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Nicotinic acetylcholine receptors and depression: a review of the preclinical and clinical literature

Noah S. Philip, Linda L. Carpenter, Audrey R. Tyrka, and Lawrence H. Price

Mood Disorders Research Program, Butler Hospital, Department of Psychiatry and Human Behavior, Warren Alpert Medical School of Brown University, 345 Blackstone Blvd, Providence, RI 02906, USA

Abstract

Many patients with depression fail to derive sufficient benefit from available treatment options, with up to a third never reaching remission despite multiple trials of appropriate treatment. Novel antidepressant agents are needed, and drugs targeting nicotinic acetylcholine receptors (nAChRs) appear to hold promise in this regard. nAChRs are involved in a variety of neurobiological systems implicated in the pathophysiology of depression. In addition to their role in cholinergic neurotransmission, they modulate dopamine function and influence inflammation and hypothalamic–pituitary–adrenal axis activity. Pre-clinical studies have suggested antidepressant-like effects of drugs targeting nAChRs, with the most consistent results observed with $\alpha 4\beta 2$ nAChR modulators such as varenicline and nonspecific nAChR antagonists such as mecamylamine. These agents appear to offer the most potential antidepressant-like efficacy when used in conjunction with other established antidepressant treatments. nAChR modulators also influence neural processes that appear to mediate the behavioral effects of antidepressants, such as hippocampal cell proliferation. Clinical evidence, while limited, shows preliminary efficacy for mecamylamine and varenicline. Taken together, the preclinical and clinical evidence suggests that drugs targeting nAChRs may represent an important new approach to the treatment of depression.

Keywords

Nicotinic acetylcholine receptor; Major depressive disorder; Antidepressants; Cytisine; Varenicline; Mecamylamine

Introduction

Major depression is one of the most common psychiatric illnesses worldwide, with significant public health impact. The World Health Organization designated major depression as the most common cause of disease burden in North America (Mathers and Loncar 2006). Despite numerous treatment options, many patients do not achieve relief with currently available medications. The Sequenced Treatment of Alternatives to Relieve

Correspondence to: Noah S. Philip.

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Depression (STAR*D) trial showed that only about half of patients receiving initial treatment with antidepressants respond to treatment, and only a third reach remission. Even after multiple levels of treatment, patients in the STAR*D study reached a cumulative remission rate of only 67% (Trivedi et al. 2006). Clearly, new pharmacologic treatments are needed.

Targeting the cholinergic system, and particularly the nicotinic cholinergic receptor (nAChR), holds promise as a novel therapeutic approach to depression. Speculation that acetylcholine might be involved in depression is not new, as early work suggested that a cholinergic/adrenergic imbalance might lead to depressive symptoms (Janowsky et al. 1972, 1974). However, these early studies were performed before the availability of drugs targeting specific receptors within the cholinergic system, making the results difficult to interpret.

This paper provides an overview of nAChRs and their relationships to other neurobiological systems relevant to depression and examines preclinical and clinical data on the antidepressant effects of drugs acting on nAChRs. The clinical efficacy of such drugs in the treatment of smoking cessation (Gonzales et al. 2006; Jorenby et al. 2006) and their potential role in the treatment of cognitive disorders, autism, attention deficit hyperactivity disorder, and schizophrenia have been addressed elsewhere (Bacher et al. 2009; Cincotta et al. 2008; Ochoa and Lasalde-Dominicci 2007; Sabri et al. 2008). Since there are multiple effects of different compounds acting on the nAChR, such as antagonism, partial agonism, and desensitization, we will refer to drugs that target nAChRs system in general as nAChR modulators after specifically discussing each drug.

Overview of the nAChR system

nAChRs are part of the larger system of cholinergic receptors (AChRs). AChRs are divided into two receptor systems, muscarinic (mAChRs) and nicotinic (nAChRs). Muscarinic receptors are G-protein-coupled acetylcholine receptors, distributed in the central and parasympathetic nervous systems (Eglen 2006). The nAChR is a ligand-gated, i.e., ionotropic, receptor for acetylcholine and can also bind to exogenous ligands such as nicotine. When activated, nAChRs open nonselective cation channels that can affect membrane polarity as well as influence intracellular messenger cascades under the control of calcium concentration. nAChRs share structural similarity with γ amino butyric acid (GABA), glycine, and serotonin type 3 (5-HT₃) receptors. They are composed of five pentameric units, formed from up to 17 different subunits coded by an extensive family of coding DNA (Albuquerque et al. 2009). There are two classes of nAChRs in the central nervous system, high- and low-affinity. High-affinity nAChRs are composed of heteromers of α and β subunits, which are antagonized by dihydro- β -erythridine and mecamylamine and stimulated in low doses by the $\alpha 4\beta 2$ partial agonist varenicline. Low-affinity nAChRs are α homopentamers, which are blocked by the snake venom α -bungarotoxin and by methyllycacinine. nAChRs are highly conserved over the course of evolution, although studies of nAChR knockout mice suggest that brain nAChRs are not required for survival or for execution of basic behaviors but rather are important for control of complex behaviors (Gotti and Clementi 2004; Ross et al. 2000).

