Nicotinic Ligands as Multifunctional Agents for the Treatment of Neuropsychiatric Disorders

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Abstract

The challenges associated with developing more effective treatments for neurologic and psychiatric illness such as Alzheimer's disease and schizophrenia are considerable. Both the symptoms and the pathophysiology of these conditions are complex and poorly understood and the clinical presentations across different patients can be very heterogeneous. Moreover, it has become apparent that the reductionist approach to drug discovery for these illnesses that has dominated the field for decades (i.e., the development of highly selective compounds or other treatment modalities focused on a very specific pathophysiologic target) has not been widely successful. Accordingly, a variety of new strategies have emerged including the development of "multitarget-directed ligands" (MTDLs), the development and/or identification of compounds that exhibit "multifunctional" activity (e.g., pro-cognitive plus neuroprotective, pro-cognitive plus antipsychotic activity), "repurposing" strategies for existing compounds that have other clinical indications, and novel "adjunctive" treatment strategies that might enhance the efficacy of the currently available treatments. Interestingly, a variety of ligands at nicotinic acetylcholine receptors (nAChRs) appear to have the potential to fulfill one or more of these desirable properties (i.e., multifunctional, repurposing, or adjunctive treatment potential). The purpose of this review (while not all-inclusive) is to provide an overview of a variety of nAChR ligands that demonstrate potential in these categories, particularly, "multifunctional" properties. Due to their densities in the mammalian brain and the amount of literature available, the review will focus on ligands of the high affinity $\alpha 4\beta 2$ nAChR and the low affinity $\alpha 7$ nAChR.

Key Words: Alzheimer's disease, Mild Cognitive Impairment, schizophrenia, cholinergic, memory

Abbreviations: AChE, acetylcholinesterase; AD, Alzheimer's Disease; DMTS, Delayed Match to Sample; MLA, methyllycaconitine; NHP, non-human primate, NOR, spontaneous novel object recognition

1. Introduction

The rising prevalence of neuropsychiatric illnesses is a major public health concern while at the same time, research and development (R&D) for new drugs to treat these conditions is declining and many pharmaceutical companies have abandoned this field of research altogether [1, 2]. There are a number of cited reasons for this decline in R&D and they include the low success rate for clinical approval of novel treatments, increased time and costs associated with the regulatory burden, litigation-related concerns with drugs that do reach the market, and the wider availability of generic drugs which reduces profits for companies that heavily invest in R&D [3]. Even during the most aggressive periods of R&D in the last 15 years, there has been a paucity of truly new chemical entities developed in the pharmaceutical industry [4] and this has been particularly apparent in the field of neurology and psychiatry.

It has also become increasingly evident that the reductionist approach to modern drug discovery that has dominated the field for decades (i.e., the development of highly selective compounds or other treatment modalities focused on a very specific pathophysiologic target) has not been widely successful [5], especially for the treatment of neuropsychiatric disorders [6]. Accordingly, a number of alternative approaches to drug discovery have emerged and they include the development of “multitarget-directed ligands” (MTDLs) “multifunctional” compounds, “repurposing” strategies, and novel “adjunctive” treatment strategies. Given the complexity of both the pathophysiology and symptom profile of conditions such as Alzheimer’s disease (AD) and schizophrenia, it would appear rational to attempt to develop compounds that modulate several therapeutic targets simultaneously (i.e., the MTDL approach) and/or that exhibit multifunctional activity (e.g., pro-cognitive plus neuroprotective, pro-cognitive plus antipsychotic). A single compound with MTDL or multifunctional activity would circumvent

the limitations associated with combining two or more drugs with potentially different degrees of bioavailability, pharmacokinetics, and metabolism [7] as well as simplify the dosing regimen (an advantage that could be especially important from a compliance perspective). Drug repurposing (also called drug repositioning), is another (increasingly popular) approach designed to increase the speed of the drug discovery process by identifying a new clinical use for an existing approved drug [6, 8, 9]. There are numerous cases in the past where clinical observations have led to the eventual use of drugs for purposes other than what they were originally approved for. To cite just a couple of examples; beta adrenergic receptor blockers (e.g., propranolol), originally approved for hypertension, are now approved for congestive heart failure and migraine headache; anticonvulsant drugs (e.g., gabapentin), originally approved for epilepsy, are now used commonly for neuropathic pain and bipolar disease. It is important to note that the “clinical observation” approach to drug discovery is not an efficient mechanism for addressing unmet medical needs and there is active interest in identifying compounds for repurposing both in clinical trials as well as in the preclinical setting. Finally, the adjunctive treatment strategy (adding a second drug to an existing approved drug), while not optimal from a pharmacokinetic and compliance standpoint, is an additional alternative to improve overall treatment outcomes. This approach is commonly used in psychiatry for treatment resistant illnesses (e.g., adjunctive antipsychotic drug with an antidepressant for treatment-resistant depression).

