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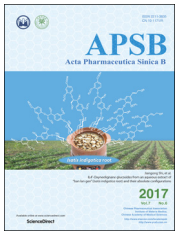

REVIEW

The current agonists and positive allosteric modulators of α7 nAChR for CNS indications in clinical trials

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KEY WORDS

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Acetylcholine;
Ion channel

Abstract The alpha-7 nicotinic acetylcholine receptor (α7 nAChR), consisting of homomeric α7 subunits, is a ligand-gated Ca^{2+}-permeable ion channel implicated in cognition and neuropsychiatric disorders. Enhancement of α7 nAChR function is considered to be a potential therapeutic strategy aiming at ameliorating cognitive deficits of neuropsychiatric disorders such as Alzheimer's disease (AD) and schizophrenia. Currently, a number of α7 nAChR modulators have been reported and several of them have advanced into clinical trials. In this brief review, we outline recent progress made in understanding the role of the α7 nAChR in multiple neuropsychiatric disorders and the pharmacological effects of α7 nAChR modulators used in clinical trials.

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Abbreviations: 5-CSRTT, five-choice serial reaction time task; 5-HT, serotonin; ACh, acetylcholine; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; Aβ, amyloid-β peptide; CNS, central nervous system; DMTS, delayed matching-to-sample; ECD, extracellular domain; GABA, γ-aminobutyric acid; MLA, methyllycaconitine; nAChR, nicotinic acetylcholine receptor; NOR, novel object recognition; PAMs, positive allosteric modulators; PCP, neonatal phencyclidine; PD, Parkinson's disease; PPI, prepulse inhibition; SAR, structure–activity relationship; TMD, transmembrane domains; α-Btx, α-bungarotoxin

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1. Structure and function of α7 nAChRs in the brain

Nicotinic acetylcholine receptors (nAChRs) are ligand-gated ion channels that are activated by the neurotransmitter acetylcholine (ACh) for signaling, and they also respond to drugs including the nicotinic receptor agonist nicotine. The nAChRs can be classified into 5 muscle nAChR subtypes ($\alpha1$, $\beta1$, γ/ε, δ) and 12 neuronal nAChR subtypes ($\alpha2$–10, $\beta2$–4)[1,2]. Among the neuronal nAChR subtypes, the α7 nAChR (also known as α7 receptor) that was first isolated and evaluated in 1990s from avian and rodents are homomeric pentamers widely distributed in the central nervous system (CNS) and periphery organs such as spleen and lymph nodes[3–7]. The five identical α7 nAChR subunits are symmetrically organized around the central pore, and each subunit consists of a large amino-terminal extracellular domain (ECD), four transmembrane domains (TMD, TM1–TM4) and a cytoplasmic domain[8]. In each homomeric α7 nAChR, there are five ACh binding sites within the ECD, which are located at the interface of every two subunits[8,9].

Compared with other subtypes of nAChRs, the α7 nAChR exhibits unique functional properties including: 1) fast activation and desensitization by agonists (on a millisecond scale); 2) high calcium permeability ($P_{Ca}/P_{Na} \approx 10$); and 3) selective inhibition by α-bungarotoxin (α-Btx) and methyllycaconitine (MLA)[3,4,10–12]. In the brain, α7 nAChRs are abundantly expressed in the regions underlying cognition and memory, such as the hippocampus and frontal cortex[8,13]. In neurons, the presynaptically localized α7 nAChRs are physiologically more important although they are widely localized in the synapses (both pre- and postsynaptically) and extrasynaptically[9,14]. Presynaptic α7 nAChRs play a major role in facilitating glutamate release in the cerebellum, auditory cortex, hippocampus and many other brain areas[15–20]. Together with α4β2 nAChRs, presynaptic α7 nAChRs also stimulate γ-aminobutyric acid (GABA) release in the hippocampus[21]. Postsynaptic and extrasynaptic α7 nAChRs are also capable of modulating neuronal activity and neurotransmission[22]. In addition, the α7 nAChRs are also expressed in non-neuronal cells in the brain, including astrocytes, microglia, microvascular endothelial cells, and lymphocytes, playing a role in immunity, inflammation and neuroprotection[9,23–28].

2. The relevance of α7 nAChR in CNS diseases and therapy

The function of α7 nAChRs is critical for cognition, sensory processing, attention, working memory, and reward. On the contrary, dysfunctional α7 nAChRs are associated with multiple psychiatric and neurologic diseases including schizophrenia, AD, attention deficit hyperactivity disorder (ADHD), addiction, pain and Parkinson's disease (PD). Thus, modulation of α7 nAChR function is an attractive strategy for potential therapy of CNS diseases.