With respect to depression, the $\alpha 4\beta 2$ nAChR subtype has received the most attention as a potential target. $\alpha 4\beta 2$ nAChRs are widely distributed in neuroanatomic regions implicated in depression, including basal ganglia, striatum, thalamus, hypothalamus, amygdala, ventral tegmental area, locus coeruleus, and dorsal raphe nucleus. Through their actions in these areas, they are thought to regulate the release of other monoamine neurotransmitters (Albuquerque et al. 2009; Gotti et al. 2006), particularly dopamine, which is strongly implicated in affect regulation and reward processing and reinforcement. nAChRs modulate dopamine neurotransmission by direct action from cholinergic projections, as well as by indirect excitatory (glutamatergic) and inhibitory (GABAergic) influences on the dopamine neuron (Fig. 1) (Albuquerque et al. 2009; Dunlop and Nemeroff 2007; Li et al. 1998; Mihailescu et al. 2002; Mihailescu et al. 1998). There is neuroimaging evidence of decreased $\alpha 4\beta 2$ nAChR binding in Parkinson's patients with depression, and this decreased binding is independent of cognitive symptoms (Meyer et al. 2009).

nAChRs are also involved in neuroendocrine systems implicated in depression, particularly the hypothalamic–pituitary–adrenal (HPA) axis. Altered HPA axis function is one of the most consistent biological findings in depression, with demonstrated effects including changes in corticotropin releasing factor (CRF) secretion, glucocorticoid receptor sensitivity, and pituitary and adrenocortical structure and function (Pariante and Lightman 2008; Tsigos and Chrousos 2002). nAChRs are located on the presynaptic terminals of CRF-releasing neurons (Okuda et al. 1993), and drugs that act on nAChRs have been shown to affect key components of the HPA axis. Mecamylamine, a nonspecific nAChR antagonist approved for use as an antihypertensive, can prevent CRF release from the hypothalamus (Raber et al. 1995). Mecamylamine can also block pharmacologically induced secretion of corticosterone (Rhodes et al. 2001). Nicotine, the classic nAChR ligand, has similarly been shown to alter HPA activity. Nicotine can stimulate CRF release (Fuxe et al. 1989) and can influence the secretion of adrenocorticotropin (ACTH) independent of its effects on CRF, possibly by modulating catecholamine activity in the tractus solitarius ascending from the locus coeruleus (Matta et al. 1998). In humans, nicotine delivered by cigarette smoke results in acute increases of salivary cortisol (Kudielka et al. 2009). Chronic administration of nicotine through cigarette smoke may result in down-regulation of the HPA axis, which may explain why habitual smokers manifest a blunted salivary cortisol response to the Trier Social Stress Test (Rohleder and Kirschbaum 2006), a paradigm often used to measure HPA axis responsivity (Kirschbaum et al. 1993).

Recent work has suggested that agents affecting the HPA axis might also affect nAChRs. For example, in mice, CRF-1 antagonists improve deficits in brain reward function during nicotine withdrawal (Bruijnzeel et al. 2009). This deficit is thought to be a proxy for the negative affective state associated with nicotine withdrawal, in which nAChRs are presumably unbound. While this evidence is indirect, it supports the possibility of a reciprocal relationship between nAChRs and a neuroendocrine system consistently associated with depression.

nAChRs play a role in inflammation, which has also been implicated in the pathophysiology of depression (Miller et al. 2009). $\alpha 7$ nAChRs mediate the effects of the vagus cholinergic anti-inflammatory pathway. When the vagus nerve is stimulated, it releases peripheral

acetylcholine, which binds to $\alpha 7$ nAChRs on macrophages, resulting in decreased macrophage activity (Gallowitsch-Puerta and Pavlov 2007; Shytle et al. 2004). This was demonstrated by assessing levels of inflammatory cytokines (such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6)) in $\alpha 7$ nAChR wild-type and knockout mice during stimulation of the vagus nerve. Stimulation decreased cytokine secretion in wild-type mice, whereas in knockout mice cytokine levels were unchanged (Wang et al. 2003). The same authors showed that vagotomized wild-type mice had greater levels of TNF during challenge with endotoxin compared to wild-type mice with an intact vagus nerve (Wang et al. 2003).