Interesting, a variety of ligands at nicotinic acetylcholine receptors (nAChRs) appear to have the potential to fulfill one or more of these desirable categories described above (i.e., multifunctional, repurposing, or adjunctive potential). The purpose of this review, therefore, is to provide an overview of a variety of nAChR ligands that demonstrate potential in these categories, particularly, “multifunctional” properties. While many of the compounds discussed

in this review may have been initially developed as part of a traditional (i.e., reductionist) drug discovery process (e.g., combinatorial chemistry and high throughput screening selected to hit a specific receptor or pathophysiologic target), follow up studies across multiple screening processes (in vitro and in vivo) suggest that they have potential as “multifunctional” compounds. Please see Table 1 for a representative list of nAChR ligands with potential as multifunctional compounds based on their positive effects across two or more therapeutic targets. Due to their densities in the mammalian brain and the amount of literature available, the review will focus on ligands of the high affinity $\alpha 4\beta 2$ nAChR and the low affinity $\alpha 7$ nAChR.

2. $\alpha 4\beta 2$ and $\alpha 7$ nicotinic acetylcholine receptors (nAChRs)

nAChRs are ligand gated ion channels that modulate the flow of cations into and out of cells, notably the influx of sodium and calcium, and the efflux of potassium. However, many (if not most) of the potential therapeutic effects of nAChR ligands have been attributed to their ability to influence neuronal excitability, synaptic plasticity, gene expression, and neurotoxicity via the regulation of intracellular calcium [184]. Neuronal nAChRs are formed through a combination of α and β subunits composing heteromeric receptors, or through homomeric α configurations. Although there have been nine α ($\alpha 2$ - $\alpha 10$) and three β ($\beta 2$ - $\beta 4$) subunits currently identified that can form many different combinations, as noted above, for the purposes of this review, the heteromeric $\alpha 4\beta 2$ and homomeric $\alpha 7$ nAChR subtypes will be primarily discussed. These two nAChR receptors (see Fig 1) are the most predominant subtypes found in the mammalian brain and the most commonly targeted in drug discovery programs for neuropsychiatric disorders. $\alpha 4\beta 2$ nAChRs possess a high affinity for acetylcholine and nicotine, they desensitize slowly, and they are engaged in paracrine-like transmission [10, 11]. Most likely, due to the high density of $\alpha 4\beta 2$ nAChRs in the brain (relative to other nAChR subtypes),

their high affinity for nicotine, as well as their previous role in reward and drug dependence, compounds active at the $\alpha 4\beta 2$ subtype were the first to be developed for cognitive enhancement in the preclinical setting. As opposed to $\alpha 4\beta 2$ nAChRs, $\alpha 7$ nAChRs exhibit low affinity for acetylcholine and nicotine; they rapidly desensitize and are involved in phasic synaptic responses [10, 11]. For several years the $\alpha 7$ -nAChR has been considered as an especially important therapeutic target in AD and schizophrenia due to the deficits in $\alpha 7$ -nAChR protein that have been observed in the brains of patients who suffered from these disorders [12-14]. $\alpha 7$ nAChRs are known to be abundant in the hippocampus and prefrontal cortex (important structures for cognition and AD [15]) and they modulate a number of calcium-dependent events in neurons including neurotransmitter release [10, 16], postsynaptic signaling [17, 18] and neuronal survival [19, 20]. Moreover, agonists of $\alpha 7$ nAChRs have been shown to increase the phosphorylation of ERK and CREB (signaling pathways linked to long term potentiation and memory formation) in the rodent brain [21, 22] and to improve performance in a variety of learning and memory-related tasks in animals (for review, see [23]).

3. Nicotine as a prototypic compound with “multifunctional” activity

Interest in the prototypic tobacco alkaloid nicotine as a cognitive enhancing agent truly began nearly 25 years ago when it was first demonstrated that not only could the compound restore cognitive function in nicotine-deprived smokers, but that it could also enhance cognition in human nonsmokers and experimental animals [24]. Specific examples to support this argument now include positive effects of nicotine on working memory [25], sustained attention [26], and recognition memory [27] in rats, short term (working) memory [28] [29] and distractibility [30] in non-human primates, and multiple domains of cognition in humans including attention, information processing and short term memory [31-34]. While nicotine

would not be classified as an antipsychotic per se, it has been shown to decrease some psychiatric symptoms in schizophrenia (particularly the negative symptoms) and to improve sensory gating and prepulse inhibition in animals and humans [35]. Interestingly, nicotine has also been shown to have neuroprotective activity in multiple disease models (i.e., both in vitro and in vivo) [36]. The mechanistic basis for the neuroprotective effects of nicotine and other nAChR ligands (see below) has not been fully elucidated, however a number of hypotheses have been proposed (based primarily on in vitro and ex vivo studies). These hypotheses include nAChR-related activation of pro-survival signaling factors such as phosphatidylinositol 3-kinase (PI3K), Akt and Bcl proteins in the brain [185], activation of calcineurin, and L-type calcium channels [184], the release of Brain-Derived Neurotrophic Factor (BDNF) and increases the cell surface expression of TrkB receptors [186], as well as the release of nerve growth factor (NGF) and increases TrkA receptors [187].