Schizophrenia, with a lifetime prevalence of approximately 1%, chronically and severely afflicts patients all over the world[29,30]. There are at least three distinct symptoms of schizophrenia, including positive symptoms (hallucinations, delusions, thought disorder, and paranoia), negative symptoms (anhedonia, social withdrawal, and thought poverty), and cognitive dysfunction (loss of intellectual abilities such as perception, understanding, working memory, and executive function)[29]. Almost all the first and second line drugs, including but not limited to chlorpromazine, clozapine, risperidone, olanzapine, and quetiapine, markedly improve positive symptoms for many patients with schizophrenia. However, they show very limited therapeutic effect on negative symptoms and cognitive dysfunction[31]. Genetic studies show that *CHRNA7*, the gene encoding α7 nAChR protein, and a partial duplication of *CHRNA7*, *CHRFAM7A*, are associated with inhibitory sensory gating deficit in schizophrenia patients[32,33]. It has also been reported that there is diminished mRNA of *CHRNA7* and decreased α-Btx binding in post mortem brain tissue samples from patients with schizophrenia[34,35]. It has been reported that exposure to the non-selective nAChR agonist, nicotine, shows the effect of improving or normalizing sensory deficits in schizophrenia[36].

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterized by a slow onset of memory loss and a late development of disorientation, mood swings and behavioral problems[37]. The cause for AD is still mostly unknown except for less than 10% of cases in which genetic variations have been identified[38]. One of the most convincing theories is that aberrant extracellular amyloid-β peptide (Aβ) deposits are the fundamental cause of AD[39,40]. Aβ is a peptide of 36–43 amino acids crucially involved in AD as the main component of the amyloid plaques found in the brain neurons of AD patients. Aβ exhibits relatively high binding affinity with α7 nAChRs, and they are co-localized in cortical regions and the hippocampus in the brains of AD patients[41,42]. It is controversial as to whether Aβ and its oligomers, $A\beta_{1-42}$, are weak agonists or antagonists, but in either role, they are capable of inhibiting endogenous ACh from activating α7 nAChRs by desensitization or non-competitive antagonism[43,44]. The Aβ–α7 nAChR interaction influences neurotransmission, synaptic plasticity, learning and memory[45–49]. Directly or indirectly, the Aβ–α7 nAChR interaction is an important aspect of AD[50]. From 1993 to 2001, several acetylcholinesterase inhibitors (AChEI) including tacrine (approved in 1993), donepezil (1996), rivastigmine (2000) and galanthamine (2001) which non-selectively enhance nAChR function have been approved for treatment of mild to moderate AD[51,52]. However, there are no AChEIs approved since then. A number of AChEIs such as eptastigmine, phenserine, huperzine A, and dimebon have failed or were discontinued in clinical trials due to adverse effects or insignificant benefits[53–56].

α7 nAChR is also reported to be relevant to other multiple CNS disorders including cigarette addiction, PD and pain[57–59]. The opioid antagonist naltrexone, which inhibits the activity of α7 nAChR, was indicated for potential application in tobacco-use cessation[60]. Application of the α7 nAChR selective agonist PNU-282987 has been shown to decrease motivation for nicotine use in rats[57,61]. In the temporal cortices of post-mortem PD patients' brains, α7-expressing neurons are significantly less abundant than in the control group[62]. Accumulating evidence also shows that activation of α7 nAChR can alleviate PD symptoms in animal models[58,63–65]. Modulation of α7 nAChR function by agonists and positive allosteric modulators (PAMs) exhibits antinociceptive effects in acute and persistent pain[66–72]. Genetic silencing of α7 reveals phenotypes of hyperalgesia and allodynia in mice, whereas α7-hypersensitive mice display decreased pain sensitivity[59]. Altogether, these studies indicate that α7 nAChR serves as a potential therapeutic target for indications such as schizophrenia, AD, ADHD, addiction, pain, PD and other related CNS disorders.

3. α7 nAChR modulators

Over the past two decades, medicinal chemists and biologists have carried out extensive studies in identification and evaluation of α7

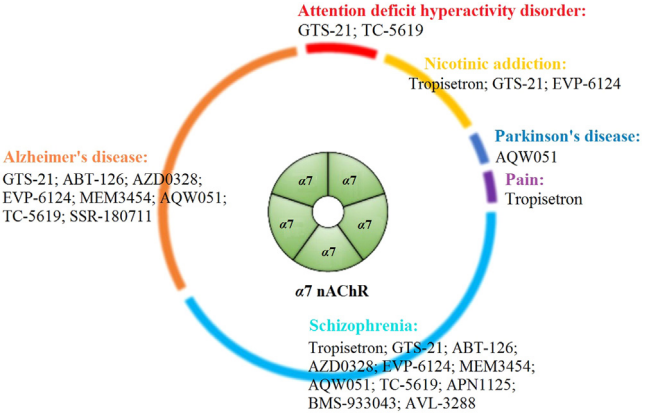


Figure 1 Current α7 nAChR agonists and PAMs in clinical trials for different indications. There are 11 drug candidates, of which ten agonists and one PAM are currently being tested for treatment of schizophrenia, nine agonists for AD, three agonists for nicotinic addiction, two agonists for ADHD, and one agonist each for PD and pain.

nAChR modulators. The major focus was in finding potent and selective compounds and bringing them into therapeutic applications. As summarized in Fig. 1 and Table 1[73–120], twelve α7 nAChR modulators were tested in clinical trials since 2006.