$\alpha 7$ nAChRs have been shown to mediate inflammatory regulation in a variety of inflammatory states, such as sepsis, endotoxic shock, and colitis (Pavlov 2008), and $\alpha 7$ agonists are under development as treatments for inflammation. GTS-21, an $\alpha 7$ agonist, decreases TNF release from endotoxin-stimulated macrophages and suppresses activation of NF- κ B, a transcription factor regulating TNF synthesis (Pavlov et al. 2007)

Given the mounting evidence for a relationship between inflammation and depression, the role of nAChRs in modulating inflammatory responses is of particular interest.

nAChRs and depression: history

In the early 1970s, Janowsky proposed a cholinergic/adrenergic theory of depression, invoking a pathogenic imbalance between these two systems that was driven by cholinergic over-activity (Janowsky et al. 1972). Evidence for this theory was supported by experiments with physostigmine, a nonspecific acetylcholinesterase inhibitor. When given to healthy controls, physostigmine induced feelings of depression, anxiety, and irritability. Similarly, administration of physostigmine to depressed patients exacerbated depressive symptoms (Janowsky et al. 1974; Janowsky and Risch 1983). The theory was given further support by animal studies showing that mice bred specifically for sensitivity to cholinergic agents demonstrated depression-like behaviors (Overstreet 1993). Other studies found that learned helplessness and swim stress, widely used preclinical models of depression, could induce sensitivity to cholinergic agents (Dilsaver and Alessi 1987; Dilsaver et al. 1986).

There are some significant limitations to the theory as it was initially formulated. This theory was advanced before the modern understanding of the role of serotonin in depression, and it relied heavily on a single experimental paradigm. However, the cholinergic/adrenergic theory suggested that antagonizing acetylcholine receptors could have antidepressant effects. This hypothesis is supported by recent clinical investigations of intravenous scopolamine, an anti-emetic and anesthetic that is a nonspecific muscarinic acetylcholine receptor antagonist, in adults with major depressive episodes.

In an initial placebo-controlled dose-finding study, Furey and Drevets (2006) administered intravenous infusions of scopolamine 2.0, 3.0, and 4.0 mcg/kg to eight depressed patients; depressive symptoms robustly improved only at the highest dose over the 3–5 days after infusion, suggesting a degree of dose-dependent effect. The authors subsequently gave intravenous scopolamine 4.0 mcg/kg to 18 depressed patients (nine unipolar, nine bipolar) in

a double-blind, placebo-controlled, crossover design following a single-blind placebo lead-in. Again, depressive and anxiety symptoms, as assessed by the Montgomery–Asberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HARS), respectively, improved significantly more with scopolamine than with placebo. Eleven of 18 patients had a full response (defined as a >50% improvement in MADRS score), and 10 of 18 experienced remission (defined as a MADRS score <10). These findings were replicated in a study of 23 unipolar depressed patients using a similar design, which showed a 32% improvement in MADRS scores in patients receiving scopolamine compared to 6.5% improvement with placebo (Drevets and Furey 2010). Of the total 40 participants in these studies with unipolar depression, 29 (72.5%) had a history of comorbid anxiety disorders, chronic medical illness, or treatment resistance, suggesting these patients would have a relatively poor prognosis with standard monoaminergic antidepressant medications and highlighting the therapeutic potential for drugs acting on cholinergic neurotransmission.

While scopolamine's intravenous formulation and sedative and amnesic properties limit its potential for clinical use, the drug's putative antidepressant effects constitute important support for the involvement of the cholinergic system in depression. Moreover, the clinical characteristics of scopolamine responders suggest that the cholinergic system may play an important role in treatment-resistant patients (Philip et al. 2010). In light of this evidence, the introduction of drugs that can specifically target individual receptors in the cholinergic system suggests a significant opportunity for the development of novel therapeutic approaches.

nAChRs and depression: smoking and nicotine

Another body of work that supports the relationship between nAChRs and depression involves tobacco smoking. Smoking rates in major depression are higher than in the general population, generally between 40% and 60% vs. 22%, respectively (Kalman et al. 2005). Smoking cessation has also been found to influence mood. Smokers with a history of major depression have a harder time quitting smoking, and patients with depression are at risk for developing a major depressive episode during smoking cessation (Dani and Harris 2005; Hughes 2007). Smokers also have lower levels of monoamine oxidase A (MAO-A), an enzyme involved in the degradation of norepinephrine, serotonin, and dopamine, which has been hypothesized to lead to depressed mood (Fowler et al. 2003).

The link between smoking and depression is likely to be through nicotine, the classic nAChR ligand that is the primary active ingredient in cigarette smoke. Nicotine has been shown to have antidepressant properties in a number of studies. Initial work in the late 1990s showed that giving nicotine over 1–2 weeks to rodents produces decreased immobility time in both the forced swim and tail suspension tests (Andreasen and Redrobe 2009b; Djuric et al. 1999; Semba et al. 1998; Tizabi et al. 1999), two laboratory paradigms that are frequently used to evaluate a candidate drug for potential antidepressant effects (Porsolt et al. 1977; Steru et al. 1985). In humans, a brief, open-label trial showed transdermal nicotine could decrease depressive symptoms in depressed nonsmokers (Salin-Pascual 2002). A second trial replicated this finding of mood benefits following a month of double-blind transdermal nicotine treatment in mildly depressed nonsmokers (McClernon et al. 2006).