Collectively, the information cited above (which is a very short overview of an extensive body of literature) would support the argument that nicotine has potential as a multifunctional compound for a number of neuropsychiatric disorders. Unfortunately, concerns about its short half-life, cardiovascular side effects, and abuse potential have limited enthusiasm regarding the use of nicotine as a therapeutic agent to date. However, it is interesting to note, that in a recent study where nicotine was delivered via a transdermal patch to patients with Mild Cognitive Impairment (MCI), improvements in cognition were noted without the appearance of significant side effects [37].

4. Cotinine as a prototypic compound with “multifunctional” activity

There is now considerable evidence that the most predominant metabolite of nicotine, cotinine, might also serve as a prototypic “multifunctional” agent. This is potentially notable,

since cotinine has advantages over nicotine including a superior safety profile [38], a much longer half-life [39] and a lower risk of abuse [40]. Studies to date indicate that cotinine might have properties that would be potentially important for the treatment of AD, schizophrenia, and depression. For example, relevant to AD, cotinine has been shown to be cytoprotective and neuroprotective as demonstrated by its ability to improve the survival of differentiated PC12 cells deprived of nerve growth factor [40], as well as to protect primary cortical neurons from the neurotoxic effects of the amyloid beta ($A\beta$) peptide or glutamate [41, 42]. Cotinine also improved working/short term memory in a delayed match to sample (DMTS) task in monkeys [43], prevented memory loss in an AD mouse model (Tg6799), stimulated the Akt/GSK3 β pathway and reduced $A\beta$ aggregation in their brains [44, 45]. In studies more relevant to schizophrenia, cotinine attenuated the deficits in prepulse inhibition (PPI) of the acoustic startle response induced in three pharmacologic impairment models in rats [43], it improved sustained attention in rats that were impaired by the NMDA receptor antagonist MK-801 [46], and it attenuated deficits in working/short term memory in monkeys produced by the NMDA antagonist ketamine [47]. More recently Grizzell et al., 2014 [48] demonstrated that in mice subjected to prolonged restraint (a chronic stress model), cotinine had antidepressant-like properties and reduced cognitive impairment and synaptic loss in the hippocampus and prefrontal cortex.

5. nAChR-Selective Ligands, Multifunctional Activity-Age-related cognitive decline and Alzheimer's disease

Given the potential limitations of nicotine as a therapeutic agent (described above), drug discovery efforts to create analogs of nicotine or nicotine-like compounds began in earnest in the 1990s. Initial discovery efforts lead to the identification of the $\alpha 4\beta 2$ nAChR agonists ABT-418

[49] and SIB-1508Y [50] and the $\alpha 7$ nAChR agonists AR-R1779 [51] and GTS-21 (DMXBA); [52] with each nAChR subtype agonist displaying distinct neuropharmacological [49, 50, 53]; and behavioral [52, 54-59] effects thereby supporting their therapeutic potential across multiple clinical populations. Indeed, early clinical “proof-of-concept” studies with ABT-418 and GTS-21 (DMXBA) showed beneficial effects on attention, cognition, and P50 auditory gating in several patient populations (i.e., ADHD, AD and schizophrenia; [32, 60-62]. While the results were encouraging, these compounds have been discontinued from further clinical development most like due to issues with their selectivity and/or side effect profiles.

With recent advances in our understanding of molecular biology and pharmacology of nAChRs, new $\alpha 4\beta 2$ and $\alpha 7$ nAChR agonists that display chemical diversity, favorable pharmaceutical properties (e.g., pharmacokinetics and safety/tolerability) and pharmacological activity (e.g., affinity, selectivity and intrinsic activity) have been developed. This next generation of $\alpha 4\beta 2$ nAChR agonists (e.g., ABT-089, AZD-3480 and varenicline; [63, 65, 69] and $\alpha 7$ nAChR agonists (e.g., ABT-107, EVP-6124, RG 3487 and TC-5619) [22, 64, 66, 67, 68] has been shown in preclinical studies to be efficacious in a variety of cognition, sensory processing and synaptic plasticity-related models. Importantly, $\alpha 7$ nAChR agonists have been shown to modulate biochemical and behavioral events associated with AD pathology [22, 70]. Moreover, several Phase 2 clinical trials with both $\alpha 4\beta 2$ (e.g., ABT-089 and AZD-3480; [71-73] and $\alpha 7$ nAChR agonists (e.g., EVP-6124 and RG 3487) [74, 75]; have been conducted in patients with age-related memory impairments and mild to moderate AD demonstrating safety, tolerability, and positive effects across multiple cognitive domains (e.g., attention, episodic memory, working memory and executive function) using different cognitive test batteries (ADAS-Cog-13, CogState and Cognitive Drug Research Battery (CDR)). Despite the important lessons acquired

from these clinical trials, EVP-6124 is the only compound currently undergoing Phase 3 clinical assessment for AD (www.forumpharma.com).