3.1. α7 nAChR agonists

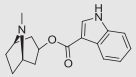
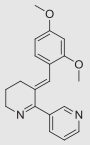
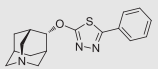
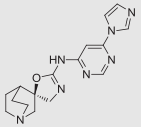
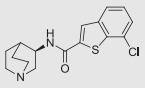
Currently, most developed α7 nAChR agonists are partial agonists. Unlike full agonists such as endogenous ACh, α7 nAChR partial agonists are orthosteric ligands that can only produce a small maximal current even at concentrations where all receptors occupied[121].

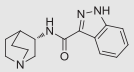
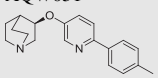
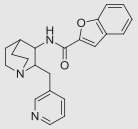
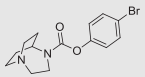
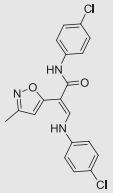
Tropisetron ([(1*R*,5*S*)-8-methyl-8-azabicyclo[3.2.1]octan-3-yl] 1*H*-indole-3-carboxylate), firstly identified as 5-HT_3 receptor antagonist (K_i=5.3 nmol/L), is used clinically in preventing and treating nausea and vomiting after cancer therapy[122,123]. In 2001, Macor et al.[123] evaluated activity of several 5-HT_3 receptor antagonists on α7 nAChRs and found that tropisetron acted as a selective α7 nAChR partial agonist (K_i=6.9 nmol/L; EC_{50} =0.6 μmol/L; E_{max}=25%). Researchers showed that tropisetron could attenuate or improve cognitive deficits in animal models[75–77]. However, tropisetron has not been shown to be effective in improving cognitive deficits in clinical trials. In a phase II clinical trial of tropisetron in patients with schizophrenia, administration of tropisetron significantly improved auditory sensory gating P50 deficits and sustained visual attention, which supports the safety and efficacy of adjunctive tropisetron for treatment of cognitive deficits in schizophrenia[124].

GTS-21 (3-(2,4-dimethoxybenzylidene)-anabaseine), also named DMXB-A, is a derivative of the natural product anabaseine identified as an α7 nAChR agonist and brought into clinical trials[125]. It has been extensively characterized *in vitro* and *in vivo*. This compound acts as a partial agonist in α7 nAChRs and displays better potency and efficacy on rat α7 nAChRs (EC_{50} =5.2 μmol/L; E_{max}=32%) than with human nAChRs (EC_{50} =11 μmol/L; E_{max}=9%) in *Xenopus* oocytes[79]. Selectivity of GTS-21 is not favorable in ion flux studies as it inhibits α4β2 nAChRs (IC_{50}=17 μmol/L) and activates α3β4 nAChRs (EC_{50}=21 μmol/L)[78]. However, in electrophysiological recordings in *Xenopus* oocytes, 100 μmol/L GTS-21 barely evoked current from α4β2 and α3β4 nAChRs[83]. Extensive *in vivo* studies were carried out to confirm the pharmacological effect of GTS-21 on cognitive deficits and sensory gating models of rodents and primates (Table 1). Scientists from Abbot and the University of South Florida found that intraperitoneally injecting GTS-21 significantly enhanced the learning and memory ability of aged rats in a water maze, 17-arm radical maze, and Lashley III maze tests[80,81]. When the cognition of aged rats was further impaired by isoflurane, GTS-21 still could mitigate such cognitive deficits[82]. Moreover, acquisition, retention and relearning abilities in eyeblink classical conditioning are much improved in GTS-21-treated aged rabbits than in the vehicle group[90,91]. Cognitive deficits or dementia in rodents and primates as induced by chemical impairment could also be attenuated or normalized by treatment with GTS-21. For instance, Chen et al.[45] reported that treatment with GTS-21 (1 mg/kg) perfectly prevented $A\beta_{25-35}$ induced depression of the α7 nAChR response, which further led to cognitive deficits in mice. These results indicate that GTS-21 may have substantive therapeutic value in the treatment of cognitive deficit in age-associated memory impairment, AD and schizophrenia. Furthermore, sensory gating deficits in rodents could be improved with GTS-21. This compound improved deficient sensory inhibition in DBA/2 mice, and normalized auditory gating in isolation-reared rats, and also ameliorated prepulse inhibition (PPI) deficits induced by apomorphine or MK-801[85–88]. These data show that GTS-21 might have a therapeutic potential for schizophrenia. In 2014, GTS-21 was in phase II clinical studies for treatment of schizophrenia, AD and ADHD. Though GTS-21 failed in improving cognition in schizophrenia patients, high dose of GTS-21 significantly improved negative symptoms in schizophrenia[126]. However, GTS-21 is not a prototypical α7 nAChR agonist due to its relatively higher affinity for α4β2 nAChRs (K_i=20 nmol/L at human and 19 nmol/L at rat) compared with α7 nAChRs (K_i=2000 nmol/L at human and 650 nmol/L at rat)[78]. Thus, the clinical benefits of GTS-21 cannot be simply attributed to α7 nAChR pharmacology.

