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Neuronal Nicotinic Acetylcholine Receptors as Pharmacotherapeutic Targets for the Treatment of Alcohol Use Disorders

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Abstract

Alcohol use disorders (AUDs) are complex and developing effective treatments will require the combination of novel medications and cognitive behavioral therapy approaches. Epidemiological studies have shown there is a high correlation between alcohol consumption and tobacco use, and the prevalence of smoking in alcoholics is as high as 80% compared to about 30% for the general population. Both preclinical and clinical data provide evidence that nicotine administration increases alcohol intake and non-specific nicotinic receptor antagonists reduce alcohol-mediated behaviors. As nicotine interacts specifically with the neuronal nicotinic acetylcholine receptor (nAChR) system, this suggests that nAChRs play an important role in the behavioral effects of alcohol. In this review, we discuss the importance of nAChRs for the treatment of AUDs and argue that the use of FDA approved nAChR ligands, such as varenicline and mecamylamine, approved as smoking cessation aids may prove to be valuable treatments for AUDs. We also address the importance of combining effective medications with behavioral therapy for the treatment of alcohol dependent individuals.

Keywords

nAChRs; ethanol; nicotine; pharmacotherapy; smoking cessation aids; varenicline; mecamylamine

INTRODUCTION

Alcohol use disorders (AUDs) are progressive relapsing disorders that affect 4% of the adult population and is the third leading cause of preventable death worldwide (National Institute on Alcohol Abuse and Alcoholism, NIAAA). The estimated economic burden of addiction-related illnesses in the United States exceeds \$366 billion a year. This estimate includes direct costs (medications, treatments, welfare services and disability benefits) and indirect costs (lost productivity and income due to reduced capability or incapacity). Left untreated, the individual's health deteriorates and further increases susceptibility to other diseases and sometimes death. There has been a growing awareness that the treatment of AUDs will require a combination of medications and behavioral interventions. Although there are a few FDA approved medications for the treatment of AUDs, including disulfiram (Antabuse®), naltrexone (ReVia®, Depade® and Vivitrol®) and acamprosate (Campral®), there remains a need to improve and develop new pharmacotherapy and treatment strategy options.

Alcohol affects multiple brain neurotransmitter and neural systems including dopamine, serotonin, GABA, glutamate, opioid, and the nicotinic acetylcholine receptors (nAChRs) [1–22]. Although, the interaction of these various pathways with each other in the presence of alcohol is largely unknown (for review, see [23]), each of these neural systems can be potential targets for the treatment of alcohol use disorders.

It is clear that ~80% of alcohol dependent individuals are also smokers and that alcohol and nicotine are commonly co-abused [24–26]. Furthermore, in animal studies, nicotine increases ethanol intake and induces reinstatement of ethanol seeking, which is reduced by a non-specific nicotinic receptor antagonist, suggesting that the nAChR system plays a role in alcohol consumption and relapse-like behaviors [18, 27–31]. Targeting the nAChR system has shown promise in modifying alcohol consumption both in preclinical and some clinical studies but the lack of suitable ligands safe for the use in humans has impeded the progress so far. There are currently two FDA approved medications that target nAChRs mecamylamine (Inversine™) and varenicline (Chantix™ and Champix™). While mecamylamine has limited efficacy as a smoking cessation medication [32, 33], varenicline has been marketed as a smoking cessation aid with excellent therapeutic efficacy [34, 35]. In this review, we discuss the role of nAChRs in the effects of ethanol and argue for the use of nicotinic receptor ligands, as a possible therapeutic strategy for the treatment of AUDs.

THE SUBTYPES OF ALCOHOL USE DISORDERS

The development of effective pharmacotherapy for AUDs requires a thorough understanding of the disorders as well as the target population. AUDs are complex and heterogeneous disorders that has been shown to be modulated by family history, co-morbidity with other substances and/or psychiatric disorders, as well as environmental influences, thus making AUDs multi-faceted and difficult to treat [36–41]. Significant effort has been put into classifying individuals with alcohol dependence and has been an ongoing process over several years by largely employing either empirical or clinical/observational strategies primarily from treatment-seeking individuals [36, 37, 42–44]. The studies were mainly conducted with people in treatment programs for alcoholism and hence a large percentage of the population with AUDs were not included, as only ~25% of alcoholics seek treatment [45].

Recently, an empirical study was carried out by NIAAA where 1,484 subjects with AUDs were sub-typed from a non-institutionalized adult population and divided into five categories [40]. The largest group (31.5%) was *young adults* (~25 years) with no family history of alcoholism or co-occurrence with other mental disorders and exhibited a 32% probability of smoking. These individuals rarely seek any help for their drinking. The second group was *young antisocial alcoholics* (~26 years, 21.1% of sample) and had an early onset of drinking and alcohol problems. More than half of the subjects (~52.5%) showed a strong family history of alcoholism with major depression, anxiety and bipolar disorder (~37%). More than 75% also smoked cigarettes. The *intermediate familial group* (~38 years, ~19% of US alcoholics) were middle aged with multigenerational history (~57%), smoked cigarettes (~57%) and had been diagnosed with clinical depression and bipolar disorders (~35%). The *functional group* (~41 years, ~19% of US alcoholics) consisted of older middle-aged individuals with stable jobs and was generally well educated. Nearly 31% of this group had families with multi-generational alcoholism and major depressive illness (~24%) at some point in their lives and nearly 45% of them were smokers. The fifth *chronic severe group* (~38 years, ~9% of US alcoholics) had a large multigenerational history (~77%), showed antisocial personality traits and criminal-like behavior. This group was reported to have the highest rate (~55%) of other psychiatric disorders such as depression, bipolar disorder, anxiety and high rates of smoking (~75%) and administering cocaine. Nearly two-thirds of

this group sought help for their drinking making them the most prevalent type in alcohol treatment. It becomes clear from these studies that most alcoholics suffer from a host of other psychiatric disorders with a high incidence of other substance use disorders of which the most prevalent is smoking (50–80% of alcoholics smoked heavily).

Sub-typing alcohol dependent individuals into clinically relevant homogeneous groups with the consideration of the age of drinking onset, drinking history, family history, and the presence or absence of other substance abuse and psychiatric disorders has the advantage of providing guidance for the treatment selection, treatment outcomes and provides with suitable prognostic indicators. The Moss *et al* study [40] highlights the importance of considering the underlying cause for an alcoholic to drink uncontrollably or what induces them to relapse. For example, as nicotine is widely co-abused with alcohol, it may be essential for people who want to reduce drinking, to give up smoking as well. The occurrence of alcoholism is approximately 10 times more likely in smokers than non-smokers [46]. It has been shown that early onset of smoking is a significant predictor for later development of alcohol dependence [47] and there is a considerable genetic overlap between alcohol and nicotine addiction (for review see [48]). Hence, treatments that are effective in smoking cessation could be considered as beneficial therapeutics for alcoholism. In the following section, we discuss the biological basis behind the co-occurrence of alcohol and nicotine use.

