then subsequently were given concurrent access to alcohol and nicotine (Funk et al., 2015; Le et al., 2014). Results from these studies indicated that while varenicline was found to decrease nicotine self-administration, alcohol self-administration was not altered. These results contrast with another study using outbred male Sprague-Dawley rats (Bito-Onon et al., 2011), which showed that nicotine pretreatment increased operant self-administration of oral alcohol, and this nicotine-induced enhancement of alcohol intake was decreased by varenicline. While this study did not use concurrent self-administration of both alcohol and nicotine, it does suggest that combined alcohol plus nicotine treatment may be sensitive to varenicline. These results are consistent

with human clinical trials discussed above where varenicline in human tobacco smokers reduced alcohol consumption (Mitchell et al., 2012).

As an alternative to concurrent schedules, a multiple schedule can be used in which animals earn either alcohol or nicotine in two alternating time components. In this schedule, only one reinforcer is available at a time and the different components are signaled by the presentation of a signal (e.g., light, tone). Multiple schedules have been used to assess the reinforcing effect of a single drug, such as cocaine, amphetamine or alcohol, in one component and food in the alternate component (Cohen, 1991; Weissenborn et al., 1995; Czachowski et al., 1999). A major advantage of multiple schedules in medication development is that the effect of a lead candidate can be ascertained relative to nonspecific actions on responding. For example, the SSRI fluvoxamine decreases alcohol intake at doses that do not reduce food intake (Ginsburg et al., 2005). Similarly, the nicotinic antagonist mecamylamine decreases nicotine self-administration at doses that do not decrease food-maintained responding (Stairs et al., 2010).

At least one study has examined alcohol and nicotine self-administration using a multiple schedule (Le et al., 2014). Results showed that nicotine increased alcohol consumption and, conversely, alcohol consumption decreased nicotine self-administration. Interestingly, the ability of naltrexone to decrease alcohol consumption was enhanced by nicotine self-administration using alternating access components, which indicates that an interactive effect of alcohol and nicotine according to this particular test with a pharmacotherapy. While these results are encouraging, selectively bred alcohol-preferring rats were not used in this latter study, and thus the amounts of alcohol consumed were relatively low.

Another procedure for examining the reinforcing effects of drugs in animals is the choice procedure. Typically, this type of procedure involves the choice between self-administration of a drug or selecting a non-drug reinforcing stimulus, such as food or water (Griffiths et al., 1981; Lenoir et al., 2013; Thomsen et al., 2014). After being trained initially to earn each reinforcer type separately, animals are given a choice to work for one of the two reinforcers. While there are many variations in the choice procedure, most procedures require an initial period of sampling both reinforcers, followed by choice trials. This procedure is often used to study differences in the reinforcing effects between two different drugs and two doses of the same drug (Hutto & Crowder, 1997; Caprioli et al., 2009). For example, a choice procedure determined that the relative reinforcing effect of cocaine was greater than the relative reinforcing effect of nicotine (Manzardo et al., 2002). The choice procedure also has been used to assess drug interaction effects in which animals learn to self-administer two drugs in order to produce a synergistic enhancement in reinforcement, e.g., the “speed-ball” effect when cocaine and heroin use are combined (Ward et al., 2005; Caprioli et al., 2009). Thus, choice procedures may find important utility for evaluating the effect of novel medications on the relative reinforcing effects of alcohol and nicotine.

Conclusions

Although much has been gained in our basic understanding of the neurobiology of addiction, major gaps exist in our understanding of polysubstance abuse, particularly the interaction of

alcohol and nicotine. As is obvious from the strikingly high rate of comorbid abuse – as high as 92% in people with AUDs (Miller and Gold, 1998) – the comorbid condition *is* the most prevalent condition. However, the main pharmacotherapeutic strategy thus far has been to develop medications that are efficacious in reducing *either* alcohol or nicotine use as separate entities. With alcohol dependence, the most common pharmacological treatments are naltrexone, acamprosate, and disulfiram; while in nicotine dependence, varenicline, bupropion, and nicotine replacement therapy are the most common pharmacological treatments. Even with these limited pharmacological options for the cessation of the individual drugs alone, none have been widely successful. While there is some promise in targeting the primary common site of action of alcohol and nicotine, the nAChRs, via the α4β2 nAChR partial agonist, varenicline, this may only be efficacious for a subpopulation of polysubstance abusers. Because people use and abuse drugs for a myriad of reasons, a similar variety of treatment approaches is necessary.