The most explored structure of α7 nAChR agonists to date is quinuclidine derivatives such as spirooxazolidinones and quinuclidine carbamates, amides, and ethers. The first spirooxazolidinone, AR-R17779 ((–)-spiro[1-azabicyclo[2.2.2]octane-3,5′-oxazolidin-2′-one]) was identified and evaluated *in vitro* and *in vivo*[127,128]. However, the cross reactivity with 5-HT_3 receptors and poor penetration of AR-R17779 into the CNS remains a great challenge for clinical development[22]. AZD0328 ((29 *R*)-spiro-[1-azabicyclo[2.2.2]octane-3,29(39*H*)-furo[2,3-*b*]pyridine] D-tartrate) is an optimized molecule identified as α7 nAChR agonist by AstraZeneca from the spirooxazolidinone series compounds based on AR-R17779 through structure–activity relationship (SAR) studies[96]. AZD0328 acts as a partial α7 nAChR agonist exhibiting an EC_{50} of 338 nmol/L and an efficacy of 65% on *Xenopus* oocytes expressing human α7 nAChRs[96]. Compared with the maximal current elicited by serotonin (5-HT) on human 5-HT_{3A} receptors and ACh on human nAChRs, maximal activity of AZD0328 was only about 12% for human 5-HT_{3A} receptors, 4% for α4β2 nAChRs and no activity on α3β4 nAChRs[96]. Studies showed that AZD0328 is very stable and has favorable pharmacokinetic (PK) properties, which suggests that this compound is acceptable for clinical trials[98,129]. Through activation of α7 nAChRs, AZD0328 is able to enhance cortical dopamine release in rats and improve novel object recognition (NOR) in mice[96,97]. AZD0328 also displays efficacy in improving working memory in a spatial delayed response task in *Rhesus macaques*[98]. In 2008,

Table 1 α7 nAChR agonists and PAM in clinical trials.

Compound	Classification	Potency & efficacy	Animal model on CNS disorders	Indication	Clinical status (Sponsor)
Tropisetron 	Partial agonist	Binding affinity: K_i: 6.9 nmol/L (in rα7)[73] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 0.6 μmol/L; E_{max} = 25%[74] Mα7 in oocytes: EC_{50} = 1.3 μmol/L; E_{max} = 36%[73]	Mice: phencyclidine-induced cognitive deficits[75]. Rats: young and aged rats[76]; naloxone-induced place aversion[77].	Pain Smoking cessation; schizophrenia	Phase IV (completed in 2009) (University Hospital, Clermont-Ferrand) Phase III (completed in 2011) (Baylor College of Medicine)
GTS-21/DMXB-A 	Partial agonist	Binding affinity: K_i: 2000 nmol/L (in hα7)[78] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 11.0 μmol/L; E_{max} = 9%[79] Rα7 in oocytes: EC_{50} = 5.2 μmol/L; E_{max} = 32%[79]	Rats: normal or isoflurane-induced cognitive impairment aged rats[80–82]; ibotenic acid-induced dementia[83]; mecamylamine-caused learning impairment[84]; auditory gating in isolation-reared rats[85]; apomorphine/MK-801-elicited PPI deficits[86,87]. Mice: Aβ-induced cognitive deficits[45]; deficient sensory inhibition[88]; aggressive behavior in mouse models[89]. Rabits: aged rabbits[90,91]. Monkeys: normal monkeys in DMTS task[78]; Ketamine-induced cognitive deficit[92].	Schizophrenia AD; ADHD Tobacco use disorder	Phase II (completed in 2015) (University of Colorado) Phase II (completed in 2008) (CoMentis) Phase II (not yet recruiting) (University of Florida)
ABT-126 	Agonist	Binding affinity: K_i: 12–14 nmol/L (in hα7, rα7 and mα7)[93,94]	Monkeys: Parkinsonian monkeys[95].	AD Schizophrenia	Phase II (terminated in 2014) (AbbVie) Phase II (terminated in 2014) (AbbVie)
AZD0328 	Partial agonist	Binding affinity: K_i: 3.0 and 4.7 nmol/L (in hα7 and rα7)[96] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 338 nmol/L; E_{max} = 64.7%[96] Rα7 in oocytes: EC_{50} = 150 nmol/L; E_{max} = 61.0%[96]	Mice: NOR in normal mice[96,97]. Monkeys: normal monkeys in delayed response task[98].	AD Schizophrenia	Phase I (completed in 2008) (AstraZeneca) Phase II (terminated in 2008) (AstraZeneca)
BMS-933043 	Partial agonist	Binding affinity: K_i: 8.1 and 3.3 nmol/L (in hα7 and rα7)[73] Ca^{2+} flux assays: Hα7 in HEK293 cell line: EC_{50} = 23.4 nmol/L[73] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 0.29 μmol/L; E_{max} = 24%[73] Rα7 in oocytes: EC_{50} = 0.14 μmol/L; E_{max} = 27%[73]	Rats: MK-801-induced cognitive deficits[73]; *S*(+)ketamine-induced sensory gating deficits[73]. Mice: MK-801-induced cognitive deficits[73].	Schizophrenia	Phase I (completed in 2013) (Bristol-Myers Squibb)
EVP-6124/ Encenicline 	Partial agonist	Binding affinity: K_i: 9.98 nmol/L (in rα7)[99] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 0.39 μmol/L; E_{max} = 42%[99]	Rats: scopolamine-induced deficit[99]; delay-dependent forgetting in the NOR[100]; low attentive rats[101].	AD; dementia Schizophrenia; impaired cognition Nicotine dependence; smoking cessation	Phase III (terminated in 2017) (FORUM) Phase III (completed in 2016) (FORUM) Phase II (terminated in 2015) (A. Eden Evins)