THE BIOLOGICAL RATIONALE FOR THE CONCURRENT USE OF ALCOHOL AND NICOTINE

It may be argued that the legal availability of alcohol and cigarettes (nicotine) with no associated social stigma likely contributes to their high co-use. In addition, there is strong biological evidence that underlies the combined use of alcohol and nicotine. Human and animal studies have found that alcohol and nicotine exert both synergistic and antagonistic effects on behavior which may contribute to their concurrent use. For example, animal behavioral studies have shown that chronic nicotine treatment increases ethanol consumption and self-administration in rodents [18, 27–31]. The influence of nicotine on ethanol intake has been shown to be dependent on the dose and the treatment duration. For instance, acute treatment of nicotine has been shown to initially suppress alcohol operant self-administration, while prolonged treatment with nicotine reverses this suppression and increases alcohol administration thereafter [30]. The initial suppression and the later enhancement of alcohol acquisition has been postulated to be related to the development of tolerance to nicotine across exposure days [49, 50]. Nicotine treatment has also been shown to potentiate ethanol-appropriate responding in rats suggesting a change in the perception of ethanol reinforcement induced by nicotine [51].

Reinforcement: Dopamine

Neurochemical studies have shown that sub-chronic nicotine treatment increases both nicotine and ethanol-induced dopamine release in the limbic forebrain [28]. Researchers administering acute systemic ethanol or acute nicotine in the ventral tegmental area (VTA) have shown a dose dependent increase in the dopamine release measured in the nucleus accumbens of the mesolimbic dopaminergic pathway [52–54]. A simultaneous administration of low dose of both these drugs resulted in an additive effect on the release of dopamine measured in the nucleus accumbens of the mesolimbic pathway [53, 54]. The authors postulated that the reason why most people drink and smoke simultaneously is to increase their pleasure, as reflected by the increase in dopamine in rodents. Furthermore, low concentrations of nicotine when combined with ethanol has been shown to produce a synergistic effect of increased firing rate of dopamine-containing neurons in the VTA using

slice recordings [55]. The mesolimbic dopamine pathway is thought to contribute to the rewarding and reinforcing properties of both these drugs (for review see [56–58]). Marszalec and colleagues, using cultured rat cortical neurons, showed that ethanol can potentiate nicotine-activated currents and thereby increase the positive reward and reinforcing effects of nicotine. Additionally, they demonstrated that ethanol can induce an opposite effect on the desensitization of receptors induced by continuous perfusion of nicotine, which they proposed as the explanation for the increase in tobacco use observed with excessive drinking [59]. It has been postulated that the co-administration of these two drugs can cause modification in the reward pathway *via* an interaction with nAChRs as reported with chronic infusion of nicotine or ethanol treatment [60, 61] and thereby cause altered responses. However it is not clear whether ethanol-nicotine interactions involve changes in the nicotinic receptors [62].

Reduction of Aversive Effects Such as Stimulant and Sedative Effects of Alcohol and Nicotine

While the co-administration of ethanol and nicotine has been shown to increase the reinforcing properties of the drugs, there is also evidence that they may help to reduce the aversive side effect of each drug. The stimulant effects of nicotine are thought to offset the acute sedative effects of alcohol, such as attenuation of ethanol-induced ataxia [63] and cognitive impairment [64–66]. Measurements using different genetic strategies suggest that the nicotinic cholinergic system modulates ethanol withdrawal symptoms [67]. These effects are also manifested in alcoholic individuals as it has been shown that increased nicotine administration can modify their cognitive deficits by decreasing the reaction time and increasing the correct responding to rapid visual information processing tasks [68]. Similarly, though not systematically investigated, the neuroprotective effects of nicotine may help mitigate some of the cytotoxic effects of alcohol measured using primary cultures of cerebellar granule cells [69, 70]. The development of cross-tolerance between alcohol and nicotine may be a possible motivation to consume higher amounts of the drug to get the same reward, as demonstrated by de Fiebre and Collins and coworkers in various rodent strains selected for differential sensitivity to ethanol [62, 71–75]. Individuals who drink and smoke regularly would need to smoke and drink more to get the same pleasurable feelings. Moreover, the combined use of alcohol and tobacco is considered more risky and harmful because of the development of cross-tolerance resulting in a higher intake of alcohol and nicotine than if the drugs were consumed individually [76].

Common Genetic Susceptibility

De Fiebre and Collins and co-workers were amongst the first to study the potential common genetic influences in the development of cross-tolerance between ethanol and nicotine using long-sleep and short-sleep mice [75]. They demonstrated that mice selectively bred for differences in duration of ethanol induced “sleep time” or anesthesia (long-sleep = sensitive line and short-sleep = insensitive line) differed in their initial behavioral sensitivities (tolerance) to ethanol and nicotine in several behavioral and physiological measures. Common genetic vulnerability has been shown to influence the development of alcohol and nicotine dependence in humans as well [77–80]. Several recent human genetic association studies have demonstrated that the gene cluster *CHRNA3*, *CHRNA5*, and *CHRNB4*, which encode the $\alpha 3$, $\alpha 5$ and $\beta 4$ subunits of the nAChRs respectively, lead to an increase in susceptibility to develop nicotine and alcohol addiction [81–88]. Human and animal studies suggest a shared genetic predisposition to develop alcohol and nicotine dependence (for review see [89]). For instance, identical twins are twice as likely as fraternal twins to be alcohol and/or nicotine dependent if the other twin is dependent [79].

Reinstatement or Relapse

Nicotine can reinstate ethanol-seeking behavior in animals [15] and provoke relapse and craving in humans [90, 91]. In a rat model of drug relapse [92], Le and colleagues (2003) demonstrated that priming the animals with nicotine injections can reinstate ethanol seeking in rats by motivating them to press the lever previously associated with ethanol deliveries [15]. Furthermore, in human studies, nicotine containing cigarettes caused at least a subset of smokers to drink more alcohol than those that had the denicotinized cigarettes [90], and additionally, cigarette smoking increased the reinforcing value of alcohol [93]. While the involvement of nicotine in ethanol mediated behaviors is well established, the mechanisms underlying such effects have not been thoroughly investigated.

NEURONAL NICOTINIC ACETYLCHOLINE RECEPTORS: A COMMON BIOLOGICAL SUBSTRATE FOR ETHANOL AND NICOTINE ACTIONS

The neuronal nicotinic acetylcholine receptor (nAChR) system is a common target for the interaction of ethanol and nicotine in the brain. It was the first neurotransmitter receptor and ion channel to be purified and its molecular properties elucidated from the Torpedo electric organ [94, 95]. While Torpedos have a very rich and homogeneous source of the nAChR proteins, binding and gene expression studies have shown that nAChRs are also widely distributed in the peripheral and central nervous systems (CNS) of humans. The isolation of the nAChR followed several decades of research and discovery leading to the characterization of nAChRs as pentameric ligand-gated ion channels consisting of different combinations of $\alpha 2 - \alpha 10$ and $\beta 2 - \beta 4$ subunits (for review see [96–102]). The endogenous agonist acetylcholine (ACh) and the exogenous agonist nicotine are the most effective ligands at inducing the open conformation of the nAChR channel which allows cations to permeate this channel (Fig. 1).

In the mammalian brain, most of the nAChRs contain both the $\alpha 4^*$ and $\beta 2^*$ subunit that form heteromeric receptors and the homomeric $\alpha 7$ subunit-containing receptors [103–108]. The asterisks (i.e., $\alpha 4^*$) here onward indicate that these subunits combine with other subunits to form functional receptors. In the peripheral nervous system, the predominant nAChR receptor subtype contains $\alpha 7$ and $\alpha 3^*$ subunits co-assembled with $\beta 2^*$ or $\beta 4^*$ subunits [109]. Although specific regions of the brain are often predominated with single classes of nAChRs, the formation of other subclasses can also occur (Fig. 2). The mesolimbic dopamine pathway consisting of the ventral tegmental area (VTA), and the nucleus accumbens (NAcc) have receptors mostly containing the $\alpha 4^*$ and $\beta 2^*$ subunits with or without the co-assembly with $\alpha 6^*$ or $\alpha 5^*$ subunits [110, 111]. The medial habenula complex has predominantly receptors containing $\alpha 3^*$ and $\beta 4^*$ subunits with few $\beta 2^*$ subunits [112, 113] while $\alpha 7$ containing receptors are predominantly found in the hippocampus along with a few $\alpha 4\beta 2^*$ and $\alpha 3\beta 4^*$ containing receptors [114–116].

