Review

Nicotinic Acetylcholine Receptor Agonists for the Treatment of Alzheimer's Dementia: An Update

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Abstract

A significant portion of the clinical phenotype observed in Alzheimer's disease (AD) occurs through nicotinic acetylcholine receptors (nAChRs). Degeneration of cholinergic neurons, combined with aberrant nAChR expression and activation partially through amyloid-beta peptide (A β)–nAChR leads to upregulation of pro-inflammatory pathways and subsequently the progressive cognitive decline of AD. Interestingly, the cholinergic anti-inflammatory pathway is also mediated through nAChR particularly $\alpha 7$ nAChR. Thus, agonists of these receptors will likely exert pro-cognitive benefits through multiple mechanisms including stimulating the cholinergic pathway, modulating inflammation, and buffering the effects of amyloid. Despite this promising theoretical use, trials thus far have been complicated by adverse effects or minimal improvement. This review will provide an update on several pharmacological nAChR agonists tested in clinical trials and reasons that further investigation of nAChR agonists is merited.

Implications: nAChRs have consistently presented a promising theoretical use in the treatment of AD; however, trials thus far have been complicated by adverse effects or minimal improvement. This review will provide an update on several pharmacological nAChR agonists trialed and reasons that further investigation of nAChR agonists is merited.

Introduction

The significance of cholinergic systems cannot be overstated in understanding the pathology and progression of Alzheimer's dementia.¹ Neurons in the basal forebrain, including the neurons that form the nucleus basalis of Meynert, hippocampus, and cerebral neocortex are lost in the disease and contribute to the symptomatic development of dementia. Two of the main histopathological markers of Alzheimer disease are the accumulation of amyloid-beta peptide (A β) and misfolded hyperphosphorylated tau forming neurofibrillary tangles.² Alzheimer's disease (AD) is also accompanied by cholinergic dysfunction as evidenced by the reduction of choline acetyltransferase, vesicular acetylcholine (ACh) transporter,^{3,4} release of ACh, and nicotinic receptors.⁵

The loss of cholinergic innervation in early AD is most prominent in the cortex and hippocampus, and the mainstay of AD symptomatic control relies on acetylcholinesterase inhibitors (AChEIs; donepezil and galantamine), which exert positive cholinergic effects mediated by indirectly increasing activity at nicotinic acetylcholine receptors (nAChRs).^{6,7} The importance of the cholinergic system in progression of AD is summarized in the cholinergic hypothesis proposed by Perry et al. in 1999, which is strengthened by the phenocopying of cognitive deficits in rodent models with antagonism of acetylcholine receptors (AChRs).^{1,8,9} More specifically, animal lesion studies that target cholinergic input to the neocortex or hippocampus from the basal forebrain and incidental human disruptions via arterial aneurysms, arterial venous malformations, and resections can reproduce similar cognitive

deficits observed in AD.^{10,11} Thus, the basal forebrain and rostral forebrain cholinergic pathways including projections to the thalamus are critical for awareness, attention, and working memory.^{12,13}

Degeneration of these pathways results in the development of cognitive decline.¹⁴ Accordingly, AChRs (nicotine and muscarinic) have been posited to play a central role in mediating AD pathology, which might offer potential treatment targets. They are cyst-loop ligand-gated ion channels composed of five heteromeric or homomeric subunits that form an ionic pore.^{15,16} These channels have been implicated in the development of memory, locomotion, attention, and anxiety.⁴ In the mammalian brain, 11 different subunits are known to exist, alpha ($\alpha 2$ – $\alpha 7$, $\alpha 9$, and $\alpha 10$) and beta ($\beta 2$ – $\beta 4$), that pentamerize to form a multimeric ligand-gated ion channel. The α and β distinction is based on the presence of adjacent cysteine groups in the extracellular domain found only in the α subunits. The unique anatomical distribution of each nAChR subtype within the structures involved in cognition (the basal forebrain, hippocampus, and cerebral cortex) implicates receptors composed of $\alpha 7$, $\alpha 4$, and $\beta 2$ subunits as important potential targets of pharmacological intervention (Figure 1).^{17–20} As discussed by Wu and Lukas²¹ and numerous others,^{22–31} the receptor subunit composition confers different functional and pharmacological properties governed by subunit composition. Despite the greater than 50 000 permutations that can be achieved with 11 subunits forming a pentameric channel, the $\alpha 7$ nAChR and $\alpha 4\beta 2$ nAChR are predominant with differing functional properties.^{3,16,32} As described by Dineley et al., the $\alpha 7$ homomeric receptor when compared to the $\alpha 4\beta 2$ nAChR has rapid activation and desensitization as well as high calcium permeability.⁴

