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Nicotinic Receptor Mechanisms in Neuropsychiatric Disorders: *Therapeutic Implications*

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ABSTRACT

Nicotinic acetylcholine receptor (nAChR) dysfunction is believed to contribute to numerous neurpsychiatric disorders. nAChRs belong to the class of ligand-gated ion channels that are present in the central nervous system. The endogenous ligand for nAChRs is acetylcholine, and nicotine directly acts on this receptor. nAChR modulation may play a modulatory role in several neuropsychiatric disorders. It may improve clinical features such as depressive symptoms; parkinsonism; and cognitive dysfunction related to working and verbal memory, executive functions, and attention. This article discusses nAChR modulation and drugs that act on the nAChR as an agonist, antagonist, or partial agonist in neuropsychiatric disorders and potential therapeutic implications in a variety of "nicotine-responsive" neuropsychiatric disorders.

FOCUS POINTS

- There is increasing evidence that nicotinic acetylcholine receptors are dysregulated in several neuropsychiatric disorders.
- This pathology may be related to the high prevalence of tobacco dependence in several of these disorders.
- These findings have tremendous implications for the development of nicotinic agents for the treatment of clinical and cognitive symptoms associated with these disorders.

INTRODUCTION

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels in the central nervous system and consist of α and β subunits. Twelve subtypes of the nAChR have been identified; the α4β2 subunit combination is the most common.[1] nAChRs are found in thalamus, basal ganglia, cerebral cortex, hippocampus, and cerebellum.[2] Acetylcholine (Ach) is the endogenous ligand of the nAChR. Nicotine is the main addictive compound in tobacco. nAChR activation by nicotine is time and dose dependent. Chronic nicotine administration causes desensitization, inactivation, and upregulation of nAChRs, in contrast to the effects of typical agonist drugs.[3] There are two classes of central nAChRs. First, the high-affinity nAChR, a heteromer of α and β subunits, is blocked by the antagonists mecamylamine and dihydro-β-erythroidine, and at low doses is stimulated by the nAChR partial agonist varenicline. Second, the low-affinity nAChR is a α subunit homopentamer and can be inhibited by the snake poison α-bungarotoxin and the antagonist methyllycaconitine. Activation of brain nAChRs by ACh, nicotine, or varenicline (the smoking cessation medication) binding causes an increase of metabolism and release of neurotransmitters like dopamine (DA), serotonin (5-HT), norepinephrine (NE), γ-aminobutyric acid, and opioid peptides.[4-6] DA plays a crucial role in the mesolimbic reward systems of drugs of abuse and the dopaminergic and serotonergic systems are involved in mood disorders.[7]

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In North America, tobacco smoking prevalence in neuropsychiatric disorders is up to five times higher and smoking cessation rates 33% to 50% of those found in the general population.[1,7-9] Nicotine and cigarette smoking modulation of clinical and cognitive symptoms differs between patients with neuropsychiatric disorders and in healthy controls. This may be due, in part, to genetic or biochemical differences in nAChR systems between healthy individuals and people with neuropsychiatric disorders.

This article reviews evidence highlighting the involvement of nAChR systems in neuropsychiatric disorders, and discusses the potential application of agents which modulate nAChR function for the treatment of these disorders.