The importance of nAChRs in the human brain is now well established and appreciated as indicated by several excellent reviews on their molecular and functional structure [97, 117, 118], anatomical distribution [119, 120], physiology [121], as well as therapeutic indication for the treatment of several diseases such as Alzheimer's disease, schizophrenia, epilepsy, pain, Parkinson's disease, and nicotine and alcohol dependence [122–125].

Both ethanol and nicotine can activate the mesolimbic dopaminergic system *via* their actions at neuronal nicotinic acetylcholine receptors (nAChRs) [126–131]. The most widely studied role of nAChRs is in the modulation of neurotransmitter release such as dopamine, which in turn is thought to mediate the pleasurable feelings of alcohol and nicotine use. There is evidence that suggests that the mesolimbic dopaminergic system is a convergent site of

action for these two drugs [52, 53]. However, it has also been suggested that nicotine and ethanol may elevate dopamine *via* different pathways and nAChR subtypes [132–134]. It is well established that the $\alpha 4\beta 2^*$ nAChRs have an essential role in mediating the reinforcing properties of nicotine [135–137]. However, the subunit composition of the nAChR involved in the reinforcing effects of ethanol remains controversial. In the following section, we will discuss in detail the interaction of ethanol with the nAChR system and the various possible subunits that may be involved in its action.

INTERACTION OF ETHANOL WITH ION CHANNELS AND nAChRs

The ability of ethanol to interfere with ligand-gated ion channels [138, 139] was first demonstrated for the GABA_A receptor at the behavioral [140, 141], cellular, and molecular level [142–144]. Then it was shown that ethanol can also act as an antagonist at NMDA receptors [145], a co-agonist at 5-HT₃ receptors [146], as well as influence strychnine-sensitive glycine receptors [147]. The interaction of ethanol with nAChRs was first demonstrated using the Torpedo nAChR, where ethanol increased the binding affinity of acetylcholine (the endogenous ligand) to this receptor [148, 149]. It was then demonstrated that ethanol stabilized the open state of the receptor and short-chain n-alcohols increased the bursting frequency by increasing the rate of channel opening [150]. Ethanol is important for the open-close-inactivation kinetic properties of the nAChR, and several groups have examined the ethanol sensitivity at specific subunit compositions of nAChRs through both *in vitro* expressions in cell lines and *in vivo*.

Engel and colleagues (1992) were the first to establish that at least a part of the effect of ethanol is mediated by the activation of the central nAChRs, and this is a reason for the high concurrent consumption of ethanol and nicotine [151]. The investigators were able to show that the non-selective nAChR antagonist mecamylamine reduced an ethanol-induced dopamine overflow in the NAcc [28, 126, 127]. Furthermore, mecamylamine administered into the VTA but not the NAcc counteracted ethanol-induced dopamine overflow was shown using *in vivo* microdialysis in awake freely moving mice, suggesting the involvement of central nicotinic acetylcholine receptors for the ethanol-induced activation of the mesolimbic dopamine system (Fig. 2). Mecamylamine was first introduced as a therapeutic drug for hypertension in the 1950s [152]. It was later recognized as a potential smoking cessation aid [32, 33].

Acute ethanol treatment (75 mM) potentiates ACh-induced currents in *Xenopus* oocytes expressing $\alpha 2\beta 4$, $\alpha 4\beta 4$, $\alpha 2\beta 2$ and $\alpha 4\beta 2$ nAChRs [153] and low concentrations of ethanol (20 mM and 50 mM) inhibited nicotine activation of the $\alpha 7$ receptor [153, 154]. In contrast, the effects of ethanol on the activation of $\alpha 3\beta 4$ nAChRs is more controversial, where both a potentiation of nicotine-inward current, as well as insensitivity to ethanol have been reported [153]. In rat pheochromocytoma (PC12) cells, low concentrations of ethanol (0.1–10 mM) in bath produced an increase in desensitization of nAChR responses [155]. It has been proposed that ethanol is a co-agonist that potentiates the effect of nicotine or acetylcholine but has no intrinsic agonist effect in the absence of acetylcholine, at least in cultured rat cortical neurons [59]. The ethanol concentration range (20 mM to 200 mM) used in cell culture studies and in *in vitro* brain slice recording [128, 156, 157] is considered behaviorally relevant [158–160]. Although it is important to note that *in vitro* conditions may be significantly different to behavior of a whole animal, these studies provide valuable directions in which to investigate the nAChR subunit compositions involved in ethanol-mediated behaviors.

To determine the nAChR subtype associated with the behavioral effects of ethanol a variety of different nAChR antagonists have been investigated. Dihydro- β -erythroidine (DH β E), a

potent antagonist at $\alpha 4\beta 2$ nAChRs, does not have any effects on systemically administered ethanol in animals; specifically the locomotor stimulatory effect and ethanol-induced dopamine overflow in the NAcc [30, 131, 133, 161]. Similarly, methyllyca-conitine citrate (MLA), a potent and selective inhibitor of $\alpha 7$ nAChRs, had no effect on ethanol-induced locomotion or dopamine activating effects [133]. Additionally, DH β E does not reduce ethanol intake while the non-specific nAChR antagonist mecamylamine has been shown to decrease ethanol consumption in rats [30]. In marked contrast both DH β E and MLA have been shown to play a significant role in the behavioral effects of nicotine, including decreasing the stimulant, rewarding, and dopamine-enhancing effects of nicotine [162, 163]. Furthermore, it was shown that $\beta 2$ nAChR knockout mice had significantly reduced nicotine self-administration [164, 165]. These studies lead to the suggestion that the $\alpha 4\beta 2^*$ and $\alpha 7^*$ nAChRs are not directly involved in at least the neurochemical and behavioral effects of ethanol. The search for new compounds selective at different nAChRs resulted in the discovery of α -conotoxin MII, an antagonist at $\alpha 3\beta 2^*$, $\beta 3^*$ and/or $\alpha 6^*$ nAChRs [102, 134]. Larsson and coworkers found α -conotoxin MII significantly reduced ethanol-induced accumbal dopamine overflow and locomotor stimulatory effects as well ethanol intake in rats and mice (Fig. 2). A second conotoxin was synthesized, α -conotoxin PIA, to discriminate nAChRs containing the $\alpha 6^*$ and $\alpha 3^*$ subunits [166]. It was shown that, α -conotoxin PIA with selectivity at $\alpha 6^*$ containing nAChRs, did not affect the stimulatory and/or accumbal dopamine-enhancing effect of ethanol [167]. This led to the conclusion that $\alpha 3\beta 2^*$ and/or $\beta 3^*$ subunits rather than $\alpha 6^*$, $\alpha 4\beta 2^*$, $\alpha 7^*$ nAChRs were important for ethanol induced locomotor stimulation and the dopamine-activating effects in the midbrain (VTA) and the NAcc [167].