Antidepressant medications used clinically for smoking cessation have antagonist properties at the nAChR. Bupropion, a norepinephrine and dopamine reuptake inhibitor, has nAChR antagonist properties, as does nortriptyline, a tricyclic antidepressant (TCA) that inhibits norepinephrine and serotonin reuptake. Indeed, it has been suggested that this property accounts for the efficacy of these drugs in smoking cessation and contributes to their antidepressant effects (Arias 2009; Damaj et al. 2004; Schofield et al. 1981).

Taken together, these data lead to an apparent paradox: nicotine, a potent nAChR agonist, manifests antidepressant effects, whereas antagonists of the nAChR, such as mecamylamine, also manifest antidepressant effects. This might be explained by a closer consideration of nicotine's effects at the nAChR. Nicotine initially activates the nAChR, but this is then followed by a rapid desensitization (Gentry and Lukas 2002; Paradiso and Steinbach 2003). Sustained binding of nicotine to the nAChR leads to continued desensitization, which is hypothesized to result in chronic antagonism (Mineur and Picciotto 2009; Picciotto et al. 2008; Shytle et al. 2002a).

nAChRs and depression: pharmacologic evidence

Most antidepressant research targeting nAChRs has focused on two kinds of ligands: mecamylamine and the plant alkaloid cytisine and cytisine-based molecules, such as varenicline.

Preclinical findings

Preclinical studies using nAChR modulators have resulted in a variety of different, and at times discordant, findings. Table 1 summarizes the preclinical literature on this topic. Popik et al. (2003) demonstrated that mecamylamine could increase the antidepressant-like effects of the TCA imipramine and the selective serotonin reuptake inhibitor (SSRI) citalopram during the tail suspension test. Nicotine also enhanced the antidepressant effects of both imipramine and citalopram in this paradigm. In contrast, dihydro-beta-erythrodine, a selective $\alpha 4\beta 2$ nAChR antagonist, increased the antidepressant-like effects of imipramine but not those of citalopram in this study, making the overall findings more difficult to interpret. This was the first study to show that nAChR antagonists might enhance the activity of primary antidepressants.

Rabenstein et al. (2006) demonstrated that mecamylamine had antidepressant-like effects on wild-type mice during the forced swim and tail suspension tests. When the experiments were repeated with either $\beta 2$ or $\alpha 7$ nAChR knockout mice, antidepressant-like effects were lost. Based on these findings, the authors hypothesized that these nAChR subunits are important for mood regulation.

Caldarone et al. (2004) showed that high-affinity nAChRs are required for the antidepressant-like effects of amitriptyline in mice. They examined performance on the forced swim test in mice treated with pharmacologic doses of mecamylamine alone and compared that with mice given sub-pharmacologic doses of mecamylamine plus amitriptyline. Pharmacologic doses of mecamylamine alone produced improved performance, suggesting clinical antidepressant potential. While neither sub-pharmacologic

mecamylamine alone nor sub-pharmacologic amitriptyline alone improved test performance, the combination of the two decreased immobility time, signaling a possible potentiating action of nAChR modulators during treatment with a conventional antidepressant such as amitriptyline. When nAChR knockout mice were subjected to the forced swim test, the previously observed antidepressant-like effects of amitriptyline at pharmacologic doses were lost, providing additional evidence of a potential synergy between the agents.

Caldarone et al. also investigated hippocampal cell proliferation, since this phenomenon has been observed with chronic successful antidepressant treatment (Malberg and Duman 2003; Malberg et al. 2000) and has been postulated as a necessary condition for the positive behavioral effects of antidepressant pharmacotherapy (Santarelli et al. 2003). They found that nAChR knockout mice did not demonstrate hippocampal cell proliferation when treated with amitriptyline, suggesting that nAChRs may play a role in the biological changes underlying the antidepressant activity of TCAs.

Andreasen and colleagues investigated nAChR modulators in two preclinical studies. In the first, nAChR antagonists, but not agonists, exhibited antidepressant-like effects during forced swim and tail suspension tests (Andreasen et al. 2009). The authors tested several different compounds, including the $\alpha 4\beta 2$ agonist RJR-2403, the $\alpha 4\beta 2$ antagonist dihydrobetaerythiodine, the $\alpha 7$ agonist PNU-282987, and the $\alpha 7$ antagonist methyllycacinine. They also included tests of hexamethonium, a nonspecific nAChR antagonist with limited penetration of the blood–brain barrier, as well as nicotine and mecamylamine, in their experimental design. Mecamylamine and antagonists of the $\alpha 4\beta 2$ and $\alpha 7$ receptors demonstrated improved performance on the forced swim and tail suspension tests. Hexamethonium had no activity, suggesting that peripheral nAChRs are not involved in responses to these tests. However, in this study, nicotine also had no effect on test performance, a finding discordant with previous evidence showing antidepressant-like effects of nicotine in mouse models (Djuric et al. 1999; Semba et al. 1998; Suemaru et al. 2006; Tizabi et al. 1999). This may be explained by a significant increase in locomotor activity during nicotine treatment compared to saline, which could confound results from the forced swim test (Porsolt et al. 1977).