6. nAChR-Selective Ligands, Multifunctional Activity-Attention-Deficit-Hyperactivity Disorder

Both $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in the prefrontal cortex have been implicated in attentional processes and compounds with agonist activity at these receptors are thought to have therapeutic potential in attentional disorders [76]. Nicotinic $\alpha 4\beta 2$ and $\alpha 7$ nAChRs have been shown to differentially modulate prefrontal cortex function via their specific effects on glutamate and acetylcholine [77] as well as dopamine release [78] and thus, might be expected to possess distinctive preclinical behavioral effects [79]. Like nicotine, $\alpha 4\beta 2$ nAChR-selective agonists (e.g., ABT-418, ABT-594, AZD-3480 and Sazetidine-A) have been shown to produce mixed results in their ability to act as “stand-alone” pro-attentional drugs, yet $\alpha 4\beta 2$ nAChR agonists have routinely been shown to reverse pharmacologic-induced impairments (i.e., scopolamine and MK-801) in operant behavioral paradigms (e.g., 5-choice serial reaction time task (5C-SRTT) [26, 80, 82, 83, 84, 85, 90] and visual signal detection task [81, 86 178]) measuring attentional and impulsivity processes in laboratory animals. Several lines of evidence also support a role of the $\alpha 7$ nAChR in modulating attention: (1) the observation that mice expressing genetic deletion of the $\alpha 7$ nAChR take longer to acquire stable task performance [83] and to make more omission errors compared to the wild-type controls when tested in a 5C-SRTT under increased attentional demand [83-85]. Young and colleagues [85] suggested that the increase in omissions for mice expressing genetic deletion of the $\alpha 7$ nAChR may reflect an inability to maintain attentiveness to the visual stimuli being presented during the behavioral sessions rather than a simple reduction in performance accuracy; (2) the observation that the $\alpha 7$ nAChR partial agonist RG 3487 improved

sustained attention comparable to that of nicotine in a rat visual signal detection task [86] and the ability of RG 3487 to improve performance accuracy in an object retrieval attentional paradigm in non-human primates [87]; (3) the observation that tropisetron improved sustained visual attention (i.e., rapid visual information processing) in schizophrenic patients provides additional support for $\alpha 7$ nAChRs in human attention [88]. Despite these encouraging findings, $\alpha 7$ nAChR agonists (i.e., AR-R17779 and PNU 282987) have not shown improvement in the 5C-SRTT [89, 90]. Since RG 3487 and tropisetron are also potent 5-HT₃ receptor antagonists and blockade of this receptor site also increases release of acetylcholine [78], the dual action at both $\alpha 7$ nAChR and 5-HT₃ receptors may account for the observed behavioral differences. Moreover, $\alpha 4\beta 2$ and $\alpha 7$ nAChR agonists have resulted in mixed outcomes in clinical trials of attention deficit hyperactivity disorder (ADHD) despite being well tolerated. ABT-089, AZD-3480 and ABT-894 were reported to improve ADHD symptoms as measured by the Conner's Adult ADHD Rating Scale-Investigator Version (CAARS-INV) [91-93] whereas AZD 1446, $\alpha 4\beta 2$ agonist, and TC-5619, $\alpha 7$ nAChR partial agonist, failed to significantly improve ADHD symptoms compared to placebo [94]; www.targacept.com). Considering all of the present evidence there appears to be a role for both $\alpha 4\beta 2$ and $\alpha 7$ nAChRs in mediating attentional processes and additional investigation is warranted especially when considering the fundamental role that attention plays in cognition and executive function.

7. nAChR-Selective Ligands, Multifunctional Activity-Schizophrenia

Schizophrenia is a debilitating psychiatric disorder characterized by positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., depressed mood, social withdrawal) and cognitive deficits (e.g., deficits in information processing, attention, working memory, and executive function, [95]. While multiple neurotransmitter systems are likely involved in the

etiology and pathophysiology of schizophrenia, the $\alpha 7$ nAChR has received considerable attention in schizophrenia research in the last several years. This is likely due to the identification of a mutation in chromosome 15q14 locus of *CHRNA7* in schizophrenia, the associations between polymorphisms in this gene and impaired P50 auditory-evoked gating and cognitive dysfunction [96, 97], and the reduction in $\alpha 7$ nAChR density observed in the hippocampus of schizophrenics [12, 98]. Interestingly, tobacco products are heavily abused by schizophrenics suggesting that nicotine consumption may represent an attempt to self-medicate the variety of cognitive symptoms, especially those associated with information (sensory) processing deficits and attention [99]. This hypothesis is supported by studies which show that nicotine improves auditory gating in the DBA/2 mouse [100] and in schizophrenic patients [101], and that $\alpha 7$ nAChR agonists (e.g., ABT-107, GTS-21 and tropisetron) improve auditory gating in DBA/2 mice [59, 68, 102] as well as P50 sensory gating in schizophrenic patients [60, 88, 103, 104]. Likewise, deficits in sensorimotor gating (i.e., prepulse inhibition (PPI) of the acoustic startle) have been observed in schizophrenic patients [105, 106] and nicotine has been shown to normalize these deficits [106, 107], an effect blocked by the non-selective nAChR antagonist mecamylamine thus implicating nAChRs [108]. Preclinical studies of $\alpha 7$ nAChR agonists (e.g., tropisetron, SEN-12333) and partial agonists (e.g., RG-3487, TC-5619) have routinely been shown to attenuate pharmacologic-induced (e.g., apomorphine and MK-801) PPI impairments [109-112] and the effects of $\alpha 7$ nAChR agonists on sensorimotor gating appear to be receptor specific as the improved PPI response is attenuated by the $\alpha 7$ nAChR antagonist methyllycaconitine (MLA) [111]. While the sensorimotor effects of $\alpha 7$ nAChR agonists have not been directly assessed in the schizophrenic population, GTS-21 and tropisetron reversed P50 auditory-evoked sensory gating deficits in this population [60, 88, 103, 104]. Despite the lack of