A caveat in the drinking models that have commonly been used in ethanol research discussed so far is that rats rarely maintain high ethanol intake following the removal of the initiation procedures such as sucrose fading [168], food and water deprivation [169], limited access to ethanol [170] and pairing drinking with electrical brain stimulation [171]. The lack of suitable preclinical oral ethanol consumption paradigms that elicit high ethanol intake has been a major obstacle in the development of new medications for the treatment of AUDs. Other attempts to increase ethanol consumption have been to either increase the concentrations of ethanol [172, 173] or to use strains that are selectively bred for high preference to ethanol [174–176]. Although there were a group of studies done in the 1970's that showed that intermittent-access to ethanol induce high voluntary ethanol consumption [177, 178], and more recently [179, 180], most research groups have largely used continuous-access drinking models or drinking models with initiation procedures that result in low ethanol consumption. Recently, our lab re-developed the intermittent-access 20% ethanol 2-bottle choice drinking paradigm [159] that can turn standard laboratory rats into high ethanol consuming rats. This paradigm allowed for robust and reproducible levels of high voluntary ethanol consumption in Wistar, Long-Evans, as well as P rats that were maintained over long period of time (up to 8 months). The intermittent-access 20% ethanol 2-bottle choice paradigms facilitated the study of effects of high ethanol consumption as well as examining the several stages of ethanol consumption including the escalation, maintenance and deprivation of ethanol consumption. Since the development of this paradigm, which is both elegant and can be replicated, it is being increasingly used by researchers as the preclinical tool for modeling several aspects of AUDs.

Despite the introduction of this new voluntary heavy drinking model, mecamylamine and α -conotoxin-MII were the only ligands that were pharmacologically effective in determining the site and the mechanism of action of ethanol at nAChRs (Fig. 2) until 2005. Then in 2006, the FDA approved varenicline (Chantix[®] and Champix[®]) as a smoking cessation aid, providing a valuable tool for probing nAChRs. Varenicline is a high affinity, partial agonist

with efficacy at $\alpha 4\beta 2^*$ nAChRs and three orders of magnitude lower affinity for $\alpha 3\beta 4^*$, $\alpha 3\beta 2^*$, $\alpha 6\beta 2^*$ and, 10-orders of magnitude lower affinity for $\alpha 7$ nAChRs [181–183].

Our lab was the first to show that varenicline selectively reduces operant ethanol self-administration and voluntary ethanol consumption in heavy drinking rats using the intermittent-access 20% ethanol 2-bottle choice drinking paradigm following long-term ethanol exposure [19]. Furthermore, we showed that varenicline has a long-lasting effect on ethanol-mediated behaviors and multiple administrations of varenicline continue to reduce ethanol self-administration without inducing a rebound increase in the ethanol seeking after the cessation of the treatment. We showed that varenicline's effect was selective for ethanol and showed no effect on sucrose seeking or water consumption. Later, varenicline was shown to improve ethanol-associated deficits in learning in mice [184] and modulate ethanol and nicotine induced dopamine overflow in the rat NAcc [52]. Hence, in recent years, the approval of varenicline as a smoking cessation aid has provided an excellent opportunity to better understand the role of nAChRs for ethanol modulation as well as evaluate the therapeutic potential of this novel compound for the treatment of AUDs.

Recently, human genetic association studies have implicated SNPs in the genes encoding the $\alpha 5^*$ (CHRNA5), $\alpha 3^*$ (CHRNA3), $\beta 4^*$ (CHRNA4) nAChR subunits as playing a critical role in the development alcohol and nicotine dependence processes [81–87]. Therefore, there is a need for $\alpha 3\beta 4^*$ nAChR ligands to be developed to pharmacologically assess the role of these receptors in addictive disorders. To the best of our knowledge, 18-methoxycoronaridine (18-MC) is the only other compound that has been reported to have activity at $\alpha 3\beta 4^*$ nAChRs [185] and to reduce ethanol- [186] and nicotine- [187] seeking behavior in rats. However, 18-MC has rather weak affinity for $\alpha 3\beta 4^*$ nAChRs ($IC_{50} = 0.75 \mu M$), as well as modest affinity at opioid and 5-HT₃ receptors [188]. The $\alpha 3\beta 4^*$ nAChRs are highly expressed in the habenular complex and have much lower densities in the mesolimbic pathway [110, 189–195] (Fig. 2). Furthermore, several studies have shown that the habenular complex can regulate midbrain dopamine neuronal activity [196–200], having both afferent and efferent connections with the ventral tegmental area (VTA), substantia nigra pars compacta, and the nucleus accumbens [97, 201–207]. In the future, a concerted effort of identifying new subtype-selective ligands at nAChRs that have a pharmacologic effect on alcohol reinforcing models, together with identifying the site of action in laboratory animals will be important in the development of efficacious therapeutics for the treatment of alcoholism.

THE RATIONALE TO DEVELOP NEURONAL NICOTINIC LIGANDS AS TREATMENTS FOR ALCOHOL USE DISORDERS

It is a long road for a target such as the nAChR or an experimental drug to be moved from the bench to one of standard care for patients, ranging anywhere from 10 to 15 or more years. Clinical trials take anywhere from months to years to determine if the treatments are safe and effective in humans. Of the several drugs tested in preclinical laboratories, only a small fraction gets tested in clinical trials and often only one of these is ultimately approved as medicine for patient use.

The FDA has approved only three drugs (disulfiram (Antabuse®), naltrexone (ReVia®), Depade® and Vivitrol®) and acamprosate (Campral®) in 51 years to treat AUDs. The good news is that there are several drugs in the pipeline either in academic laboratories or in pharmaceutical companies that show therapeutic potential. The bad news is that many of these therapies still require expensive large scale Phase III clinical trials. Given the high probability of a heavy drinker to also be a heavy smoker, approved nicotinic ligands for smoking cessation present a unique opportunity to fast track development of novel

medications for the treatment of AUDs. A promising candidate that can modify alcohol reactivity and drinking behavior can have immediate clinical relevance, with the added benefit of being FDA approved and can safely be administered to alcohol and nicotine dependent individuals seeking treatment.

Previously, mecamylamine was the only FDA approved drug, with activity at nAChRs, for humans showing limited efficacy as a smoking cessation agent. Recently, varenicline was approved as a smoking cessation aid with high efficacy. Given the effect of mecamylamine and varenicline for tackling the reinforcing properties of ethanol in animal studies and small scale human studies suggests that they also may have a predictive value in the medical treatment of AUDs. In the following section, we discuss the findings leading to the discovery of mecamylamine and varenicline and their new potential clinical use as a treatment for AUDs.

CLINICAL EVALUATION OF MECAMYLAMINE (INVERSINE®) AND VARENICLINE (CHANTIX™ AND CHAMPIX™) FOR ALCOHOL USE DISORDERS

Mecamylamine

Mecamylamine (Inversine®) was first made available as an oral antihypertensive drug in the early 1950's originally distributed by Merck & Co Inc. Due to its ability as a useful peripheral ganglionic blocking agent, it was used clinically as a drug for hypertension. However, after a few decades in 1984, it fell out of favor because of its widespread ganglionic side effects at the high recommended doses (30–70 mg/kg). Recently, mecamylamine (2.5 mg tablet) was approved to be redistributed by Layton Biosciences, albeit at lower doses to prevent side effects, for severe and uncomplicated cases of malignant hypertension [152]. Unlike other ganglionic agents, mecamylamine has been shown to be completely absorbed and effectively cross the blood brain barrier where it acts as a nAChR antagonist [208]. It is this central activity at the nAChRs, demonstrated at low doses, that has made mecamylamine emerge as a potential therapeutic agent for other clinical indications such as substance abuse disorders. Mecamylamine became one of the first and most widely used pharmacological tools because of its potential to block nicotinic receptors in the brain at low doses (2.5–10 mg/day) without any significant effect on parasympathetic functions [209]. It has been investigated over several years both in the preclinical and clinical studies for the treatment of both smoking cessation [32, 33] and ethanol abuse [126, 210].