EVIDENCE FOR NICOTINIC RECEPTOR MODULATION SPECIFIC TO NEUROPSYCHIATRIC DISORDERS: *THERAPEUTIC IMPLICATIONS*

Schizophrenia

Schizophrenia is a neuropsychiatric disorder characterized by deficits in neurocognition, hallucinations (primary auditory), and delusions.[10] Post-mortem studies suggest a dysregulation of both high- and low-affinity nAChR systems, with low levels of the nAChR subtypes (α and β) in hippocampus and frontal cortex.[11-13] A link between schizophrenia and abnormalities of the α7 gene was observed in numerous studies[14-17]; no association was found between variations in the α2 nAChR gene and schizophrenia.[18] Abnormalities in central dopamine systems are proposed in schizophrenia, including hyperfunctional subcortical, and hypofunctional prefrontal cortex DA system activities.[19] It is hypothesized that the DA deficit in the cortex causes mesolimibic DA hyperactivity, leading in positive, negative, and cognitive symptoms of schizophrenia.[19,20] Administration of nicotine and tobacco smoking ameliorates cognitive deficits in individuals with schizophrenia.[21,22] A double-blind, randomized cross-over design (n=12) was used to deternimine the effectiveness of 3[(2,4-dimethoxy)-benzylidene]-anabaseine (DMXB-A), a partial α7 nicotinic cholinergic agonist and a weak antagonist at α4β2 nAChRs and serotonin 5-HT_3 receptors on cognition in non smokers with schizophrenia.[23] Administration of a single dose of DMXB-A, a natural alkaloid derivative, significantly improved cognition using the Repeatable Battery for the Assessment of Neuropsychological Status total scale score and P50 inhibition.[24]

In another study,[25] a dose of 150 mg BID DMXB-A was administered to 31 subjects with a diagnosis of schizophrenia and led to significant improvements on the Assessment of Negative Symptoms (SANS) total score. No improvements were observed in the Brief Psychiatric Rating Scale and SANS when given 75 mg. This was measured in a 4-week long placebo-controlled, double-blind, cross-over phase 2 study.[25] A partial and potential agonist on human α7 receptor JN403 ((S)-(1-Aza-bicyclo[2.2.2]oct-3-yl)-carbamic acid (S)-1-(2-fluoro-phenyl)-ethyl ester) ameliorated cognition, sensory gating, epilepsy, and pain in animal models.[26] This agent has yet to be tested in the human population.

Antipsychotics (eg, haloperidol) can induce side effects like cognitive and sensory gating deficits, and it is hypothesized that people with schizophrenia may smoke to remedy their cognitive deficits and antipsychotic-induced side effects.[27,28] Switching patients from first-generation (eg, haloperidol) to second-generation antipsychotics (eg, clozapine) can reduce cigarette smoking[29-31] and may facilitate smoking cessation with standard treatments like nicotine-replacement therapy (NRT) and bupropion.[22,32] George and colleagues[33] demonstrated that several weeks of smoking abstinence can cause disruption of cognitive functioning, such as spatial work memory deficits, in smokers with schizophrenia. Nicotine administration through smoking increases working memory in smokers with schizophrenia; this phenomenon is not observed in non-psychiatric smokers.[34] One small open-label study[35] suggested that the α4β2 partial agonist and α7 full agonist varenicline, a Food and Drug Administration-approved agent for smoking-cessation treatment in adults, may be particularly effective for smoking cessation in schizophrenia.

Mood Disorders

Among mood disorders, major depressive disorder (MDD) and bipolar disorder are the most common diagnoses. In contrast to MDD, where people experience low and depressed mood, patients with bipolar disorder experience both depression and mania.[36] Hypercholinergic neurotransmission is associated with depressed mood and mediated through excessive nAChR activation.[37,38] Antidepressants fluoxetine and bupropion have nAChR antagonist properties and may act in part by normalizing hypercholinergic tone present in depressed states in addition to their monoamine reuptake inhibitory properties.[39] Mecamylamine has an antidepressant effect in wild type mice but has a lack of effect in α7 or β2 knock-out mice and potentiates the antidepressant activity of amitriptyline in rodents.[40,41] An antidepressant effect of mecamylamine was also confirmed in two preliminary studies in depressed patients, but further controlled studies are still warranted.[42,43] Central 5-HT levels are low in MDD, and nicotine causes a release of 5-HT, which might, in part, explain the high smoking prevalence in people with depression.[8] Results from studies in depressed non-smokers using transdermal nicotine were not supportive of the hypothesis that nicotine itself exerts

antidepressant effects.[45,46] In contrast, self-administration of nicotine appears to improve depression-prone smokers' emotional response to a pleasant stimulus.[46] Typical symptoms during smoking withdrawal include depression, anxiety, and nervousness, among others, whereas depressive mood predicts higher withdrawal symptoms.[47] NRT for smoking cessation in history-positive depressed smokers, however, was almost as successful as in healthy smokers.[48] Varenicline has shown antidepressant effects in animal models.[49] Varenciline was recently tested in an 8-week open-label trial. Fourteen (87%) out of 18 depressed subjects completed the study and led to a significant improvement in depression symptoms. Reasons for dropout were gastro-intestinal side effects (n=3) and worsening of mood (n=1).[50]