The $\alpha 4\beta 2$ nAChR and $\alpha 7$ nAChR localize presynaptically and somatodendritically on hippocampal principal glutamatergic neurons, and GABAergic interneurons that modulate principal cell activity. This modulation is thought to occur through several mechanisms, including direct large Ca^{2+} conductance through $\alpha 7$ nAChRs, by depolarization with subsequent activation of voltage-gated Ca^{2+} channels, and Ca^{2+} -mediated release from intracellular stores.³³

Furthermore, in vivo studies demonstrated that activation of $\alpha 7$ nAChRs potentiated hippocampal-prefrontal cortex synapses.^{34,35} Interestingly, the gene encoding the $\alpha 7$ subunit harbors a high degree of variability and polymorphism.³⁶ A study conducted by Carson et al. identified a single nucleotide polymorphism affecting the $\alpha 7$ nAChR promoter and 5'UTR as protective against AD. This finding led to the conclusion that this haplotype may result in increased $\alpha 7$ nAChR expression with improved cholinergic neurotransmission and ultimately decreased susceptibility to AD.³⁷

The nAChRs are widely distributed throughout the central nervous system (CNS) and are expressed in both neurons and glia.^{38–40} Neuroinflammation mediated by the neuroimmune system, mainly microglia, is hypothesized to play a central and complex role in the progression of AD.⁴¹ On the one hand, microglia clear A β , likely to serve a protective role during early stages of AD.^{42–47} However, in aged brains and later stages of AD, microglia lose their protective ability and become overactive resulting in uncontrolled inflammation.^{48–51} A role of the $\alpha 7$ nAChR as a potent mediator of anti-inflammatory pathways was reviewed by Campbell⁵² and Egea et al.⁵³ who described the engagement of the Jak2/STAT3 pathway to potentiate subsequent inhibition of nuclear factor- κ B nuclear translocation and activation of the master regulator of oxidative stress, Nrf2/HO-1, following $\alpha 7$ nAChR activation. They concluded that $\alpha 7$ nAChR activation may be a potential therapeutic target for AD treatment because oxidative stress and neuroinflammation are currently thought to be the most important pathological mechanisms in neurodegenerative diseases such as AD.

Physiology of nAChR and A β in AD

The discovery of a direct A β –nAChR interaction led to a significant expansion in the molecular understanding of their role in AD.⁵⁴ This interaction has been observed in rodent experimental models, as well as postmortem AD brains.^{54,55} Interestingly, A β enriches in regions abundant in $\alpha 4\beta 2$ and $\alpha 7$ nAChRs; this observation may provide important insight into the selectivity of hippocampal and

Figure 1. Cholinergic circuitry of the nucleus basalis with relative expression of $\alpha 7$ and $\alpha 4\beta 2$. (Based on data presented in Mesulam¹⁸ and Paterson and Nordberg.⁴⁰)

neocortical toxicity in AD.^{56–58} Under normal conditions, low levels of the $\alpha 7$ nAChRs–A β complex are thought to play a physiological role by enhancing learning and memory.^{59,60} However, at elevated levels, the $\alpha 7$ nAChRs–A β complex leads to disruption of the cholinergic phenotype, synaptic plasticity, and ultimately cognitive dysfunction.^{60–62}

Inflammation and AD

It has been shown that nAChRs play a central role in the cholinergic anti-inflammatory pathway, demonstrated in blood-borne macrophages.⁶³ In non-neuronal cells of the nervous system, an important observation regarding the role of nicotine-mediated anti-inflammatory effects is demonstrated by the reduction of lipopolysaccharide-induced tumor necrosis factor- α release by microglia. In these studies, activation of the $\alpha 7$ nAChR is thought to reduce inflammation by an increase of cyclooxygenase 2 expression and the synthesis of prostaglandin E2.³² Furthermore, blockade of ionic flux through the receptor did not alter tumor necrosis factor- α release, suggesting an alternate metabotropic mechanism. This mechanism has been shown to be crucial for neuroprotection in both in vitro and in vivo models of lipopolysaccharide-mediated neuronal death; in particular, nicotine has been demonstrated to prevent neuronal death in the substantia nigra after the injection of lipopolysaccharide.⁶⁴ Nicotine induces the expression of a wide plethora of genes in human microglia such as TGF- $\beta 1$, IL4, CX3CL1, CCR2, CXCR6, and has potent anti-inflammatory effects by reducing tumor necrosis factor- α and interleukin-1 β release.