Mecamylamine as an Aid to Smoking Cessation—Preclinical studies have shown mecamylamine reduces the rewarding properties of nicotine effectively. In humans, Rose and colleagues demonstrated that mecamylamine co-administered with transdermal nicotine is useful as a smoking cessation aid [32, 33]. In a previous study by these investigators, eight subjects were asked to evaluate qualities of cigarette smoke after various dosages of mecamylamine with their subjective response [211]. Low doses of mecamylamine were shown to decrease the self-rated strength and harshness of cigarettes having high nicotine dose level. Precessation treatment with mecamylamine prolonged the duration of continued smoking abstinence and the combined intake of nicotine skin patches (21mg/24 hr) and mecamylamine (2.5–5.0 mg/day) has been shown to reduce smoking satisfaction and craving more than each drug alone [33]. Therefore, mecamylamine combined with nicotine patch therapy is more beneficial than nicotine patch treatment alone. The combined therapy of mecamylamine and transdermal nicotine in the above studies is thought to be favorable from the balance of agonist and the antagonist effect produced, causing a reduction in the nicotine withdrawal symptoms while providing some of the rewarding effects of nicotine

delivery. However, no large scale studies were done confirming these earlier reports and the combined treatment of mecamlamine and transdermal nicotine have not yet become an established treatment for smoking cessation. Mecamlamine use has been limited by its dose limiting side effects such as drowsiness, dryness of the mouth and skin, dilation of the pupil, urinary retention, and constipation.

Mecamlamine as a Drug for Alcohol Use Disorders—Mecamlamine has been an important tool in determining the importance of the interaction of ethanol and nAChRs in animals [28, 30, 126, 133, 212]. A few human studies have evaluated the effect of mecamlamine on the subjective response of healthy individuals to moderate intake of alcohol. In a small scale study [213] of 10 men and woman, healthy volunteers with no history of other substance use disorders were given alcohol-containing drinks. Two hours prior to the drink (0.8 g/kg in men and 0.7 g/kg in women) the subject were given either mecamlamine (7.5–12.5 mg on the basis of body weight) or placebo. Primary measures included the Drug Effect Questionnaire, Alcohol Sensation Scale and the stimulant subscale of the Biphasic Alcohol Effects Scale. To monitor the pharmacokinetics of the interaction of mecamlamine and alcohol, breath alcohol levels were also measured. Mecamlamine reduced the breath alcohol levels in comparison to placebo during the ascending limb of the blood alcohol levels. Mecamlamine also reduced the drug effect questionnaire and alcohol sensation scale, thereby showing the potential to reduce both the pharmacokinetic and the rewarding profile of alcohol in human subjects. Another small scale study of non-smokers demonstrated mecamlamine pre-treatment (15 mg) followed by an alcohol beverage reduced the self-reported euphoric and stimulant effects of alcohol and the desire to consume additional alcohol beverages, an effect which was more pronounced in men [214].

In a separate study, 12 healthy men and 12 healthy women volunteers were assessed for alcohol preference after being given a choice between money and alcohol following pretreatment with either mecamlamine or placebo. Mecamlamine (15 mg) treatment amongst these subjects was reported to reduce the stimulating ratings after alcohol intake, supporting the finding of the Blomqvist study [151]. When the subjects had the opportunity to choose alcohol versus money, mecamlamine did not necessarily reduce alcohol consumption in the group. However, the participants that experienced the most stimulant-like subjective effects from alcohol did show a tendency to reduce alcohol consumption with the treatment [210]. Interestingly, in this study, there was no difference in the effects of mecamlamine between the males and females.

It is encouraging that the effects of mecamlamine on the stimulant effects and the desire for alcohol in human studies draw parallel to the results in animals. It has been postulated that those individuals who experience a stimulating effect during the ascending limb and fewer sedative-like effects during the descending limb of the blood alcohol concentrations have a greater risk of having AUDs [215, 216] and mecamlamine effectively demonstrated the ability to reduce the stimulant effects of alcohol. Although the studies examining subjective alcohol reactivity are promising, a reduction in alcohol consumption with mecamlamine has yet to be demonstrated. However, the human studies, at that time, were largely limited by their small sample size when considering the variability in the behavioral and subjective response. In addition, only healthy volunteers participated in these studies and mecamlamine effect on subjects with AUDs, which are highly complex, were thought necessary. These studies were inconclusive of whether mecamlamine is more effective for men or for women as the difference could have been related to the characteristics of the participant sample such as weight, subjective stimulation from alcohol and alcohol dose. Most importantly, only the effects of acute administration of mecamlamine were demonstrated and, therefore, how well chronic administration of mecamlamine is tolerated in alcohol dependent individuals would have to be determined if mecamlamine is to be

considered as a pharmacological agent for AUDs. Since these published results, new larger clinical trials are currently underway (started in 2004) initiated by Dr Petrakis and colleagues, to evaluate for the first time the treatment with mecamylamine in smoking and non-smoking alcohol dependent patients (Study NCT00342563-Yale University) (Table 1).

Varenicline

At the beginning of this decade, the only approved therapies available for tobacco dependence were nicotine replacement with multiple delivery methods (eg: patch, inhaler, nicotine gum and lozenge) and the antidepressant bupropion (Zyban[®]), which is thought to inhibit the reuptake of dopamine and norepinephrine [217, 218]. However these therapies had high long-term relapse rates [219]. The discovery of varenicline by Pfizer Inc as a smoking cessation aid (Chantix[®] and Champix[®] in 2006), was based on the need to find improved long-term efficacious treatment [220, 221]. Varenicline was developed with partial agonist activity (45% vs nicotine) and strong binding affinity (0.06 nM) at $\alpha 4\beta 2^*$ nAChRs. Nicotine's strong agonist activity at $\alpha 4\beta 2^*$ nAChR leading to the dopamine activating effects in the mesolimbic pathway have been implicated in mediating several aspects of tobacco dependence. Varenicline was generated from the starting natural product cystine, with the key strategy of identifying partial agonist ligands with activity at $\alpha 4\beta 2^*$ nAChRs for smoking cessation.

It was hypothesized that an effective agent would be one that exhibits intrinsic partial agonist activity at $\alpha 4\beta 2^*$ nAChR eliciting a moderate sustained release of mesolimbic dopamine. It was anticipated that the intrinsic partial agonist activity would then counteract the low dopamine levels experienced in the absence of nicotine during smoking cessation attempts which mediate craving and eventually relapse to smoking behavior. The high-affinity partial agonist would have the advantage of blunting craving and withdrawal, as well as blocking nicotine-induced dopamine activation of $\alpha 4\beta 2^*$ nAChRs by competitively binding to this receptor subtype. The blocking of the nicotine-induced elevation of dopamine would thereby prevent the reinforcing and rewarding properties of tobacco. Similar to the successful attempts of combining mecamylamine and transdermal nicotine, and thus providing a balance of agonist and antagonist, varenicline with its optimal partial agonist profile and physiochemical properties would be an optimal pharmacotherapeutic agent for patients trying to quit smoking.