MEM3454/ RG3487 	Partial agonist	Binding affinity: K_i: 6 nmol/L (in rα7)[102] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 0.8 μmol/L; E_{max} = 63%[102] Hα7 in QM cell line: EC_{50} = 7.7 μmol/L; E_{max} = 69%[102]	Rats: attentional performance in normal rats[103]; aged rats[102]; apomorphine-induced deficits in sensorimotor gating[102].	AD	Phase II (completed in 2007) (Memory)
				Schizophrenia	Phase II (unknown) (Memory)
AQW051 	Partial agonist	Binding affinity: K_i: 27 nmol/L[104] Ca^{2+} flux assays: Hα7: EC_{50} = 7.4 μmol/L; E_{max} = 73%[105] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 7.5 μmol/L; E_{max} = 75%[105]	Rats: aged rats05[105] Mice: NOR in normal mice[105] Monkeys: Parkinsonian monkeys[106]	Schizophrenia	Phase II (completed in 2013) (Novartis)
				Levodopa-induced dyskinesia in PD	Phase II (completed in 2013) (Novartis)
				AD	Phase II (terminated in 2009) (Novartis)
TC-5619 	Full agonist	Binding affinity: K_i: 1 and 1.4 nmol/L (in hα7 and rα7)[107,108] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 33 nmol/L; E_{max} = 100%[108,109] Rα7 in GH4C1 cell line: EC_{50} = 17 nmol/L; E_{max} = 76%[107]	Mice: *th*(tk⁻)/*th*(tk⁻) mice[108]; apomorphine-induced PPI deficits[108]; NOR in normal mice[108].	Schizophrenia	Phase II (completed in 2013) (Targacept)
				AD	Phase I (completed in 2011) (Targacept)
				ADHD	Phase II (completed in 2012) (Targacept)
SSR-180711 	Partial agonist	Binding affinity: K_i: 14 and 22 nmol/L (in hα7 and rα7)[110] Electrophysiology activity: Hα7 in oocytes: EC_{50} = 4.4 μmol/L; E_{max} = 51%[110] Hα7 in GH4C1 cell line: EC_{50} = 0.9 μmol/L; E_{max} = 36%[110]	Rats: MK-801/PCP-induced cognitive deficits[111]; depressive disorders rates[111]; neurodevelopmental latent inhibition models of schizophrenia[112]. Mice: chronic mild stress model[113]; Aβ-induced memory deficits[114]; phencyclidine-induced cognitive deficits[115]; forced swim and tail suspension tests[116]	AD	Phase II (terminated in 2008) (Sanofi)
APN1125 (Structure Undisclosed)	Partial agonist	Electrophysiology activity: Hα7 in oocytes: EC_{50} = 1.16 μmol/L; E_{max} = 41%[117]	Rats: NOR in normal rats[117]	Schizophrenia	Phase I / Phase II (suspended in 2016) (CoMentis)
AVL-3288/ XY4083/CCMI 	Type I PAM	Electrophysiology activity: Hα7 in oocytes: EC_{50} = 0.7 μmol/L; E_{max} = 9 folds[118]	Mice: DBA/2 mouse model of sensory-gating deficit[118]; MK-801-induced hyperlocomotion mode eight-arm radial maze in normal mice[118]; NOR in normal mice[119]. Rats: 5-CSRTT in normal rats[119]; ketamine-induced cognitive deficits and social withdrawal[120].	Schizophrenia; schizoaffective disorder	Phase I (recruiting) (New York State Psychiatric Institute; University of Colorado)