Little evidence for the involvement of the nAChR system in bipolar disorder is available. Administration of mecamylamine stabilized the mood of two individuals suffering from Tourette's syndrome with comorbid bipolar depression.[51] A genetic study found no association between bipolar disorder and the α2 nAChR subunit gene.[52]

Attention-Deficit/Hyperactivity Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a highly prevalent, worldwide disorder estimated to affect 5% to 10% of children[53] and 3% to 6% of adults.[54] ADHD is characterized by a persistent pattern of inattention as well as distractibility and/or hyperactivity to the extent that it comprises academic or occupational functioning.[55] Longitudinal ADHD studies in youths demonstrate that while hyperactivity and impulsivity symptoms decrease over time, inattention tends to persist.[56] An estimated 50% of adults with ADHD have clinically relevant levels of hyperactivity and impulsivity while >90% have prominent attentional symptoms.[57] Moreover, individuals with prominent cognitive impairments are at a greater risk for more academic and occupational difficulties.[58]

Theories of the neurobiologic basis of ADHD have largely focused on the dysregulation of catecholamine systems. The primary pharmacotherapy approach for ADHD is the prescription of psychostimulants such as methylphenidate and amphetamines, which enhance activity of DA and NE, resulting in reduced symptomatology. However, it has been proposed that other neurotransmitter systems may be implicated in the specific cognitive deficits of ADHD.

Studies investigating nicotinic agents in individuals with ADHD have shown promising symptomatic and cognitive improvements. Levin and colleagues[59] examined the acute effects of transdermal nicotine in adults smokers and nonsmokers with ADHD and found significant improvements in self-rated vigor, concentration, and observer-rated severity illness in both groups. McClernon and colleagues[60] reported that cognitive processes, especially those associated with reaction time variability, are more disrupted in smokers with ADHD following smoking abstinence, compared to non-ADHD smokers. Nicotine treatment has also been shown to normalize inhibitory behavior in people with ADHD.[61]

A preliminary study[62] of 10 smokers with ADHD receiving nicotine patch, methylphenidate, or combination of the two, showed that nicotine patches and stimulant medication alone and in combination reduced difficulty concentrating and core ADHD symptoms compared with placebo patch only. Borderline improvement in impatience and self-control was seen with nicotine patch administration. Wilens and colleagues[63] studied the nicotinic agonist ABT-418, selective for the high-affinity nAChR, in 32 adults with ADHD. Significant improvements in subjective ratings of attentiveness and observer-rated severity illness were observed following treatment. Wilens and colleagues[64] tested ABT-089, a newer more selective high-affinity nAChR agonist, in adults with ADHD. The drug was administered in a multidose, randomized, double-blind, placebo-controlled trial and results indicated greater improvements in symptoms scores, ADHD index hyperactive/impulsive ratings, and clinical global impression. These findings suggest that stimulation of nicotinic cholinergic receptors do not only target cognitive domains but also address the overt behavioral symptoms of ADHD. Further studies are necessary to clarify if nicotine's effects on cognition in ADHD are mediated by cholinergic systems or cholinergic modulation of dopamine function.