Clinical Efficacy of Varenicline as a Smoking Cessation Agent—Large scale phase 3 clinical trials were conducted to determine the efficacy and safety of varenicline as a smoking cessation agent. Two different randomized double-blind parallel group placebo-active treatment-controlled trials were held between 2003 and 2005 comparing varenicline (1 mg twice daily), sustained-release bupropion (150 mg twice daily) or placebo on a 12 week treatment program and a follow-up of smoking status at week 52 [34, 35]. There were 1025 [35] and 1027 [34] healthy smokers in each study at 19 and 14 US research centers respectively. The outcome measures for the studies was exhaled carbon monoxide with measurement of continuous abstinence during the last 4 weeks of treatment (between 9 and 12 weeks) and through the non-drug follow up periods (week 9 through 24 and week 9 through 52). Varenicline was significantly more efficacious than placebo and bupropion for short-term continuous abstinence during the last 4 weeks of the treatment period as well as for long-term abstinence measured from the last 4 weeks of treatment to the non-drug period at the end of one year. Overall, varenicline was well tolerated with reduced craving and negative effects associated with smoking withdrawal in these individuals. Varenicline, marketed as CHANTIX[®], became approved by regulatory agencies as an aid to smoking in USA in May 2006 based on its high binding affinity and partial agonist activity at $\alpha 4\beta 2^*$

nAChR, good oral bioavailability, high absorbance, low plasma protein binding, and almost complete renal excretion as unchanged varenicline.

Varenicline as an Aid for Alcohol Dependence—Soon after varenicline was marketed as a smoking cessation aid, preclinical [19, 52, 184] and subsequently clinical studies investigating the pharmacotherapeutic potential of this novel drug for the treatment of AUDs were initiated. The first small scale human study of 20 heavy-drinking smokers was conducted by McKee and colleagues in a double-blind, placebo-controlled investigation to test the medication effects of varenicline on the reactivity to a priming drink and subsequent alcohol self-administration behavior [222]. After 7 days of pretreatment with varenicline (2mg/day) or placebo, a priming dose (0.3g/kg) of alcohol was administered for which the subjective and physiologic responses were assessed. This was followed with a 2-hour self-administration period during which the subjects could choose to consume up to 8 additional drinks (0.15 g/kg). In this study, varenicline significantly reduced the number of drinks compared to placebo and increased the likelihood of remaining abstinent during the 2-hour self-administering period. Varenicline also attenuated alcohol craving and subjective reinforcing alcohol effects following the consumption of the priming alcohol drink. The authors suggested that since the effect of varenicline on drinks consumed and craving responses were similar to the effects of naltrexone using an identical laboratory paradigm [223], the observed effects, albeit in a small sample, had clinical relevance.

In this study, varenicline was well tolerated in heavy drinking smokers and the side effects experienced during the pretreatment were minimal and did not differ between the varenicline and placebo treatment groups. During the self-administration session, varenicline in combination with alcohol showed no visible effect on mood ratings, physiologic reactivity or adverse effects such as nausea, anxiety, or dizziness. Although, there are some reports that have raised concerns regarding varenicline's association with neuropsychiatric side effects [224], a recent study showed varenicline to be effective and safe as a smoking cessation aid with or without mental illness (including alcohol dependence) [225].

Therefore, varenicline administered with low doses of alcohol appears safe and well tolerated in heavy-drinking smokers. Although this study was conducted in heavy drinking smokers, they were not deprived of cigarettes and hence varenicline's effect was independent of nicotine withdrawal. Moreover, Bartlett and colleagues [19] have also demonstrated that the reductions in alcohol consumption and seeking with varenicline were in nicotine-naïve rats. Future studies with larger sample sizes of heavy drinkers who are smokers and non-smokers need to be conducted for the development of this compound for AUDs.

INCORPORATING OLD TREATMENT DESIGN AND STRATEGIES TO VARENICLINE FOR AN ALCOHOL DEPENDENT PERSON

So far, we have discussed the role of the nAChR system as a therapeutic target for AUDs and the emerging evidence that varenicline (Chantix[®] or Champix[®]) may represent a novel approach for the treatment of alcoholism. There is yet another strong component in the vulnerability of an alcohol dependent person which involves the individual's behavioral components such as the drinking –abstinence- relapse history, as well as the influences of the environment. Social and cultural aspects can change the severity and the time course of this disorder. There is variability in AUDs amongst people as well as variability in the response to treatment. A single medication will not likely be effective for all those with these disorders. In addition genetic polymorphisms have been shown to lead to difference in the response to medication. Subjects with a specific allele variation have been shown to have a lower rate of relapse and longer time to heavy drinking with naltrexone than those without

the genetic variation [226]. It is likely that a single approach with either medication or behavioral intervention, to treat AUDs won't suffice as is the case with other chronic mental disorders. In a recent review, Mattson and colleagues from NIAAA highlight the important reasons and the various methods and strategies of combining therapies and/or behavioral interventions for effective alcoholism treatment [227].

One such program is Combining Medication and Behavioral Interventions (COMBINE) which is a multisite clinical trial launched by NIAAA in 1997 to determine if improvements of treatment outcomes could be achieved by combining pharmacotherapy and behavioral intervention. At the time of initiation of this program, the two most promising medications were naltrexone, which was FDA approved (1994) for alcohol dependence, and acamprosate, approved in Europe, was under consideration for review by the FDA in the United States (approved in 2006). Both medications had shown efficacy in the treatment of AUDs in placebo controlled clinical trials in the United States [228–232]. COMBINE aims to evaluate the efficacy of these medications either singly or together, with the combination of two types of behavioral treatments. The first type being Medical Management primarily delivered at primary care units by nurses to discuss medication information, to improve medication adherence and motivation and discuss any medication side effects. Secondly a more aggressive combined behavioral intervention method delivered by trained psychotherapists in specialized alcohol- treatment facilities

Since the introduction of the concept of COMBINE, various investigators have begun testing the strategies of combining medications with behavioral therapies. The first large-scale multisite randomized control trial was conducted between 2001 and 2004 amongst 1383 recently alcohol-abstinent volunteers [233] to evaluate the efficacy of the COMBINE program. Eight groups of subjects received medical management with naltrexone or acamprosate, both, and/or both placebos, with or without a combined behavioral intervention. The outcome of this clinical trial showed that subjects receiving medical management with naltrexone, combined behavioral intervention or both performed better on drinking outcomes than those that received medication management alone. Acamprosate treatment was not effective with or without behavioral support in this study. It remains controversial whether naltrexone adjunct with psychosocial intervention is superior to supportive medical advice [234–238]. Medical management of alcohol dependence with naltrexone appears to be feasible and, if implemented in primary, and other health care settings, has the potential to greatly extend patient access to effective treatment.

However, both naltrexone and acamprosate are not effective medication treatments for all subjects. With the significant advances of several new potential pharmacotherapy interventions such as the neurokinin 1 (NK1) receptor antagonist LY686017 [239], 5-HT receptor antagonist ondansetron [240, 241] and now varenicline, studies need to be initiated on a systematic basis to test these new medications in combination with the existing options, as well as singly with effective behavioral therapies. Clinical trials should be initiated by both the pharmaceutical industry and academia alike to evaluate the efficacy of these treatments. With the high co-occurrence of smokers amongst heavy alcohol drinkers, varenicline with its convenient administration route can be made available at primary care settings. Varenicline with the support of medical therapy can potentially be suggested for those alcohol dependent individuals who are seeking help and show no adverse treatment effects.