nAChR agonists are being developed as symptomatic treatments for Alzheimer's dementia (summarized in Table 1).

Cholinergic dysfunction is a key feature in the pathology of AD. The degeneration of cholinergic neurons, a decrease in ACh-mediated signaling via reduction in choline acetyltransferase, and loss of cholinergic receptors form the cornerstone of our current understanding of AD and therapy. The role of the nAChRs has been evaluated

extensively in human AD as well as numerous animal models of the disease. Here we discuss the role of nAChR in AD as well as the potential pharmacological interventions that may serve in the ameliorating and possibly reversing AD progression.

The history of AChEIs, including physostigmine,⁶⁵ tacrine,^{66,67} tetrahydroaminoacridine,⁶⁸ donepezil,^{69,70} metrifonate,⁷¹ and others, showed some promise in improving memory and cognitive deficits seen with AD. Xanomeline, an orthosteric muscarinic agonist, has also been investigated.⁷² However, there is less research available on nAChR agonists. In the past two decades, there have been nAChR agonists developed for symptomatic AD dementia, including encenicline, pozanicline, ABT-418, and WAY-317538.

The selective partial agonist of the $\alpha 7$ nAChR, encenicline, a member of the quinuclidines with high specificity for $\alpha 7$ nAChR, demonstrated procognitive effects at low nanomolar concentration in animal and human subjects. Pharmacokinetic analysis demonstrated linear kinetics with increasing doses, with a long plasma half-life of approximately 60 hours and a high volume of distribution. Thus, it can be given in once-daily dosing. Encenicline was also found to improve neuropsychological test performance in a U-shaped dose–response manner and increased relative power of α waves (8–12 Hz) on electroencephalogram, a bandwidth known to be affected in AD and mild cognitive impairment.^{73,74} Thus, a clear pharmacodynamic effect was demonstrated on the CNS in favor of a potential treatment of cognitive impairment. However, a phase 3 study at doses of 3 mg/day versus 2 mg/day was started in 2014 that resulted in suspension of further studies of encenicline in the fall of 2015 due to a rare but serious gastrointestinal issue in elderly patients. No further details regarding the gastrointestinal presentation were made available.⁷⁵

Pozanicline (ABT-089) is a partial agonist that binds with high affinity to the $\alpha 4\beta 2$ nAChR and has partial agonism to the $\alpha 6\beta 2$ subtype, but not the $\alpha 7$ and $\alpha 3\beta 4$ subtypes. A phase 2 double-blind adaptive study evaluating safety and efficacy for pozanicline when combined with AChEIs was conducted. The study (which included randomization of 337 patients) was stopped when futility criteria were met. There were no clinically meaningful differences among the treatment groups

Table 1. Summary of Investigational Drugs Targeting Nicotinic Acetylcholine Receptors (nAChRs) in AD

Compound/Clinicaltrials.gov ID	Mechanism of action	Participant's characteristic	Status
Encenicline	Partial agonist of the $\alpha 7$ nAChR, with long half-life	Mild-to-moderate AD	Some improvement from baseline; suspended after phase 3 trial due to serious complications
Pozanicline (ABT-089)	Partial agonist with high affinity for $\alpha 4\beta 2$, and low affinity for $\alpha 6\beta 2$, not $\alpha 7$, and $\alpha 3\beta 4$	Mild-to-moderate AD	No improvement, futility criteria met
ABT-418	Bioisostere of nicotine; agonist binding with high affinity to the $\alpha 4\beta 2$, $\alpha 7/5$ -HT3, and $\alpha 2\beta 2$	Moderate AD (small sample size)	Robust improvement in verbal learning and recall
WAY-317538/SEN-12333	$\alpha 7$ agonist	Rodent model	Improved cognition in experimental model
RG3487	$\alpha 7$ agonist and 5-HT3 antagonist	Mild-to-moderate AD	Press release with cognitive improvements, drug has been discontinued, reason unknown
Neloneline (ABT-126)	$\alpha 7$ allosteric modulator	Mild-to-moderate AD	No significant improvement
AZD-3480 (TC-1734, ispronicline)	$\alpha 4\beta 2$ partial agonist	Mild-to-moderate AD	Similar to donepezil, development halted
Varenicline	$\alpha 4\beta 2$, $\alpha 3\beta 4$, $\alpha 7$, 5-HT3 partial agonist	Mild-to-moderate AD	No improvement in cognition, psychiatric, and gastrointestinal side effects