Autism

Autistic individuals are, in stark contrast to individuals with ADHD, hyper-focused. Core symptoms include deficits in all aspects of social reciprocity—pragmatic communication deficits, language delays, and behavioral problems.[65] Autopsy studies[66,67] show depletion of nAChRs in certain areas of the cortex, cerebellum, and thalamus, which are involved in attention and sensory processes in autism. A decrease in three of the four nicotinic receptor subtypes in the cerebellum was observed.[68] Some authors[69] hypothesize that selective antagonism of neuronal nAChRs may ameliorate the core symptoms of autism by normalization of cholinergic tone. Children and adolescents with autism were given the acetylcholinesterase inhibitor (AChEI) donezepil in one open-label trial over 2 months. Decreases in the irritability and hyperactivity were observed, but no changes in inappropriate speech, lethargy, and stereotypies. Lack of a significant effect could be explained by the low number of study participants (n=8) and the concomitant psychoactive medications they received.[70] Results from a case study[71] in three adults diagnosed with autism showed that galantamine (a competitive, reversible AChEI and an allosteric potentiating ligand for nAChRs) might increase expressive language and communication. A significant reduction in parent-rated irritability and social withdrawal as well as significant improvements in emotional

lability and inattention was measured in an open-label study[72] where 13 children and adolescents were given galantamine over 12 weeks. The dual-action AChEI rivastigmine tartrate enhanced significantly expressive speech and overall autistic behavior in 32 autistic children in on open-label 12-week study.[73] Further studies are needed to elucidate the role of the cholinergic system in autism.

Alzheimer's Disease

Alzheimer's disease is the most common neurodegenerative disorder and the most common type of dementia in the elderly.[74] Patients with Alzheimer's disease show a deficit in cholinergic innervation in hippocampus and cerebral cortex with a significant reduction in choline acetyltransferase activity in these regions.[75-77] Pharmacologic compounds used for treatment of Alzheimer's disease are AChEIs such as physostigmine or donazepil. A loss of α4β2 nAChR as well as a neurotoxic effect of β-amyloid peptides in neurotic plaques on α7 nAChRs were observed.[78] Newhouse and colleagues[79] demonstrated that intravenously administered nicotine (.125, .25 and .50 μg/kg/min) produced dose-dependent improvement in intrusion errors on a word recall task in non-smokers with Alzheimer's disease, and that maximum effects occurred at .25 μg/kg/min, suggesting an "inverted-U" dose-response pattern. Administration of transdermal nicotine improved performance on a repeated acquisition task in patients with probable Alzheimer's disease,[80] however, other studies have not supported this finding since performance on a letter memory test did not improve with transdermal nicotine patch (TNP). A study by White and colleagues[81] all found that performance on a letter memory test did not improve with TNP. Using a within-subjects placebo-controlled study design of three doses of the nAChR channel activator ABT-418 in patients with moderate Alzheimer's disease, Potter and colleagues[82] demonstrated that this agent improved dose-dependently deficits in total recall in a verbal learning task, a seven item selective reminding task, and in non-verbal tasks such as spatial learning and memory and repeated acquisition. Methodologic differences amongst these studies, including dose and route of nicotine administration, may explain these disparate effects of nicotine on learning and memory in Alzheimer's disease.

In the domain of attention, one study[83] found that intravenous nicotine improved detection performance on the critical flicker fusion test in patients with Alzheimer's disease, and improved their ability to discriminate stimuli and their reaction times, suggesting effects of nicotine on visual perceptual and attentional cortical mechanisms. Similarly, perception in patients with Alzheimer's disease improved on the flicker fusion task in response to subcutaneous nicotine administration.[84] Thus, nicotine administration appears to improve some forms of attentional function in Alzheimer's disease.

Several epidemiologic studies[85-87] of Alzheimer's disease suggested a possible protective effect of cigarette smoking. However, other authors[88] suggested that cigarette smokers are more likely to develop Alzheimer's disease compared to those who have no smoking history. Data regarding the correlation between Alzheimer's disease and smoking are conflicting, probably due to methodologic errors in case-control studies.

Memantine is an FDA-approved agent for the treatment of Alzheimer's disease symptoms.[89] Its main mechanism of action is the non-competitive blockage of central NMDA receptors. However, studies[90,91] in cell cultures like HEK or K177 show that memantine also has a non-competitive antagonistic effect on the α7 nicotine receptor.

