Neuropharmacology 170 (2020) 108053

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited Review

α7 nicotinic acetylcholine receptors as therapeutic targets in schizophrenia: Update on animal and clinical studies and strategies for the future

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HIGHLIGHTS

- Cognitive impairment is a core feature of schizophrenia that is debilitating.
- Currently, there are no clinically effective treatments for these impairments.
- α7-nAChRs are considered viable therapeutic targets for cognition in schizophrenia.
- However, to date no α7-nAChR ligand has been approved for schizophrenia.
- This review discusses the relevant α7-nAChR literature and future directions.

ARTICLE INFO

Keywords:
Cholinergic
Pro-cognitive
Psychosis
Cognition
Executive function
Attention

ABSTRACT

Schizophrenia is a devastating mental illness and its effective treatment is among the most challenging issues in psychiatry. The symptoms of schizophrenia are heterogeneous ranging from positive symptoms (e.g., delusions, hallucinations) to negative symptoms (e.g., anhedonia, social withdrawal) to cognitive dysfunction. Antipsychotics are effective at ameliorating positive symptoms in some patients; however, they are not reliably effective at improving the negative symptoms or cognitive impairments. The inability to address the cognitive impairments is a particular concern since they have the greatest long-term impact on functional outcomes. While decades of research have been devoted to the development of pro-cognitive agents for schizophrenia, to date, no drug has been approved for clinical use. Converging behavioral, neurobiological, and genetic evidence led to the identification of the α7-nicotinic acetylcholine receptor (α7-nAChR) as a therapeutic target several years ago and there is now extensive preclinical evidence that α7-nAChR ligands have pro-cognitive effects and other properties that should be beneficial to schizophrenia patients. However, like the other pro-cognitive strategies, no α7-nAChR ligand has been approved for clinical use in schizophrenia thus far. In this review, several topics are discussed that may impact the success of α7-nAChR ligands as pro-cognitive agents for schizophrenia including the translational value of the animal models used, clinical trial design limitations, confounding effects of polypharmacy, dose-effect relationships, and chronic versus intermittent dosing considerations. Determining the most optimal pharmacologic strategy at α7-nAChRs: agonist, positive allosteric modulator, or potentially even receptor antagonist is also discussed.

article is part of the special issue on 'Contemporary Advances in Nicotine Neuropharmacology'.

1. Introduction

Schizophrenia is a debilitating mental illness characterized by positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., depressed mood, anhedonia, social withdrawal) and cognitive impairments (e.g., deficits in information processing, attention, working memory, executive function, Green and Braff, 2001). Among these diverse symptoms, cognitive impairment is a core feature of schizophrenia that often appears prior to the onset of psychotic symptoms, it persists throughout the course of the illness, and it has the greatest long-term impact on functional outcomes (reviewed, Kahn and Keefe, 2013; Green and Harvey, 2014, Kahn, 2019). Unfortunately, the most commonly prescribed treatments for schizophrenia, the antipsychotics, while effective at improving positive symptoms in some

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https://doi.org/10.1016/j.neuropharm.2020.108053
Received 22 January 2020; Received in revised form 10 March 2020; Accepted 11 March 2020
Available online 15 March 2020
0028-3908/

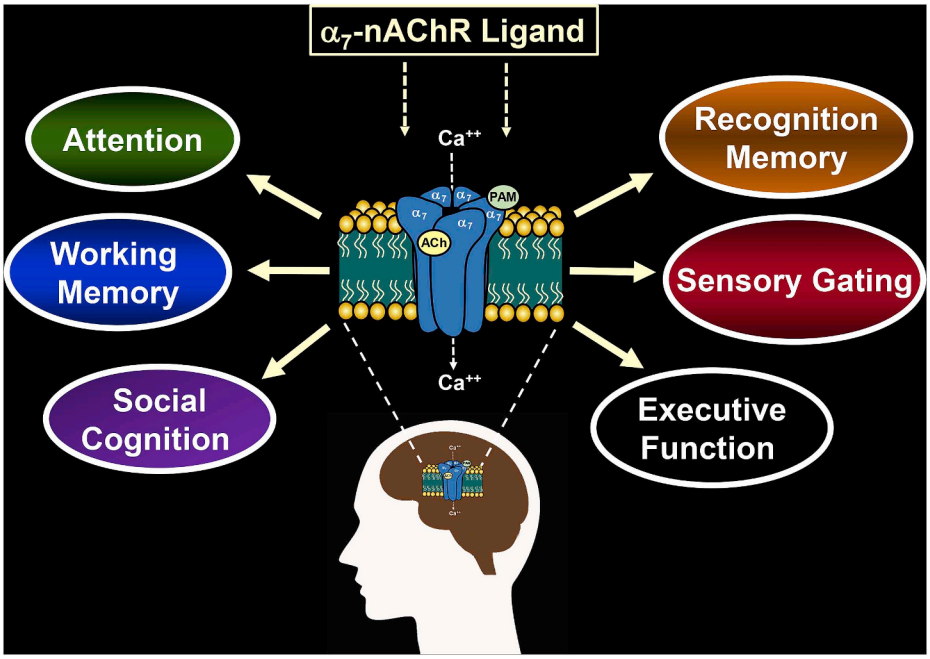

Fig. 1. Diagram illustrating several domains of cognition and other behaviors often targeted in drug discovery programs for schizophrenia and other neuropsychiatric disorders. The homomeric, low affinity α7-nicotinic acetylcholine receptor (α7-nAChR) is abundant in regions of the brain (e.g., hippocampus, prefrontal cortex) that are important for cognitive function. The receptor consists of five subunits arranged around a central channel that opens when endogenous ligands such as acetylcholine or exogenous ligands (nicotine) bind at the orthosteric site allowing cations (e.g., Ca^{++}) 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.

patients, are not reliably effective at improving cognitive function. This unmet medical need has been an important focus of drug discovery efforts in both academia and the pharmaceutical industry for several decades; however, to date no pro-cognitive agent has been approved for clinical use in schizophrenia.