for any of the demographics or baseline characteristics in regard to AD when administered as adjunctive therapy to AChEIs.^{76,77}

ABT-418 acts as an agonist binding with high affinity to the $\alpha 4\beta 2$, $\alpha 7/5$ -HT₃, and $\alpha 2\beta 2$ receptors. It has been studied in both attention deficit hyperactivity disorder and AD. One study found that the most robust effects after ABT-418 administration were seen in verbal learning and recall. This initial study was published in 1999, and no follow-up studies regarding AD are currently available. There are mixed results regarding adverse effects, though some studies noted patients experienced nausea.^{78–80}

WAY-317538/SEN-12333 is a potent, selective, small $\alpha 7$ nAChR agonist that has also been investigated for use in AD. It was shown to have excellent brain penetration and oral bioavailability with a favorable pharmacokinetic profile. Initial results in a structure–activity relationship study and biological evaluation showed procognitive efficacy in multiple behavioral cognition assays.⁸¹ Despite these initial results, there are currently no trials to further investigate this agonist as a therapeutic medication.

RG3487 is a novel $\alpha 7$ nAChR selective partial agonist having 5-HT₃ receptor antagonist properties. Initially tested in age-impaired rats, RG3487 improved object recognition memory and reversed spatial learning deficit and impairments in executive function tasks.^{82,83} Initially, RG3487 was tested in cognitive symptoms of schizophrenia. When further assessed in 2014 in patients with schizophrenia, cognitive symptoms did not improve, though negative symptoms associated with schizophrenia did improve.⁸⁴ In 2006, Memory Pharmaceuticals announced positive preliminary data from a phase 1 trial.⁸⁵ In 2007, they announced positive phase 2a results from a proof-of-concept trial in 80 patients with AD that ran over 8 weeks. The primary endpoint of the trial looked at change from baseline in the Quality of Episodic Secondary Memory factor score of the Cognitive Drug Research battery. Results for the trial noted that subjects receiving 5 and 15 mg of RG3487 demonstrated a statistically significant effect on the Quality of Episodic Secondary Memory compared to placebo.⁸⁶ In 2009 and 2010, a phase 2 dose ranging study in 389 people with mild-to-moderate AD compared 1, 5, or 15 mg/day of RG3487 to placebo. Results of this phase 2 study have not been announced to the public. Development of this drug has been discontinued.⁸⁵

Nelonicline (ABT-126) is an $\alpha 7$ nAChR allosteric modulator developed to treat cognitive deficits in schizophrenia and AD. For AD, a phase 2 study in 2009 in 274 subjects with mild-to-moderate AD compared 5–25 mg of ABT-126 to placebo and to donepezil. Results showed good tolerability for ABT-126 with side effects similar to donepezil.⁸⁷ In 2012, AbbVie started two 24-week phase 2b trials with 400 patients each, comparing doses from 25 to 75 mg. The first of the two trials compared ABT-126 combined with an AChEI to placebo. The second trial compared ABT-126 as a monotherapy to placebo. The studies found no efficacy at these higher doses was insufficient to continue further development.^{88,89} Each trial offered a 28-week, open-label extension to participants who completed the blinded portion of the study. These studies were terminated with formal results showing insufficient efficacy to continue development.^{87,90}