In a subsequent study, the same group examined the effects of nAChR antagonists as “augmenting” agents for enhancing the antidepressant-like effects from several commonly used drugs (Andreasen and Redrobe 2009b). They investigated whether nicotine or mecamylamine could augment the antidepressant effects of SSRIs or selective norepinephrine reuptake inhibitors (SNRI) on the mouse forced swim test and the tail suspension test. Pharmacologic and sub-pharmacologic doses of the SSRI citalopram and SNRI reboxetine, alone and in combination with nicotine or mecamylamine, were administered. Nicotine improved performance on the forced swim and tail suspension tests in conjunction with both pharmacologic and sub-pharmacologic doses of citalopram and reboxetine. Mecamylamine monotherapy improved performance in some tests, but did not augment the effects produced by sub-pharmacologic or pharmacologic doses of citalopram or reboxetine. One reason for the negative results using mecamylamine in this study may have been under-dosing; in their 2006 study, this group found improved test performance with at least 3 mg/kg of mecamylamine, and in this 2008 study, the upper limit of

mecamylamine dose was 3 mg/kg. Another reason for discrepant results may have been the use of different mouse strains in different experiments, resulting in different responses to the behavioral paradigms administered (Andreasen and Redrobe 2009a).

Mineur et al. (2007) demonstrated that the alkaloid cytisine, the $\alpha 4\beta 2$ partial agonist from which varenicline was derived, has antidepressant-like effects in mouse models. They administered cytisine and measured acute antidepressant-like effects via the forced swim and tail suspension tests and chronic antidepressant-like effects via the novelty-suppressed feeding test, comparing the results to similar experiments conducted with mecamylamine. They also assessed expression of c-fos, a genetic marker of neuronal activity associated with antidepressant action (Beck and Fibiger 1995). C-fos has been shown to upregulate during acute antidepressant treatment and down-regulate with more chronic treatment (Slattery et al. 2005). Mice treated with cytisine had significantly improved performance on all three tests, and results with mecamylamine were comparable to those found with cytisine. Cytisine resulted in an overall reduction of c-fos activity after 21 days. The greatest reduction in c-fos was seen in the basolateral amygdala region. Mecamylamine also reduced c-fos activity, although its effects were more pronounced in the hypothalamus, nucleus accumbens, and suprachiasmatic nucleus. The authors hypothesized that these drugs might exert antidepressant effects by influencing neuronal activity in these areas.

The same group then conducted a series of experiments with other compounds derived from cytisine to assess for specific antidepressant effects (Mineur et al. 2009). They examined cytisine and two derivatives with more specific antagonism at the $\alpha 4\beta 2$ receptors, 3-(pyridin-3'-yl)-cytisine (3-pyr-Cyt) and 5-bromo-cytisine (5-Br-Cyt). 3-pyr-Cyt and cytisine, but not 5-Br-Cyt, had generally dose-dependent antidepressant-like effects in both the tail suspension and forced swim tests using intraperitoneal injections. Because 5-Br-Cyt does not penetrate the blood-brain barrier, they repeated the tail suspension test using intraventricular administration of 5-Br-Cyt and found significant improvement with this compound. Based on their findings, the authors suggested that more specific $\alpha 4\beta 2$ nAChR antagonists might be candidates for drug development for depression.

Lippiello et al. (2008) tested the s-enantiomer of mecamylamine in rodent models for potential antidepressant-like effects. They found that s-mecamylamine improved performance on the forced swim and behavioral despair tests. They subsequently assessed s-mecamylamine in a social paradigm model for anxiety-like behavior and also found significant improvement associated with the s-enantiomer on that behavioral assay. The drug was well tolerated without any acute or chronic toxicity.

Rollema et al. (2009) examined whether varenicline had effects on the forced swim test and whether it could augment the antidepressant-like effects of the SSRI sertraline. These investigators evaluated varenicline alone, sertraline alone, and combination treatment of varenicline plus sertraline. All three groups were compared with a control group of rats treated with amitriptyline alone. Varenicline and sertraline monotherapies significantly improved performance on the forced swim test, although these drugs' effects were inferior relative to the effect observed in the amitriptyline control condition. The combination of sertraline plus varenicline did result in significantly improved test performance, achieving an

effect comparable to that observed in rats treated with amitriptyline. Augmentation-like effects were significantly more prominent at lower doses of varenicline, suggesting an inverse dose-dependent effect of varenicline augmentation.