In addition, medications that target different drinking behaviors could be administered in combination. For example, acamprosate which is known to attenuate alcohol craving, could be combined with varenicline that attenuates the rewarding properties of alcohol. Similar approaches with acamprosate and naltrexone have been studied previously. The naltrexone-

acamprosate combination was shown to be superior to acamprosate alone but not to naltrexone alone [242, 243]. Similarly, varenicline and the NK1 receptor antagonist LY686017 with antiemetic properties, both targeting the rewarding properties of alcohol but not the same biological substrate (nAChRs vs neurokinin-1 receptor) could be combined to evaluate if the efficacy of the medication in combination is superior to either of them alone. Combinational drug trials use suboptimal dosages to get the desired effect and could produce reduced toxicity and side effects as an added benefit, especially since a large subset of alcohol dependent individuals can have other concurrent psychiatric or chronic disorders. These combinational therapies could be administered along with behavioral programs to engage subjects to adhering to the medications. Such protocols that pay attention to the subjects' satisfaction with medication and the likelihood for them to adhere to the regimen have been established [244].

SIDE EFFECTS OF VARENICLINE USE

Although varenicline is the most effective smoking cessation aid available, anecdotal and case study reports of suicidal and other psychiatric adverse events have generated concerns for varenicline use [245–249]. The FDA has recently made a requirement for a boxed warning on the drug's label to alert patients and physicians of the potential risks of behavioral changes, depression, aggression and suicidal thoughts [245]. FDA has urged the manufacturer of varenicline (Pfizer) to conduct randomized controlled trials that include individuals with pre-existing mental health conditions which forms a high proportionate of smokers. The belief is that the risks of taking varenicline needs to be weighed against the health benefits from quitting smoking [249–251].

To address the growing concerns of the risk of suicidal behavior associated with varenicline, a very large scale study (n=80,660) of men and women between the ages 18–95 was recently conducted [252]. Gunnell and colleagues (2009) measured outcomes such as fatal and nonfatal self-harm, suicidal thoughts, and depression following varenicline prescription and alternative smoking cessation treatments such as bupropion and nicotine replacement products (transdermal patch, inhaler, nasal spray, gum or lozenge). In this study, the authors found no clear evidence that varenicline treatment produced an increased risk of self-harm, depression or suicidal thoughts, compared with the alternative smoking cessation treatments. Additionally, others studies have shown that individuals, including some mentally-ill subjects, have benefited from taking varenicline with negligible side effects, with no worsening of neuropsychiatric symptoms or mood disturbances [225, 246, 253–257]. Therefore, it may be that varenicline is effective as a smoking cessation aid for some individuals and not for others, and patients prescribed this drug need to be monitored carefully for behavioral changes to prevent any serious psychiatric outcomes. It is worth noting that for the treatment of AUDs, the effect of varenicline appears to be effective, safe, and well tolerated in heavy-drinking smokers, albeit in a small scale study [222]; future large scale study is imperative.

DRUG ADDICTION, DECISION MAKING, AND nAChRs

Another aspect of prolonged drug exposure involves the modification of brain circuits that are crucial for the normal control of behavior, including the decision-making process, as demonstrated by a growing number of studies [258–260]. In this section, we will briefly discuss the effect of chronic use of alcohol on neural circuits regulating cognitive activities such as decision-making, behavioral inhibition and problem solving and the potential use of nAChR-targeted compounds to improve cognitive functions impaired by alcohol use in these brain regions.

The prefrontal cortex, which is the anterior part of the frontal lobes in the brain, is a highly evolved region involved in cognitive functions that are central to drug and alcohol dependence (see review see [261]). Apart from alcohol's affect in modulating the rewarding sensation through the brain dopamine system, prolonged alcohol use has also been shown to alter frontal cortex structure and function impairing decision making and response inhibition operations [262–264]. For example, imaging studies in substance users reveal abnormalities in blood flow in the orbitofrontal cortex (OFC) which is part of the prefrontal cortex [265, 266]; over-activation of the OFC correlates with craving [267]. In addition, a reduction in spine density in the OFC of rat brain during abstinence from amphetamine self-administration has been shown [268]. An overall decline in frontal lobe function is seen in alcohol-dependent individuals with associated cognitive impairment [269–271]. During a decision making process, such as Iowa Gambling Task [272], alcohol dependent individuals were shown to have significant impairment in their performance compared with control subjects [273]. Studies have shown that active and abstinent alcoholics exhibit performance favoring larger immediate rewards while disregarding long-term consequences [266, 272, 274–276]. Compromised decision-making is also observed with other substance use such as cocaine, amphetamine, and heroin with functional abnormalities in the prefrontal neural circuitry [277–280]. The poor decision-making and behavioral inhibition to negative consequences of excessive drinking is thought to be a factor in compulsive drug-seeking behavior [281]. While cognitive deficits play a factor in developing alcohol dependence, a longitudinal study has shown that continuous substance use during adolescence can lead to larger neurocognitive deficits [282]. Investigators in this field hypothesize that the extent of decision-making impairment may reflect vulnerabilities to drug addiction and enhancement of these cognitive tasks may be important for treatment.

Understanding the role of nAChRs in cognitive functions has made progress over the years [283–285]. Cholinergic projections from the nucleus basalis magnocellularis to the cortex is thought to be particularly important in cognitive processes [286] (for review see [287]). The nAChRs target ligands have been of great interest for drug discovery research especially with regard to their capacity as cognitive enhancers [288–291] for diseases such as Alzheimer's disease, Parkinson's disease, attention deficit/hyperactivity disorder and schizophrenia [292–294]. Cognitive enhancers have been shown to facilitate the detection of signals by augmenting the transient increase of prefrontal cholinergic activity *via* the modulation of glutamatergic neurotransmission in an attention behavioral context [295]. nAChR target compounds can modulate the release of several neurotransmitters [127] and can improve cognitive function through the interaction of various neurotransmitter systems. This has led to the development of several nicotinic compounds (ABT-418, SIB-1508Y, SIB-1553A, GTS-21, AZD3480, AZD1446) synthesized in various biotech and pharmaceutical companies, and the initiation of clinical trials for the above mentioned indications.

Given the large number of studies that have demonstrated cognitive impairment in alcohol-dependent individuals, novel nAChRs ligands that improve cognitive dysfunction should be developed. In order to find a treatment for AUD, serious initiatives with clinical evaluations of such ligands are imperative. A systematic screening of approved nicotinic ligands, such as those mentioned previously, with demonstrated safety in humans needs to be initiated in patients with alcohol dependence.

CONCLUSIONS

Lastly, even with the significant advances made both in preclinical and clinical settings, only about of 10% to 15% of those affected with alcohol use disorders get treated, mostly with the help of social and behavioral therapy. There is strong evidence from both biology and

behavioral studies to show that alcohol addiction cannot be resolved with will power alone. Medication along with cognitive behavioral therapy is important and needs to be implemented by practitioners as part of the standard treatment options present to patients and their family as soon as possible in our society.