a causal relationship between the sensory gating response and cognitive dysfunction [113], PPI improvements in schizophrenic patients following nicotine appear to correlate with improved prefrontal executive function [114] and further, $\alpha 7$ nAChR agonists and partial agonists that have been shown to improve sensory gating have commonly also been shown to improve cognition [60, 88, 103, 104]. Collectively, this evidence suggests that sensory gating paradigms may serve as translational research tools to assess potential treatment strategies for cognitive deficits associated with schizophrenia.

There are a number of additional lines of evidence to suggest a potential for $\alpha 7$ nAChR agonists in the treatment of schizophrenia (i.e., positive effects across multiple domains of cognition that have a major impact on daily functioning [115, 116]). For example, in preclinical studies with $\alpha 7$ nAChR agonists, robust improvements in recognition memory, working memory and executive function have been observed in young and aged rodents [52, 64, 66, 74, 86, 117] and non-human primates [22, 53, 87].

Additional evidence also suggests an important role of $\alpha 7$ nAChR agonists as therapeutic agents for schizophrenia. For example, NMDA antagonists have been shown to produce many of the neurochemical, behavioral and cognitive impairments associated with schizophrenia [118-120] suggesting their use as pharmacological research tools. In animal models bearing resemblance to schizophrenia, $\alpha 7$ nAChR agonists have been shown to be effective in reversing the acute and chronic effects of NMDA receptor antagonists (ketamine, PCP and MK-801) on learning and memory function in rodents [74, 109, 112, 117, 121] and non-human primates, [47, 122] thereby providing a role for $\alpha 7$ nAChRs in modulating NMDA receptor function.

Despite the extensive evidence to support the positive effects of $\alpha 7$ nAChR agonists in preclinical models of cognition, clinically, $\alpha 7$ nAChR agonists (e.g., GTS-21, tropisetron) and partial agonists (e.g., EVP-6124, RG 3487, TC-5619) have yielded mixed results in their ability to consistently meet the primary objective of cognitive improvement in schizophrenic patients [88, 104, 123-126]. However, $\alpha 7$ nAChR agonists are often effective in reducing the negative symptoms associated with schizophrenia (as measured by the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS); [123, 124, 126, 127]. At present, EVP-6124 has entered into Phase 3 clinical assessment for the treatment of cognitive impairment associated with schizophrenia (www.forumpharma.com).

8. nAChR Positive Allosteric Modulators-Role as Standalone and Adjunctive Treatments for Neuropsychiatric Disorders

In addition to the development of orthosteric $\alpha 4\beta 2$ and $\alpha 7$ nAChR agonists, nAChR positive allosteric modulators (PAMs) have been identified as a novel drug discovery approach with therapeutic opportunities across multiple targets (e.g., cognition, pain and traumatic brain injury). PAMs avoid direct receptor activation by utilizing binding sites away from the orthosteric site targeted by traditional $\alpha 4\beta 2$ and $\alpha 7$ nAChR agonists and thus, may offer some pharmaceutical advantages. For example, in contrast to traditional nAChR agonists, PAMs require endogenous ligand (i.e., acetylcholine or choline) to elicit a nAChR response and thus, would maintain the natural temporal phasic stimulation pattern of the cholinergic receptor. PAMs may also reduce the likelihood of nAChR desensitization following continuous administration and maintain pharmacological activity. A potential concern, however, is that the efficacy of a PAM would be dependent on the presence of sufficient levels of endogenous cholinergic activity to elicit a therapeutic effect and with regards to dementias (e.g., AD) where

endogenous acetylcholine levels would likely be compromised, an exogenous agonist, “promoter”, might be necessary to improve cognitive function [128, 129].