(E)-3-(2,4-dimethoxybenzylidene)-3,4,5,6-tetrahydro-2,3'-bipyridine dihydrochloride, an experimental α7 agonist, improved attention and memory in 16 healthy subjects in a randomized, placebo-controlled, double-blind, multiple dose study[92] and could be considered as a novel treatment for dementia. Another experimental compound, the positive allosteric modulator of the α7 nAChR, 1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea, was tested so far in rodents and shows cognition-enhancing properties.[93]

Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder characterized by slowed processing speed, abnormal visuospatial processing, and central motor dysfunction such as muscular rigidity, tremor, and sustaining movement.[94] nAChR activation plays a crucial role in regulating striatal dopaminergic function, and these dopaminergic systems are critical in motor control, as evidenced by findings that their disruption results in movement disorders such as Parkinson's disease.[95] Symptoms of Parkinson's disease are a result of the loss of nicotinic binding sites and degeneration of dopaminergic neurons in part of the midbrain known as substantia nigra, and the neuronal degeneration is paralleled by the loss of high-affinity nicotine-binding sites.[96] Even moderate lesions in the striatum lead to a decrease in α6β2 nAChRs. In contrast, α4β2 subtypes are affected only in severe degeneration and α7 nAChRs seem to be to some extent affected.[95] Human binding and immunoprecipitation studies demonstrate that the decrease in α6β2 nAChRs are significantly greater than in α4β2 receptors in some striatal regions.[97-99] The surviving DA neurons contain inclusions called Lewy bodies and Lewy neurites.[100] Fibrillation of α-synuclein, a compound found in Lewy bodies and Lewy neurites, plays a crucial role in the pathogenesis of Parkinson's disease. Nicotine blocks this fibrillation and stimulates striatal dopamine neurons that are damaged in Parkinson's disease.[101,102] Nicotine treatment enhances expression of some nAChR subtypes decreased with nigrostriatal damage, which may suggest that function mediated through these receptors is restored closer to control levels with nicotine treatment.[103] Indeed, nicotine administration improves extrapyramidal symptoms and some cognitive

function in Parkinson's disease patients.[104-106] However, there are also studies[107-109] demonstrating no improvement or even worsening of Parkinson's disease symptoms under nicotine.

Results from >50 studies show that smokers are protected against Parkinson's disease.[102] One explanation could be the attribution metabolites of nicotine, like cotinine and nornicotine. Cotinine exhibited a non-receptor mediated cytoprotective effect and nornicotine reduced β-amyloid aggregation in *in vitro* studies.[110,111] Nicotine also ameliorates L-dopa- (the gold standard for the treatment of Parkinson's disease) induced dyskinesia in non-human primates.[112] Still, the underlying mechanism between the neuroprotective effects of smoking and nicotine in Parkinson's disease needs further investigation. In 77 patients with early Parkinson's disease, no antiparkinsonian or cognitive-enhancing effects were demonstrated in a placebo-controlled, double-blind study[113] with the non-approved selective α4β2 nicotinic agonist SIB-5008Y (altinicline; (S)-(-)-5-ethynyl-3-(1-methyl-2-pyrrolild-inyl) pyridine maleate). Galantamine synergistically enhances the neuroprotective effect of nicotine against dopaminergic neuronal loss through an allosteric modulation of α7 nAChR activation in rodents.[114] Accordingly, agonists on nAChR may represent a new approach in the treatment of Parkinson's disease due to their potential neuroprotective effect.

Tourette's Syndrome

Tourette's syndrome is a hyperkinetic disorder, characterized by the presence of involuntary motor and verbal tics that first manifest in childhood. Tourette's syndrome is commonly associated with other learning and behavioral difficulties. Its pathogenesis is unknown.[115] Tourette's syndrome is frequently treated with haloperidol, a typical antipsychotic and dopamine antagonist. Studies suggest that neuronal nAChRs are effective in mediating the symptoms of Tourette's syndrome.[116] Demonstrations with laboratory rats showed that low doses of nicotine administered chronically can potentiate the cataleptic effect induced by haloperidol.[117] It was hypothesized that this effect could be replicated in humans, independent of their smoking status. The combination of transdermal nicotine and haloperidol significantly reduced tic frequency and severity, compared to neuroleptic treatment alone.[118,119] Nicotine gum was also shown to augment haloperidol treatment, compared to placebo gum which had no effects. However, nicotine gum was only effective during the period of chewing.[120] Long-term benefits of the transdermal nicotine patch have been reported. Shytle and colleagues[121] found that each application of a single transdermal nicotine patch (7 mg/24 hour) produced a significant reduction in tics for ~1–2 weeks following application, as measured by the Yale Global Tic Severity Scale. Nicotine also appears to improve Tourette's syndrome symptomatology in the absence of neuroleptics. The use of nicotinic antagonist treatment for Tourette's syndrome has also been proposed. However, the classic nAChR antagonist mecamylamine administered as a monotherapy had no effect on tics in an 8-week trial.[122]