Clinical findings

Clinical data targeting nAChRs are limited; most research has been done with the two compounds available for clinical study, mecamylamine and varenicline. These studies are summarized in Table 2.

Mecamylamine

Shytle et al. (2002b) reported that mecamylamine reduced depression and irritability in four children and adolescents (ages 8–17) with Tourette disorder and comorbid major depression. Following this preliminary report, George et al. (2008) conducted an 8-week, double-blind, placebo-controlled trial of mecamylamine 10 mg/day augmentation in 21 depressed adults who were currently taking an SSRI for at least 3 months with either no or partial response and baseline Hamilton Depression Rating Scale (HDRS) scores of 12 or higher. The investigators hypothesized that antidepressant response to mecamylamine would be more robust in patients who smoked, given that nAChRs may be up-regulated in smokers due to chronic nicotine administration (Dani and Harris 2005). Patients taking mecamylamine had a significant improvement in HDRS score by the 8-week endpoint compared with those on placebo. Counter to their hypothesis, there was a trend-level ($p=0.06$) *positive* association between nonsmoking status and antidepressant response. The authors discussed how larger trials would be needed to replicate this effect and suggested that smokers may have chronically up-regulated levels of nAChRs which may make them less likely to respond to nAChR antagonist treatment. Larger trials of mecamylamine and s-mecamylamine antidepressant augmentation are not yet publicly available, but commercial press releases have reported efficacy with these compounds (Targacet IW-S, NC); at present, it is not possible to objectively evaluate these claims.

Varenicline

To evaluate the effects of varenicline on mood and cognition during smoking cessation, Patterson et al. (2009) performed a double-blind placebo-controlled study in 67 subjects undergoing smoking cessation with a scheduled smoking relapse. The authors assessed two phases of treatment with varenicline. In an initial phase, they first compared changes in affect (as measured by the Positive and Negative Affect Schedule), attention, and working memory during varenicline treatment compared to placebo. On day 14 of treatment, they exposed patients to a scheduled cigarette smoking “relapse” and measured levels of satisfaction with smoking during this relapse. During the cessation phase, varenicline treatment decreased withdrawal symptoms, increased positive affect, and decreased negative affect. Compared with placebo, patients treated with varenicline also had improved performance on tests of attention and working memory during cessation. During the scheduled relapse, patients treated with varenicline reported less intense feelings of reward compared to the placebo group. The authors concluded that varenicline improved mood and

cognition during smoking cessation and suggested varenicline be explored as a potential treatment for mood disorders.

Following similar clinical observations, our group conducted an open-label study of varenicline augmentation in 18 adult smokers with an Axis I depressive disorder and pharmacotherapy-resistant symptoms (Philip et al. 2009). Depressive symptoms (using the Quick Inventory of Depressive Symptoms, Self-Report (QIDS-SR16)), anhedonia, and overall illness severity were measured. Varenicline produced a robust antidepressant response that was generally early and sustained. Forty-four percent of patients met criteria for categorical response (defined as a greater than 50% improvement in the QIDS-SR), and 33% achieved remission (QIDS-SR score less than five). Improvement in depressive symptoms correlated with cessation status late in the trial. There was also significant improvement in overall depressive illness severity, but no changes in anhedonia were observed. No evidence of treatment-emergent suicidality was found.

Although there have been few clinical studies of varenicline specifically for treatment of depression, the drug has seen widespread clinical use for smoking cessation. Some case reports described worsened mood in patients with schizophrenia, bipolar disorder, and unipolar depressive disorders (Freedman 2007; Kohen and Kremen 2007; Popkin 2008). These reports led to a black-box warning from the US Food and Drug Administration advising clinicians to monitor for changes in behavior, hostility, agitation, depressed mood, suicidal thoughts and behavior, and attempted suicide in patients receiving varenicline and sustained-release bupropion (Administration 2009). In meta-analyses of phase 2 and 3 trials of varenicline ($n=5,096$), the drug has not been shown to induce these effects in otherwise healthy smokers (Tonstad et al. 2010), and other studies have not confirmed a varenicline-associated increase in adverse mood and behavioral symptoms in at-risk populations. A large ($n=1,117$) open-label trial used telephone reports of mood state during smoking cessation to investigate this issue in individuals with a possible history of depression and compared them with another group of individuals without such a history (McClure et al. 2009). Significant improvement in depressive symptoms at 21 days and 3 months of treatment was seen for the pooled sample, although the authors found that patients with a probable history of depression were more likely to report depressive symptoms during the trial. There was no significant difference in adverse mood or behavioral symptoms between the two groups. Another report of 208 smokers showed that varenicline did not produce worsened mood or emergence of suicidality when used for smoking cessation in smokers with comorbid psychiatric illnesses including unipolar depression, bipolar disorder, and psychosis (Stapleton et al. 2008). In the largest study to date, comprising about 80,000 primary care patients who received new prescriptions for smoking cessation products over a 2-year period (including $n=10,973$ that received varenicline), there was no difference in suicidal behavior or depression between patients given nicotine replacement products, bupropion, or varenicline (Gunnell et al. 2009). There was also no difference between the three groups in the rate of new antidepressant prescriptions, another marker for emerging depressive symptoms. About 11,000 patients in this study received varenicline, 10% of whom had a previous history of self-harm or suicidal thoughts before study entry. An important consideration is the confounding effect of smoking cessation on mood, which has been

shown to induce major depressive episodes and suicidality in susceptible individuals (Hughes 2007).