To date, only a few $\alpha 4\beta 2$ PAMs (e.g., desformylflustrabromine, LY-2087101, NS9283 and its analogue NS206) have been identified and characterized preclinically [129]. NS9283 has received the greatest preclinical attention possibly due to its receptor selectivity and brain/plasma ratio in rats [130]. NS9283 was associated with improvements in animal models of attention (i.e., 5-choice serial reaction time task), social recognition memory, spatial reference memory (PCP-deficit model) and sensorimotor gating (PCP-deficit model), effects that were sensitive to mecamylamine antagonism [130]. NS9283 has also been shown to have beneficial analgesic effects in a number of preclinical pain models (e.g., neuropathic and inflammatory pain), but only when the compound was co-administered with the $\alpha 4\beta 2$ nAChR agonist ABT-594 [131, 132] or the $\alpha 4\beta 2$ partial agonist NS3956 [133]. Importantly, the adverse autonomic side effects associated with ABT-594 were not enhanced by NS9283 suggesting that PAM-based approaches may widen the therapeutic window of other therapeutic compounds. A similar lack of “stand-alone” effect of NS9283 was also observed in the auditory discrimination task [134] and in the nicotine drug discrimination task in rats [135]. In the nicotine drug discrimination task, NS9283, but not ABT-594, failed to generalize to the interoceptive nicotine cue. However, co-administering a fixed low dose of either nicotine or ABT-594 with increasing doses of NS9283 resulted in a complete substitution for the nicotine discriminative stimulus [135]. Overall, the findings with NS9283 point to discrete differences in endogenous cholinergic levels within neural substrates responsible for mediating specific neurobiological activities (e.g., cognition vs. pain) and thus, regional cholinergic tone dictates whether the nAChR PAM will activate the nAChR channel directly (“stand-alone”) or require the presence of an exogenous agonist

(“adjunctive or promoter”) to produce the neurobiological response. Certainly, these distinctions will become especially important as $\alpha 4\beta 2$ PAMs enter clinical investigations across multiple therapeutic targets (e.g., AD, chronic pain and schizophrenia).

Discovery efforts have also identified selective $\alpha 7$ PAMs that can be categorized as either Type I or Type II modulators based on their distinct electrophysiological properties [128]. Type I PAMs (e.g., 5-hydroxyindole, NS1738 and AVL-3288) increase agonist-evoked maximum peak current amplitude and maintain desensitization response kinetics, whereas Type II PAMs (e.g., ABT-779, PNU 120596 and RO5126946) increase agonist-evoked peak amplitude but significantly reduce the rate of channel desensitization. Behaviorally, Type I PAMs (e.g., NS-1738, AVL3288) have been associated with “stand-alone” improvements in recognition memory, working memory and executive function in rats [136-138] and Type I modulators have the ability to reverse scopolamine-induced deficits in the Morris water-maze task in rats [136] and in the object recognition task [139]; the latter behavioral effect blocked by $\alpha 7$ nAChR antagonism (MLA). AVL-3288 also has positive effects in the DBA/2 mouse auditory gating model [137] and interestingly, the 5-HT_{2B/C} receptor antagonist SB-206553 which displays Type I PAM activity, restored MK-801-induced sensorimotor gating (PPI) deficits in a manner similar to the $\alpha 7$ nAChR agonist SSR-180711 [140].

Type II PAMs (e.g., ABT-779, PNU 120596 and RO5126946) have also been shown to improve cognition [138, 141-144] and sensory gating (auditory-evoked potentials and PPI; [140, 142, 145, 146] in animal models. Similarly, JNJ-1930942 (described as an intermediate type $\alpha 7$ PAM with characteristics falling between the profiles of Type I and Type II modulators) has beneficial effects on the auditory-evoked sensory inhibition deficits in DBA/2 mice [147]. Interestingly, Stevens and colleagues [146] recently reported that while PNU 120596 was

efficacious in reversing the sensory gating deficits in DBA/2 mice, the modulator was inactive in C3H *Chrna7* heterozygote mice which display greater decreases in hippocampal $\alpha 7$ nAChRs (50-60%) than DBA/2 mice (~30%) and therefore, more closely matches the $\alpha 7$ nAChR deficits (~50) found in post-mortem brains of schizophrenics. Briefly, C3H *Chrna7* heterozygote mice were created by breeding the null mutation for the $\alpha 7$ nAChR (*Chrna7*) onto the C3H background strain of mice [146]. In these mice, it was necessary to co-administer a low dose of choline chloride, which alone was inactive, with the test doses of PNU-120596 in order to improve the auditory sensory gating response. These data provide important insights into the lack of P50 auditory gating effect observed with JNJ-39393406 in schizophrenic patients [148] and highlights the importance of understanding the underlying neurobiological conditions associated with compromised patient populations (e.g., AD and schizophrenia) particularly when administering nAChR PAMs as therapeutic agents. Our laboratory recently demonstrated PNU 120596-related improvements in cognition in aged (cognitively-impaired) rats and aged non-human primates (which have been shown in other laboratories to have a variety of AD-related neurochemical deficits including decreases in hippocampal acetylcholine levels [149]). In our studies, PNU 120596 failed to improve Morris water maze performance in rats or delayed-match-to-sample (DMTS) performance in monkeys when given alone and required the addition of a low dose of donepezil with PNU 120596 in order to improve cognitive performance [141]. Overall, the results of these studies, suggest that Type I and Type II PAMs possess therapeutic potential across multiple neurological and neuropsychiatric populations based on their preclinical efficacy at improving information processing, attention and cognition. Unfortunately, there are active clinical trials with $\alpha 7$ nAChR PAMs so we will have to wait to determine the translational

relevance of the PAMs preclinical efficacy and any potential advantage over orthosteric $\alpha 7$ nAChR agonists.