DMTS, delayed matching-to-sample; NOR, novel object recognition; PCP, neonatal phencyclidine; 5-CSRTT, five-choice serial reaction time task.
Indications and clinical status of α7 nAChR modulators above are obtained from https://clinicaltrials.gov/.

AstraZeneca terminated AZD0328 for a phase II clinical trial for being "unlikely to meet the current target product profile"[130].

Reported in 2016, a new spirooxazolidinone named BMS-933043 ((2 *R*)-*N*-(6-(1*H*-imidazol-1-yl)-4-pyrimidinyl)-4′*H*-spiro [4-azabicyclo[2.2.2]octane-2,5′-[1,3]oxazol]-2′-amine) was identified by Bristol-Myers Squibb as a selective partial agonist for the α7 nAChR (K_i = 8.1 nmol/L at human α7 nAChRs)[73]. Preclinical studies showed cognition enhancement and sensory gating improvement in rodents[73]. This compound was advanced into a phase I clinical trial for schizophrenia in 2012.

Analogs with quinuiclidine, aromatic moieties, and functional linkers such as amides and ethers have been substantially explored. EVP-6124 (((*R*)-7-chloro-*N*-quinuclidin-3-yl)benzo[*b*] thiophene-2-carboxamide) is a representative quinuclidine amide analog developed by FORUM (formerly EnVivo) that acts as a potent partial agonist at α7 nAChR (EC_{50} = 0.39 μmol/L, E_{max} = 42%) and an antagonist at 5-HT_3 receptors (IC_{50} < 10 nmol/L)[99]. It is also reported that EVP-6124 enhanced dopamine, acetylcholine, and glutamate efflux in the rat cortex and nucleus accumbens[131,132]. *In vivo*, EVP-6124 reversed scopolamine-induced deficit and improved natural forgetting and low attention in rats[99,101]. Treatment with EVP-6124 in phase I and II trials for mild-to-moderate AD was well tolerated and showed statistically significant improvements compared with placebo on cognitive and functional measures[133,134]. A phase II, a double-blind, randomized, placebo-controlled, parallel-design clinical trial conducted for schizophrenia showed statistical significant cognition improvement in schizophrenia patients[135]. However, the results of phase III clinical trial from 2012 to 2016 for schizophrenia did not meet the primary clinical end point as high efficacy in placebo group. Consequently, the other two Phase III trials for AD and dementia were suspended in 2017. Like EVP-6124, MEM3454 ((*R*)-3-(6-*p*-tolyl-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane) developed by Memory Pharmaceuticals also exhibited antagonism at 5-HT_3 receptors and procognitive effects in normal and aged rodents[102,103]. Similarly, MEM3454 enhanced dopamine efflux by nAChR stimulation and ACh efflux primarily mediated *via* 5-HT_3 receptor antagonism[136]. In a phase II clinical trial, MEM3454 failed to improve cognitive deficits in patients with schizophrenia, but moderate negative symptoms in patients were significantly improved[137]. Through homology modeling, molecular docking, and pharmacophore elucidation techniques, Targacept designed and synthesized a series of amide quinuclidine compounds, among which TC-5619 (*N*-[2-(pyridin-3-ylmethyl)-1-azabicyclo[2.2.2] oct-3-yl]-1-benzofuran-2-carboxamide) exhibits excellent activity and selectivity on α7 nAChR (K_i = 1 nmol/L at human α7 nAChRs, 2800 nmol/L at human $\alpha4\beta2$ nAChRs, IC_{50} > 10 μmol/L at human 5-HT_3 receptors)[107,108]. This compound acted as an α7 nAChR full agonist with an EC_{50} of 33 nmol/L in *Xenopus* oocytes expressing human α7 nAChRs[108,109]. *In vivo* studies showed adequate properties of TC-5619, including PK profiles, rapid CNS permeability and procognitive effect in rodents[108,109]. However, after two phase II clinical trials were conducted, it was confirmed that TC-5619 did not improve cognitive deficits and negative symptoms in schizophrenia[138–140].