AZD-3480 (TC-1734, ispronicline) is an $\alpha 4\beta 2$ nAChR partial agonist. It showed memory-enhancing properties in rodents. Two phase 1 studies were performed evaluating pharmacokinetics, safety profile, and bioavailability. The first study was a double-blind, placebo-controlled crossover design with a rising single-dose scheme, whereas the second used a double-blind, placebo-controlled, parallel group design with a rising multiple-dose scheme.⁹¹ Adverse events were generally mild with dizziness and headache being reported

most frequently.^{91–93} A phase 2b monotherapy trial was performed on 293 patients with mild-to-moderate AD. However, the trial failed to show superiority when compared to donepezil at 52 weeks and development as a pharmaceutical drug was halted.⁹⁴

Varenicline (Chantix) is a partial $\alpha 4\beta 2$ nAChR agonist that also acts on $\alpha 3\beta 4$ and $\alpha 7$ nAChRs. It is most commonly prescribed to aid smoking cessation. It also acts as an agonist at 5-HT₃ serotonin receptors, which may explain its effects on mood. In 2009 and 2010, a phase 2 trial comparing varenicline to placebo was performed.⁹⁵ This 6-week trial involving 66 patients with mild-to-moderate AD measured for improvement in cognition. The results showed that varenicline did not improve cognition and patients developed worsening neuropsychiatric state and gastrointestinal side effects. Development of varenicline for AD was discontinued.⁹⁶

Discussion

The nAChRs are widely dispersed throughout the CNS, making them a reasonable target when treating degenerative diseases. This is particularly true in patients with AD as targeted treatment would be both disease and target specific. AD is well documented to result from cholinergic deficit, with loss of production of ACh and loss of cholinergic neurons, specifically the $\alpha 4\beta 2$ nAChR subtype. Despite this increasing understanding of the pathophysiology behind AD, there has been limited success with nAChR agonists in clinical trials as outlined earlier. Although this may create some hesitation to continue to pursue nAChR agonists as a potential treatment option, we contend that there are several reasons that this endeavor should not be abandoned.

There is evidence that the cholinergic pathway can alter the course of AD. This has been demonstrated by two decades of AChEIs use. As nAChR agonists develop, there should be further investigation exploring the synergy between AChEIs and nAChR agonists. This would need to be evaluated cautiously to avoid any potentiating side effects, particularly gastrointestinal, that can arise from increased ACh in the body.

There is a growing consensus among experts that clinical trials with AD must enroll patients during the earliest stages of disease. A central issue to date in studies evaluating nAChR agonists is that patient selection often involves subjects with moderate-to-severe disease. As advances in reliable diagnostic tools become available (biomarkers, brain imaging, and cognitive testing), patients can be treated earlier and potentially alter the course of their disease.^{97,98} There are many ongoing trials regarding early diagnosis including identifying mild cognitive impairment due to AD prodrome. These patients, if willing, must be identified and enrolled in these studies. Along a similar theme, as there is early loss of the $\alpha 4\beta 2$ receptor subtype, there have been advances to attempt to detect early loss of these receptors. This includes single photon emission computed tomography and positron emission tomography radioligands as potential diagnostic tools and biomarkers. As this early identification improves, so too may the disease-modifying potential of these medications.

Although researchers continue to develop nAChR agonists, it is possible that a more specific pharmaceutical that targets the $\alpha 4\beta 2$ or $\alpha 7$ nAChRs would minimize non-CNS effects and have a safer side effect profile.¹⁶

Future drug development might continue to explore targeting the $\alpha 7$ nAChR with the aim of mitigating inflammation and amyloid toxicity due the well-described $\alpha 7$ nAChR–A β interaction as well as the modulation of inflammatory pathways.

In addition to being widely distributed throughout the peripheral nervous system and CNS, the nAChRs are also found within the immune system. The inflammatory response mediated by the immune system within the CNS leads to the classical maladaptive features of stroke, neurodegenerative disease, spinal cord injury, and autoimmune-mediated disease such as multiple sclerosis. Activation of inflammatory pathways serves many important functions in the human body such as tissue remodeling, repair, and metabolic adaptations.⁹⁹ The neuroimmune system, represented by microglia, a type of macrophage that drives neuroinflammation, has a beneficial effect on scavenging cellular debris, tissue healing, and repair. However, chronic activation of microglia leads to the noxious effect on neurons and thus contributing to the pathophysiology of neurodegenerative diseases. Thus, continuing to pursue the cholinergic pathway as a potential therapeutic target in AD will likely be efficacious if implemented during the early prodromal stage prior to symptom onset.

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Declaration of Interests

JLH and YA-H declare no conflict of interest.

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