9. nAChR Ligands, Repurposing Strategies

To date the only nicotinic ligands available as therapeutic agents (either by prescription or over the counter) are nicotine (as a gum or transdermal patch) and the $\alpha 4\beta 2$ nAChR partial agonist varenicline and both are currently used to improve smoking cessation. There is significant evidence that each of these agents might be repurposed for other indications, however. While a detailed review of the specific literature on nicotine (as a repurposed compound) is beyond the scope of this review, there have been literally hundreds of preclinical studies designed to evaluate its potential as a therapeutic agent for conditions as diverse as AD, MCI, ADHD and schizophrenia (as noted above), as well as Parkinson disease, depression, anxiety, pain, obesity, and ulcerative colitis [150]. Some of these preclinical studies have been followed by clinical investigations with variable results.

In preclinical studies, varenicline has been shown (in rats) to improve sustained attention in a signal detection task, sensorimotor gating in a PPI task, and recognition memory in a novel object recognition task [69], thus indicating its potential for conditions such as AD and schizophrenia. In a study with relevance to cocaine addiction, varenicline significantly improved delayed match to sample (DMTS) performance in both cocaine-naïve and cocaine-experienced monkeys [151] indicating a potential for its use in drug addiction as well as other disorders. There have been a few clinical studies designed to evaluate the effect of varenicline in schizophrenia and schizoaffective disorder [152], mild to moderate AD [153], and as adjunctive treatment with antipsychotic medications to treat cognitive impairments in schizophrenia [154].

While typically short in duration and with a relatively small sample size, most of the studies (with the exception of the Kim, et al. 2014 [153]) have had promising results.

10. Differential Effects of nAChR Ligands

As can be observed in Table 1, compounds referred to as nAChR agonists or partial agonists can have what appears to be quite diverse behavioral and/or physiologic effects. Some of the apparent differences may simply be due to the fact that a particular compound in question has not yet been evaluated across all of the relevant types of tasks or procedures. There are a host of other factors, however, that could contribute to real differences in responses in vivo [188, 189]. The potency and efficacy of a compound at a nAChR composed of specific subunits is important since nAChR subtypes show distinct anatomical localization and they can display markedly diverse physiological and pharmacological properties [190]. Responses secondary to the activation (or inhibition) of specific nAChRs including effects on the release of neurotransmitters and hormones may also contribute to differential responses [191]. The unique pharmacokinetic properties of a nicotinic compound, whether it generates active metabolites in vivo, and whether it has been administered acutely or chronically may also be important. As an example, nicotine has a short half-life in mammals; however, it generates a metabolite (cotinine) that has a long half-life that has been shown to have important electrophysiological and behavioral effects [177]. Another factor that may be important is how effective a particular nAChR agonist is at desensitizing nAChRs. Interestingly, previous work has indicated that desensitization of nAChRs may in fact be an important component of a compounds efficacy as a pro-cognitive agent [47]. Another important factor (noted above in section 6) is whether the compound has activity at receptors for neurotransmitters other than acetylcholine such as

serotonin 5-HT₃, as is the case for many compounds that also have activity at $\alpha 7$ nAChRs (e.g., tropisetron [78]).

11. Summary and Conclusions

The currently available treatments for neurologic and psychiatric illness such as AD and schizophrenia remain inadequate despite the decades of research devoted to novel drug discovery and development. While the original intent of developing nAChR ligands for neuropsychiatric disorders may have followed the traditional reductionist approach (e.g., the creation of selective ligands at specific nAChR subtypes for the treatment of cognitive deficits) in neuropsychiatric disorders, there is now considerable evidence that a number of these compounds may exhibit additional features that would qualify them as “multifunctional” agents. By possessing pro-cognitive as well as antipsychotic-like activity and/or neuroprotective actions, some of these agents may have the potential to not only treat several key symptoms of neuropsychiatric disorders, but they could also have potential to modify the disease outcome. Other studies suggest that nicotinic PAMs might be effective either alone or as adjunctive agents to be combined with currently available treatments to enhance therapeutic efficacy. Finally, there is considerable evidence to suggest that the clinically available nAChR ligands, nicotine and varenicline could be repurposed for several indications beyond smoking cessation.

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Figure Legends

Fig 1. Diagram illustrating potential “multifunctional” activities (e.g., pro-cognitive, antipsychotic-like, and neuroprotective effects) of ligands of the heteromeric, high affinity $\alpha 4\beta 2$ nAChR and the homomeric, low affinity $\alpha 7$ nAChR. These subtypes are the two most abundant nAChRs found in the mammalian brain. Both receptors consist of five subunits arranged around a central channel that opens when endogenous ligands such as acetylcholine (ACh) or exogenous ligands (nicotine) bind at the orthosteric site allowing cations to flow through the channel into the neuron causing depolarization. Allosteric sites are the target of positive allosteric modulators (PAMs) and they are located at a site which is distinct from the orthosteric where they serve to indirectly influence (modulate) the effects of the agonist. The $\alpha 7$ nAChR is composed of five $\alpha 7$ subunits and the $\alpha 4\beta 2$ nAChR is composed of two $\alpha 4$ subunits and three $\beta 2$ subunits. The $\alpha 4\beta 2$ nAChR allows passage of both calcium (Ca^{++}) and sodium (Na^{+}) ions, whereas the $\alpha 7$ nAChR principally allows passage of calcium ions. In neurons, most $\alpha 4\beta 2$ and $\alpha 7$ nAChRs are found at presynaptic sites, however they can be also found at both postsynaptic, perisynaptic and somatodendritic sites. Moreover, both subtypes can be found on cholinergic, dopaminergic, noradrenergic, GABAergic, glutamatergic, and other neuronal phenotypes [191, 192, 193, 194].