Recently, Novartis disclosed a quinuclidine ether α7 nAChR partial agonist, AQW051 ((*R*)-3-(6-*p*-tolyl-pyridin-3-yloxy)-1-aza-bicyclo[2.2.2]octane). *In vitro* characterization with human α7 nAChR expressed on *Xenopus* oocytes yielded an EC_{50} of 7.5 μmol/L and an efficacy of 75%[106]. Not only did it show a favorable PK profile and procognitive effects in rodents, this compound also displayed potential in the therapy of PD by reducing L-dopa-induced dyskinesias and extending the duration of L-dopa effects in parkinsonian monkeys[104–106]. AQW051 has been advanced in phase II clinical trials for schizophrenia, AD, and L-dopa-induced PD. It was reported in a phase II randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of AQW051 in patients with PD and levodopa-induced dyskinesia that AQW051 did not significantly reduce dyskinesia or parkinsonian severity[141].

Additionally, structural diversity of α7 nAChR agonists is continuously expanding in the literature from the series of quinuiclidine-based moieties. ABT-126 (2-(((1*R*,3*R*,4*S*,5*S*,7*S*)-1-azaadamantan-4-yl)oxy)-5-phenyl-1,3,4-thiadiazole), developed by AbbVie (formerly Abbott), is an azaadamantane derivative that acted as an α7 nAChR agonist (K_i = 12–14 nmol/L)[93]. In a phase II clinical trial in patients with mild-to-moderate AD, ABT-126 demonstrated significant improvement compared with placebo in the primary efficacy endpoint[93,94]. A phase II trial of ABT-126 for treatment of cognitive impairment in schizophrenia was also conducted and revealed that this compound demonstrated a procognitive effect in nonsmoking subjects[142]. However, in a phase IIb clinical trial, ABT-126 did not demonstrate a consistent effect on cognition in nonsmoking subjects with schizophrenia but a trend toward an effect on negative symptoms[143].

Researchers from Sanofi described a diazabicyclononane α7 nAChR partial agonist named SSR180711 (4-bromophenyl (1*S*,5*S*)-1,4-diazabicyclo[3.2.2]nonane-4-carboxylate, K_i = 14 nmol/L at human α7 nAChRs)[110]. SSR180711 displayed effects of antidepression, procognition and sensory gating improvement in multiple *in vivo* studies in rodents[112–114,116]. However, the phase II clinical trial was terminated in 2008 for insufficient expected benefit and risk. APN1125 developed by Comentis with an undisclosed structure also acted as an α7 nAChR partial agonist (EC_{50} = 1.16 μmol/L; E_{max} = 41% at human α7 nAChRs)[117]. It is currently suspended in a phase I/phase II clinical trial for schizophrenia for business reasons[144].

Most of the clinical trials conducted with α7 nAChR agonists showed a paucity of effects. With limited clear reports, we can only assume the lack of sufficient selectivity over 5-HT_3 receptors and improper designation of clinical trials might be the cause of the discontinued compounds. However, the crucial function of α7 nAChRs in the brain and the compelling evidence of preclinical studies still suggest that selective agonists activating α7 nAChRs may be an attractive therapeutic strategy for schizophrenia, AD and other CNS diseases.

3.2. *α7 nAChR PAMs and ago-PAMs*

A large number of compounds modulate α7 nAChR function by binding to allosteric sites instead of the orthosteric site that binds agonists and antagonists. α7 nAChR-positive allosteric modulators (PAMs) are a category of these compounds that can potentiate α7 currents in the presence of an agonist such as acetylcholine. On the basis of their macroscopic effects, α7 nAChR PAMs have been classified and distinguished as type I and type II. Type I PAMs mainly enhance agonist-evoked peak currents without delaying desensitization and do not reactivate desensitized receptors, whereas type II PAMs can delay desensitization and reactivate desensitized receptors[22]. When compared with agonists, α7 nAChR PAMs are more promising therapeutic tools because of their maintenance of endogenous activation characteristics, better selectivity profile, higher structural diversity and better final effects with an extra neuroprotection effect[145]. α7 nAChR ago-PAMs can

activate receptors from non-orthosteric sites while still retaining the properties of PAMs.

AVL-3288 ((*E*)-*N*-(4-chlorophenyl)-3-((4-chlorophenyl)amino)-2-(3-methylisoxazol-5-yl)acrylamide), which also named XY4083 or CCMI, is a representative type I α7 nAChR PAM. Screened from a small library of $GABA_A$ receptor PAM analogs, researchers from University of California, Irvine identified a highly selective type I α7 nAChR PAM, AVL-3288[118]. In rodent models, treatment with AVL-3288 in the presence or absence of agonist both corrected the sensory deficits and improved cognition[118–120,146]. In 2017, AVL-3288 has advanced into a phase I clinical trial for schizophrenia and schizoaffective disorder, which demonstrated that a type I PAM can be safely administered to humans and that it has potential positive neurocognitive effects in CNS disorders[147].