Recent funding initiatives such as the Collaborative Research on Addiction at NIH (CRAN) supplements have resulted in significant steps forward in our understanding of how these two drugs interact in the brain. However, as has been reviewed above, major research needs still are apparent and in areas that go beyond the obvious need for a better understanding of the pharmacological interactions of alcohol and nicotine and the discovery of novel targets and pharmacophores for new therapeutic approaches. There are critical needs for a better understanding of the various subpopulations within this comorbid condition and that knowledge must be integrated with the generation of better, valid models of polysubstance abuse. As Koob (2009) reviewed, the novel pharmacological targets discovered in these new models forms a heuristic framework for the successful development of novel medications to treat addiction. Thus, by better understanding the human disease state, which clearly involves more polysubstance abuse than we care to admit or have taken the time to investigate because of the complexities involved, drug discovery can be driven forward.

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Abbreviations

AUD	Alcohol Use Disorder
FDA	Food and Drug Administration
$GABA_AR$	γ-aminobutyric acid receptor
NAc	nucleus accumbens
nAChRs	nicotinic acetylcholine receptors
NMDAR	N-methyl-D-aspartate receptor
P rat	alcohol-preferring rat

SSRI	selective serotonin reuptake inhibitor
THC	Δ^9-tetrahydrocannabinol
VTA	Ventral tegmental area

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Table 1

Current approved and experimental therapeutics for nicotine cessation.

	Drug	Mechanism	Efficacy
Approved	NRT	Nicotine replacement	50–70% success at 12 weeks 20% success at 1 year (Stead et al., 2012)
	Bupropion	Allosteric antagonist at α3β4, α4β2, α6β2, and α7 nAChRs; NE & DA reuptake inhibitor	44% success at 7 weeks 23% success after 1 year (Hurt et al., 1997)
	Varenicline	Partial α4β2 nAChR agonist α7 agonist	44% success at 9–12 weeks (Gonzales et al., 2006) 23% success at 1 year (Jorenby et al., 2006)
Experimental	Naltrexone	Opioid receptor antagonist Inhibits DA release in NAc	No evidence of increased abstinence on its own or added to NRT (David et al., 2013)
	Mecamylamine	nAChR antagonist	Failed clinical trials
	GSK598809	D3 antagonist	Preclinical reduction of self-administration (Mugnaini et al., 2013)
	NicVAX	Anti-nicotine vaccine	Failed phase III clinical trials

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Table 2

Current approved and experimental therapeutics for alcohol use disorders.

	Drug	Mechanism	Efficacy
Approved	Naltrexone	Competitive opioid receptor antagonist	23% relapse at 12 weeks (Volpicelli et al., 1992) 35% relapse at 6 months (Volpicelli et al., 1997)
	Extended release Naltrexone	Competitive opioid receptor antagonist	Reduces heavy drinking more reliably than relapse prevention (Garbutt et al., 2005)
	Disulfiram	Acetaldehyde dehydrogenase inhibitor	Reduced number of drinking days by 35–43% *in compliant patients* (Fuller et al., 1986)
	Acamprosate	Enhance GABAA receptor function mGluR1-family antagonist	36% abstinence at 6 months (Mann et al., 2004)
Experimental	Topiramate	Increases GABAergic activity; AMPA/kainate receptor antagonist	67% success at 4 weeks; 46% success at 12 weeks (Baltieri et al., 2008)
	Gabapentin	Inhibits voltage-gated calcium channels	17% abstinence and 45% no heavy drinking at 12 weeks (Mason et al., 2014)
	Baclofen	GABAB receptor agonist	Not different from placebo (Garbutt et al., 2010)
	Sertraline	Selective serotonin reuptake inhibitor	No difference from placebo in participants with a history of depression (Pettinati et al., 2001)
	Ondansetron	5HT3 receptor antagonist α7 nAChR antagonist	Reduces alcohol consumption in early-onset alcohol dependence (Kranzler et al., 2003)
	Aripiprazole	DA D2 partial antagonist 5HT1A partial agonist 5HT2 antagonist	No difference from placebo, treatment-related adverse events? (Anton et al., 2008)
	Nalmefene	κ opioid receptor antagonist	Reduces alcohol consumption in detoxified alcohol-dependent individuals, especially in combination with cognitive therapy (Gual et al., 2013)

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