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ABBREVIATIONS

AUDs	Alcohol use disorders
ACh	Acetylcholine
CNS	Central nervous system
FDA	US Food and Drug Administration
MHb	Medial habenula
nAChRs	Nicotinic acetylcholine receptors
NAcc	Nucleus accumbens
OFC	Orbitofrontal cortex
VTA	Ventral tegmental area

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nAChRs as pentameric ion channels

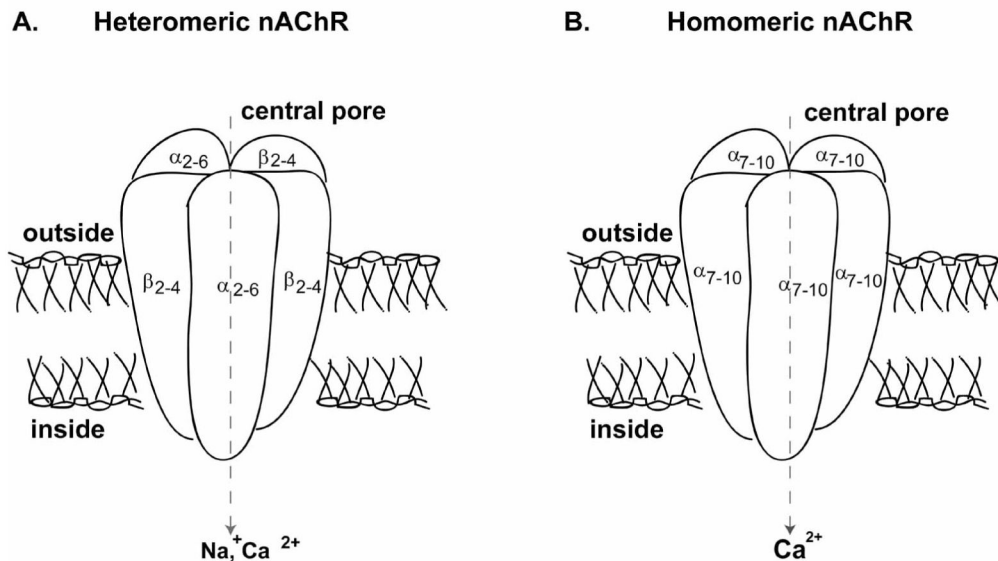


Fig. 1. The neuronal nicotinic acetylcholine receptor (nAChR) structure and the possible subtypes. The nAChRs are pentameric ligand-gated ion channels forming either heteromeric or homomeric receptors. The heteromeric receptors (**A**) are α -bungarotoxin insensitive receptors consisting of α ($\alpha 2$ – $\alpha 6$) and β ($\beta 2$ – $\beta 4$) subunits with the ligand-binding site at the interface of α and β subunits. The α -bungarotoxin insensitive receptors (**B**) are predominantly homomeric consisting of $\alpha 7$, $\alpha 8$ or $\alpha 9$ subunits and can seldom be heteromeric with $\alpha 7$ – 8 or $\alpha 9$ – 10 subunit compositions and contains five identical ligand binding site.

Diversity of nAChRs in the brain

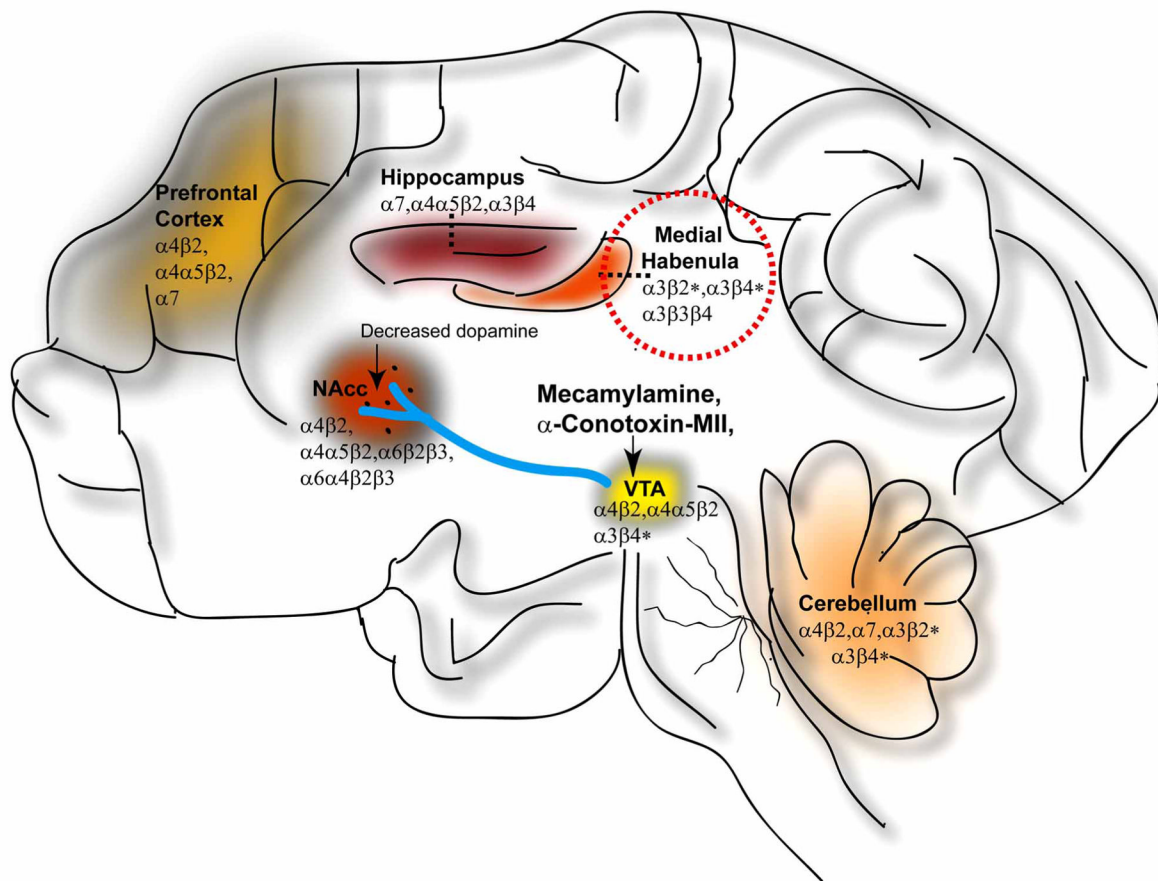


Fig. 2.

The diversity and localization of the possible nAChR subtypes in the brain. Several subunit compositions of nAChRs exist and are widely distributed as shown here in brain regions: ventral tegmental area (VTA), nucleus accumbens (NAcc), medial habenula, hippocampus, prefrontal cortex and cerebellum. The activation of nAChRs in the mid brain which consists of VTA and NAcc has been implicated to be important for ethanol mediated effects. Mecamylamine and α -conotoxin- MII are the only nAChR ligands that have been administered locally into the VTA resulting in a decrease of ethanol-induced dopamine overflow in the NAcc. Genetic-association studies have indicated nAChRs containing the $\alpha 3^*$, $\alpha 5^*$ and $\beta 4^*$ subunits to be important for alcohol dependence. Medial habenula (dashed line) indicates a brain region with the highest density of these subunits with afferent and efferent connections with the midbrain.

Table 1
Preclinical, Small Scale Clinical Findings and Future Clinical Studies for Currently Approved Neuronal nAChRs Ligands

Treatment	Pre-Clinical Findings		Small Scale Clinical Findings			Future Clinical Trials
	Effect	Citation	Sample Size	Effect	Citation	
Mecamylamine (Inversin [®] , marketed 1950)	Counter-acted ethanol induced dopamine overflow; Reduced ethanol intake; Reduced ethanol induced-stimulation of locomotor activity.	[30, 126, 133, 212]	20-24	Reduced self-reported euphoric and stimulant effects to alcohol, reduced breath alcohol levels	[210, 213, 214]	ClinicalTrials.gov Identifier: NCT00342563 Yale University Phase II: n=60;
Varenicline (Chantix [®] and Champix [®] , marketed 2006)	Reduced ethanol voluntary consumption and self-administration; Modulate dopamine mediated activity by ethanol and nicotine.	[19, 52]	20	Reduced self-reported alcohol reactivity; decreased alcohol self-administration	[222]	