Depression exacerbation and suicidality have not been reported during mecamlamine treatment. This may be due to several factors. Poor tolerability has limited its use as an antihypertensive, and other side effects might be observed if the drug were more widely used for treatment of depression. Additionally, these drugs have substantially different effects on nAChRs, as mecamlamine is a nonspecific antagonist and varenicline is a partial agonist, and the consequences of such differences with respect to the reported behavioral toxicity is unknown.

Conclusions

nAChRs are located in areas of the brain implicated in depression, and are involved in regulating neurobiological systems that are similarly implicated, including monoamine neurotransmitters, the HPA axis, and certain inflammatory processes. Preclinical studies consistently demonstrate beneficial effects of nAChR modulators in animal models of depression. Mecamlamine, cytosine, and varenicline have all been shown to have antidepressant-like effects in such models, and negative results in preclinical models appear to be driven by either inadequate dosing or confounding effects of control conditions rather than lack of efficacy. The most consistent preclinical support for antidepressant effects involves $\alpha 4\beta 2$ antagonism in the context of concomitant treatment with an established monoaminergic-mechanism antidepressant.

Clinical evidence, while more limited, also suggests that the nAChR may be a viable target for the development of novel antidepressant treatments. There are preliminary data supporting the use of mecamlamine as an antidepressant-augmenting agent, and positive results of larger trials with mecamlamine and s-mecamlamine are currently pending peer review and publication. It is unlikely that there will be appreciable differences in clinical efficacy between racemic mecamlamine and its individual constituents, since there are no significant preclinical differences in efficacy between S-mecamlamine, R-mecamlamine, or their racemate (Papke et al. 2001). Preliminary work in open trials and in samples of smokers with psychiatric comorbidity suggests that varenicline may have efficacy in enhancing antidepressant response. The available literature for varenicline has significant limitations, as studies were either not in populations with depression or were limited by small sample size and open-label design. However, these clinical results mirror preclinical findings and should be examined in larger, controlled trials.

The concern surrounding varenicline and suicidality may require more study, since reports from trials of mecamlamine have not generated similar reports. This may be due to different mechanisms of action or limited use of mecamlamine. The possible relationship between nAChR modulators and induction of suicidal thoughts/actions or other adverse behavioral effects merits attention as the field moves forward, although this relationship may also reveal an endophenotype of depression characterized by disturbances in nAChR function. A confounding feature in the available safety literature from clinical trials of varenicline is the effect of tobacco dependence and nicotine withdrawal, which produce

independent effects on mood and suicidality (Hughes 2007; Wilhelm et al. 2006). This potential confound should be addressed explicitly in future studies by comparing behavioral health outcomes in varenicline-treated individuals with and without tobacco dependence.

An intriguing question is how targeting nAChRs mediate potential antidepressant effects. It appears that blockade of the nAChR is the necessary component for antidepressant activity, whether obtained through constant agonism (such as with a nicotine patch), initial agonism and likely subsequent desensitization (such as with varenicline), or direct antagonism (such as with mecamylamine). Another question is why nAChR modulators appear to function better as augmenting or adjuvant agents rather than as a monotherapy. An unsatisfying hypothesis is that nAChR modulators may simply be weak antidepressants, building additional antidepressant efficacy in an incremental fashion, but this would not explain why significant additional efficacy was gained when continuing patients on medications with limited antidepressant results. There are several other possibilities regarding mechanism of action of nAChRs and depression. One hypothesis is that there is a relationship between the nAChR and monoamine or other neurotransmitter systems. nAChR modulators work by increasing dopamine neurotransmission (Albuquerque et al. 2009), likely through the dopamine-reward processing pathway, which may lead to antidepressant effects in and of itself. Another hypothesis is that antidepressant medications may act nonspecifically on nAChRs (Arias et al. 2010; Santamaria and Arias 2010), and nAChR modulators trophic to mood-regulating regions in the brain may potentiate this effect, leading to efficacy with a combination of drugs. An alternative mechanism of action may involve a relationship between cholinergic and *N*-methyl-D-aspartate (NMDA) receptors. Both nicotinic and muscarinic receptors have been shown to interact with NMDA receptors (Figueredo et al. 2008; Livingstone et al. 2010), which may suggest a convergence of cholinergic modulation resulting in antidepressant effects mediated by the NMDA system. This may explain the antidepressant efficacy of both muscarinic and nicotinic systems, and the relationship between cholinergic and glutamatergic systems in depression has not been addressed in the literature.