CONCLUSION

The comorbidity of psychiatric disorders and tobacco dependence is high when compared with the average population, and the biologic significance of this comorbid association suggests that therapeutic approaches that treat the underlying neuropsychiatric illness should be taken. This proof of concept has been well described in the literature under the auspices of "nicotine-responsive neuropsychiatric illness" (Table 1).[123,124] Moreover, smoking cessation is more difficult in many of these patient groups because of the intrinsic dysregulation in nAChR systems associated with this disorder (eg, schizophrenia, mood disorders, Tourette's syndrome, ADHD), but in some cases

TABLE 1

NICOTINE-RESPONSIVE NEUROPSYCHIATRIC DISORDERS

Strong Evidence	*Modest Evidence*
• Schizophrenia	• Autism
• Major depressive disorder	• Bipolar disorder
• Tourette's syndrome	
• Attention-deficit/hyperactivity disorder	
• Tobacco dependence	
• Alzheimer's disease	
• Parkinson's disease	

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TABLE 2

NICOTINIC AGENTS FOR THE TREATMENT OF "NICOTINE-RESPONSIVE" NEUROPSYCHIATRIC DISORDERS

FDA-Approved	*Experimental/Non-Approved*
• NRTs – transdermal patch, gum, lozenge, inhaler, nasal spray)	• TC-1707 (α4β2 nicotinic agonist)
• Mecamylamine (non-competitive ion channel blocker)	• DMXB-A (α7 nicotinic partial agonist)
• Galantamine (nAChR allosteric modulator)	• MEM-3454 (α7 nicotinic partial agonist)
• Varenicline (α4β2 nAChR partial agonist)	• ABT-089 (α4β2 nicotinic agonist)
	• JN403 (partial agonist on α7 receptor)
	• GTS-21 (agonist on α7 receptor)
	• SIB-5008Y (selective α4β2 agonist)

FDA=Food and Drug Administration; NRTs=nicotine replacement therapies; nAChR=nicotinic acetylcholine receptors.

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this nAChR dysregulation may actually protect against the initiation and maintenance of nicotine addiction (eg, Alzheimer's disease, Parkinson's disease, autism). Accordingly, further research is needed to parse underlying mechanisms that confer vulnerability to tobacco addiction in these populations, and to determine the optimal strategy to use nAChR-based therapeutics to treat these "nicotine-responsive" neuropsychiatric disorders. Since prolonged treatment with nicotine leads to nAChR desensitization, there is now clear evidence that administration of nAChR antagonists (eg, mecamylamine) could have therapeutic value in the treatment of several disorders, including Tourette's syndrome[123] and MDD.[42] Several available nicotinic agonists (including allosteric moduators such as galantamine, and partial agonists such as varenicline) and others in development (eg, the α7 nAChR partial agonist DMXB-A, and the α4β2 nAChR agonists TC-1707 and ABT-089) could have enormous potential in treatment of such "nicotine-responsive" illnesses (Table 2). Additional studies in animal models are required to provide more insight into the underlying mechanisms of nAChR system. Given the tremendous promise of agents treating these neuropsychiatric illnesses, it has been suggested to develop academic-industry partnerships in order to identify and screen nicotinic agents that are safe for human use and carry the most therapeutic potential. Further pre-clinical and translational research is warranted in order to understand the biobehavioral mechanisms that will guide such medications development. ***PP***

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