Table 1. Representative nAChR Ligands with Multifunctional Activity					
Compound Name	nAChR subtype	Receptor Effect	Cognitive Domain Enhanced	Additional Properties	References
ABT-418	$\alpha 4\beta 2$	agonist	attention, working memory, spatial learning, associative learning	Analgesic, Neuroprotective (glutamate excitotoxicity)	49, 54, 57, 155
ABT-594	$\alpha 4\beta 2$	agonist	attention, working memory	analgesic	82, 158, 159
ABT-894	$\alpha 4\beta 2$	agonist	attention, executive function	analgesic	94, 160
AZD 1446 (TC-8863)	$\alpha 4\beta 2$	agonist	attention, working memory, spatial learning/memory		161, 162
SIB-1508Y	$\alpha 4\beta 2$	agonist	attention, short-term memory , working memory	Antidepressant	55, 58
Sazetidine-A	$\alpha 4\beta 2$	agonist, 'silent desensitizer'	attention	analgesic, antidepressant	178, 179, 180
NS9283	$\alpha 4\beta 2$	PAM	attention, social recognition, spatial reference memory	Sensorimotor gating	130
AZD-3480 (TC-1734)	$\alpha 4\beta 2$	partial agonist	attention, episodic memory, working memory and executive function	neuroprotective (glutamate), antidepressant	181, 182
Varenicline	$\alpha 4\beta 2$	partial agonist (+ $\alpha 7$ agonist)	attention, recognition memory, working memory		69, 151
ABT-107	$\alpha 7$	agonist	attention, episodic, working and recognition memory, executive function	Neuroprotective (6-OHDA lesion model), sensory gating	21, 22, 164
AR-R1779	$\alpha 7$	agonist	working memory, social recognition,		51, 56, 165
GTS-21 (DMXBA)	$\alpha 7$	partial agonist (+ weak $\alpha 4\beta 2$ antagonist)	associative learning, working memory, recognition memory	P50 sensory gating	23, 47, 109

SEN-12333	$\alpha 7$	agonist	attention, episodic, object and memory, executive function	Neuroprotective (quisqualate lesion model), Sensorimotor gating (PPI)	112
Tropisetron	$\alpha 7$	partial agonist (+ 5HT3 antagonist)	attention, recognition memory, spatial learning	Sensorimotor gating (PPI)	88, 102, 103, 111, 166, 167, 168
EVP-6124	$\alpha 7$	partial agonist (+ 5HT3 antagonist)	attention, episodic memory, working memory and executive function		66
TC-5619	$\alpha 7$	agonist	attention, recognition memory, executive function	Sensorimotor gating (PPI)	64, 124
RG 3487	$\alpha 7$	partial agonist (+ 5HT3 antagonist)	attention, spatial learning, episodic, recognition and working memory, executive function	Sensorimotor gating (PPI)	67
JNJ-39393406	$\alpha 7$	mixed Type I & II PAM	attention, recognition memory, executive function	sensory gating	148
AVL-3288	$\alpha 7$	Type I PAM	episodic recognition memory, working memory and executive function	Neuroprotective (glutamate excitotoxicity, amyloid- β), Sensory gating	137
Galantamine	$\alpha 7$	Type I PAM + AChEI	attention, recognition memory, cognitive flexibility, spatial learning	Sensorimotor gating (PPI)	138, 169, 170, 171
Genistein	$\alpha 7$	Type I PAM	associative learning	neuroprotective (3-Nitropropionic acid model)	171, 174
NS1738	$\alpha 7$	Type I PAM	recognition memory, spatial learning, working memory and executive function		136, 171
PNU 120596	$\alpha 7$	Type II PAM	recognition memory, spatial learning, working memory, cognitive flexibility	Sensory gating	138, 141, 146

Cotinine	$\alpha 7$	sensitizer	attention, recognition memory, working memory, executive function	Neuroprotective (amyloid), Sensorimotor gating (PPI)	41, 42, 43, 46, 175, 176, 177
Nicotine	$\alpha 4\beta 2 + \alpha 7$	agonist	attention, working memory, recognition memory	Neuroprotective (amyloid), Sensorimotor gating (PPI)	25, 26, 27, 28, 29, 30, 36, 183
ABT-089	$\alpha 4\beta 2 + \alpha 6\beta 2$	$\alpha 4\beta 2$ agonist + $\alpha 6\beta 2$ partial agonist	attention, episodic memory, working memory, spatial learning, executive function	Neuroprotective (glutamate excitotoxicity)	38, 172, 173