While it is still unclear which exact properties of the nAChR are necessary for antidepressant activity, the concordance between preclinical and clinical evidence suggests this is an area with tremendous potential. Based on the available evidence, targeting the $\alpha 4\beta 2$ nAChR for depression appears to yield the best results, although to be clinically useful, positive findings for the available medications need to be replicated and consideration should be given to the potential use of these drugs as antidepressant monotherapies in selected patients. Investigation into a potential role of the $\alpha 7$ nAChR and other receptor subunit conformations should also be pursued, and characterization of mutations in the nAChR and their effect on response to nAChR modulators may also be a fruitful avenue for future research. The growing body of preclinical evidence and the promising preliminary clinical findings in this area constitute a compelling argument for further evaluation of the nAChR as a target for novel antidepressant drug development.

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Fig. 1. Modulation of dopamine with nAChRs. A rendition of nAChR modulation of dopamine neurotransmission with a focus on $\alpha 4\beta 2$ and $\alpha 7$ nAChRs. Adapted from Albuquerque et al. (2009). *ACh* acetylcholine, *DA* dopamine, *Glu* glutamate, *GABA* γ -aminobutyric acid

Table 1

Preclinical evidence for targeting nAChRs in depression

	Medication	Total N	Results
Popik et al. (2003)	Nicotine+citalopram/imipramine	5–13/	Improved FST
	MEC+citalopram/imipramine	group	Improved FST
	DHB ($\alpha 4\beta 2$ antagonist)+citalopram/imipramine		Improved FST with citalopram only
Rabenstein et al. (2006)	MEC	8–14/group	Improved FST and TST No effect on $\alpha 7$ or $\beta 2$ knockout mice
Caldarone et al. (2004)	MEC	8–13/group	MEC improved FST/TST
	MEC+AMI		MEC+AMI further improved performance Sub-therapeutic MEC+AMI also improved performance
Andreasen et al. (2009)	RJR-2403 ($\alpha 4\beta 2$ agonist)	5–13/ group	No effect
	DHB		Improved FST/TST
	PNU-282987 ($\alpha 7$ agonist)		No effect
	Methyllycacinine ($\alpha 7$ antagonist)		Improved FST/TST
	Nicotine		No effect
	MEC		Improved FST/TST
Andreasen and Redrobe (2009a, b)	Nicotine+citalopram	6–10/ group	Improved FST/TST
	Nicotine+reboxetine		Improved FST/TST
	MEC+citalopram		No effect
	MEC+reboxetine		No effect
Mineur et al. (2007)	Cytisine	8/group	Improved FST/TST
	MEC		Improved FST/TST Changes in c-fos expression also noted with both compounds
Mineur et al. (2009)	Cytisine	10/group	Improved FST/TST
	3-pyr-Cyt ($\alpha 4\beta 2$ antagonist)		Improved FST/TST
	5-Br-Cyt ($\alpha 4\beta 2$ antagonist)		No effects due to lack of CNS penetration
Rollema et al. (2009)	VNCL	10/group	VNCL improved FST
	VNCL+SERT		VNCL+SERT at low VNCL doses comparable to AMI FST performance

MEC mecamlamine, FST forced swim test, TST tail suspension test, AMI amitriptyline, DHB dihydrobetaerythiodine, 3-pyr-Cyt 3-(pyridin-3'-yl)-cytisine, 5-Br-Cyt 5-bromo-cytisine, VNCL varenicline, SERT sertraline

Table 2

Clinical evidence for targeting nAChRs in depression

	N, study design	Medication	Results
Shytle et al. (2002a, b)	4, open-label study of children with Tourette disorder and comorbid depression	MEC	Improvement in depression component of TODS-CR
George et al. (2008)	21, double-blind, placebo-controlled, depressed patients non- responsive to SSRI	MEC+SSRI	Improvement in HAMD ($p<0.05$)
Patterson et al. (2009)	67, non-depressed patients, double-blind, smoking cessation trial	VNCL	Improvement in positive affect ($p=0.046$)
Philip et al. (2009)	18, open-label augmentation, patients with depression and nicotine dependence	VNCL+previous regimen	Improvement in QIDS-SR ($p>0.001$) Improvement in CGI-S ($p=0.039$)

MEC mecamylamine, *TODS-CR* Tourette's Disorder Scale-Clinician Rated, *SSRI* selective serotonin reuptake inhibitor, *HAMD* Hamilton Rating Scale for Depression, *VNCL* varenicline, *QIDS-SR* Quick Inventory of Depressive Symptomatology Scale-Self-Report, *CGI-S* Clinical Global Impressions-Severity Scale