NS1738 (1-(5-chloro-2-hydroxy-phenyl)-3-(2-chloro-5-trifluoromethyl-phenyl)-urea) developed by NeuroSearch and LY2087101 ([2-[(4-fluorophenyl)amino]-4-methyl-5-thiazolyl]-3-thienylmethanone) by Eli Lilly are also type I α7 nAChR PAMs[148,149]. NS1738 was also reported to enhance agonist potency in rescuing scopolamine-induced cognitive deficits[148]. Both of NS1738 and LY2087101 have not brought into clinical trials yet.

The first selective type II PAM PNU-120596 (1-(5-chloro-2,4-dimethoxy-phenyl)-3-(5-methyl-isoxazol-3-yl)-urea) developed by Pfizer was shown to not only potentiate the peak α7 current but also delay desensitization of α7 nAChRs[150]. Though this compound augmented the procognitive effects of an acetylcholinesterase inhibitor in rodents and non-human primates, it was not able to advance into clinical trial for its potential toxic effects resulting from excessively high calcium influx[118,151]. A-867744 (4-(5-(4-chlorophenyl)-2-methyl-3-propionyl-1*H*-pyrrol-1-yl)benzenesulfonamide) is type II PAM with moderate potency and efficacy (EC_{50} = 1.12 μmol/L; E_{max} = 733% to ACh-evoked α7 current in *Xenopus* oocytes) developed by AbbVie[152]. Other reported type II PAMs such as TQS (4-naphthalene-1-yl-3*a*,4,5,9*b*-tetrahydro-3*H*-cyclopenta[*c*]quinoline-8-sulfonic acid amide), JNJ-1930942 (2-[[4-fluoro-3-(trifluoromethyl)phenyl]amino]-4-(4-pyridinyl)-5-thiazolemethanol), and RO5126946 ((5-chloro-*N*-[(1*S*,3*R*)-2,2-dimethyl-3-(4-sulfamoyl-phenyl)-cyclopropyl]-2-methoxy-benzamide) also exhibited α7 potentiation effects *in vitro* and precognition effects *in vivo*[153–155].

On the basis of the conventional type II α7 nAChR PAM TQS, researchers from Eli Lilly identified a compound named GAT-107 or 4BP-TQS (4-(4-bromophenyl)-3*a*,4,5,9*b*-tetrahydro-3*H*-cyclopenta[*c*]quinoline-8-sulfonamide), which exhibited potent allosteric agonism and allosteric potentiation at α7 nAChRs[156]. Moreover, with GAT-107 as a tool, it is reported that the direct allosteric activation site is located in the interface of α7 nAChR subunits[157,158].

Exploiting α7 nAChR PAMs and ago-PAMs is still in its early stages, and clinical trials of these compounds are still in their infancy. However, with the property of modulating α7 nAChR activity, α7 nAChR PAMs and ago-PAMs represent an additional therapeutic possibility for CNS diseases.

4. Concluding remarks

Abundant literature has shown us the critical role of α7 nAChRs in cognition, learning, memory, and sensory processing in animal models. Compelling preclinical evidence has shown that α7 nAChR agonists and PAMs could enhance cognition and alleviate sensory gating deficiency.

Most clinical trials of α7 nAChR agonists are terminated or suspended. With the limited data, we are not able to assign the cause of clinical failure. However, almost all of the α7 nAChR agonists show cross-activity with $5\text{-}HT_3$ receptors. Thus, we assume that the lack of selectivity over $5\text{-}HT_3$ receptors might be one reason for the failure of α7 nAChR agonists in clinical trials. In phase II clinical trials for cognitive deficits in schizophrenia, GTS-21 and ABT-126 showed significant improvement in negative symptoms but not in ameliorating cognitive deficits. In addition, EVP-6124 failed to reach the primary clinical endpoint because of the unexpected high effect of the placebo. Therefore, improper design of clinical trials might be another reason for the failure of α7 nAChR agonists in clinical trials.

As for α7 nAChR PAMs and ago-PAMs, the cytotoxic effect of PNU-120596 indicates that a too-potent activity of type II PAM is not favorable in drug discovery. However, the reported procognition and sensory gating improvement effects in animal models demonstrates a promising future for α7 nAChR PAMs. Moreover, positive results of AVL-3288 in a phase I clinical trial indicates that an α7 nAChR PAM is a potential new therapy for cognitive deficit in schizophrenia. Pharmacological studies on α7 nAChR ago-PAMs have not been reported yet. However, based on the activity of GAT-107 in enhancing α7 nAChR function, ago-PAMs remain a positive choice in developing therapeutic solution in CNS disorders.

Taken together, α7 nAChR agonists and PAMs (including ago-PAMs) remain a viable therapeutic strategy for the treatment of AD, schizophrenia, and other neuropsychiatric disorders. While developing α7 nAChR modulators, selectivity and toxicity profiles should be further improved. And before clinical trials, scientific and well-rounded clinical plans should be designed.

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