A key challenge to developing novel treatments for the cognitive dysfunction in schizophrenia is the complex and poorly understood etiology and pathophysiology of the illness. Multiple neurotransmitter systems have been implicated in the illness (Goff and Wine, 1997; Kapur and Mamo, 2003) including dopaminergic, serotoninergic, glutamatergic, adrenergic, and cholinergic pathways and accordingly, new compounds designed to target these various systems have been developed and evaluated. Cholinergic targets, particularly nicotinic acetylcholine receptors (nAChRs) have been a focus of a number of drug discovery programs over the last 20–25 years based on multiple lines of behavioral, neurobiological, and genetic evidence. From the behavioral perspective, a remarkable observation in schizophrenic patients is their especially heavy abuse of tobacco products. According to the National Institute on Drug Abuse (NIDA, 2020) tobacco smoking rates in schizophrenia patients range as high as 70–85%, which is dramatically higher than the general population (~19–20%) and significantly higher than in any other mental illness (George and Krystal, 2000). Smokers with schizophrenia have also been documented to extract more nicotine per cigarette and to smoke a higher number of cigarettes per day compared to smokers in the general population (Olincy et al., 1997; Strand and Nybäck, 2005). It has been suggested that this high level of nicotine consumption may represent an attempt of schizophrenia patients to self-medicate the cognitive symptoms, particularly deficits of information processing and attention (Olincy et al., 1997; Leonard et al., 2007).

2. Focus on α7-nAChRs

In drug discovery programs for neuropsychiatric illnesses, the heteromeric α4β2 and homomeric α7-nAChRs have been the most commonly targeted nAChR subtypes to date since they are the most predominant subtypes found in the mammalian brain. However, the α7-nAChR has been more commonly targeted for the cognitive deficits in schizophrenia. This is likely based, in part, on several factors including postmortem evidence of α7-nAChR deficits in the frontal cortex and hippocampus of schizophrenic patients (Guan et al., 1999) and linkage analysis implicating chromosome 15q14 (the region that includes the α7-nAChR gene). Polymorphisms in the core promoter of the α7-nAChR gene (CHRNA7; GeneBank accession no. Z23141) have been associated with reduced inhibition of the P50 evoked response to repeated auditory stimuli in schizophrenic patients, which is indicative of sensory gating abnormalities (reviewed, Freedman et al., 2003). α7-nAChR deficits may also contribute to abnormalities of smooth pursuit eye movements, sustained attention, and other domains of cognition in schizophrenia (reviewed Martin et al., 2004). In addition to schizophrenia, the CHRNA7 gene is also linked to multiple disorders where cognitive deficits are present including bipolar disorder, autism spectrum disorders, attention deficit hyperactivity disorder, Alzheimer disease, epilepsy, and sensory processing deficits (reviewed in Corradi and Bouzat, 2016).

The information in the paragraph above regarding the importance of α7-nAChR as a potential therapeutic target for the cognitive defects in schizophrenia is also supported by extensive preclinical evidence. From a neurobiological and neuropharmacological perspective, α7-nAChRs modulate multiple (cognition-related) processes in neurons that are calcium-dependent including neurotransmitter release (McGehee et al., 1995; Gray et al., 1996), postsynaptic signaling (Chang and Berg, 1999; Hefft et al., 1999) and neuronal survival (Messi et al., 1997; Berger et al., 1998). Moreover, α7-nAChRs are also abundant in regions of the brain that are important for learning and memory and executive function such as the hippocampus and prefrontal cortex (Gotti et al., 2007). In addition, agonists of α7-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 (Bitner et al., 2007, 2010). There is also extensive evidence that α7-nAChR ligands improve behavioral processes that are relevant to schizophrenia (see Fig. 1) such as auditory-evoked gating and prepulse inhibition in rodents, as well as multiple domains of cognition including attention, working memory, reference memory, social cognition, and executive function in rodent models as well as non-human primates (see reviews, Young and Geyer, 2013; Freedman, 2014; Bertrand and Terry, 2018). Table 1 provides a list of representative α7-nAChRs ligands that have been developed as pro-cognitive agents for potential use in schizophrenia and other disorders of cognition. Although not all-inclusive, Table 1 includes α7-nAChR

Table 1
In vivo Pharmacological Effects of α7-nAChR Ligands.

Compound Name	α7 nAChR activity & other actions	Cognitive Domain Enhanced	Additional Behavioral Improvements	References
ABBF	α7 full agonist & 5-HT3 antagonist	object and social recognition, working memory		Boess et al. (2007)
ABT-107	α7 full agonist	attention, working memory, social recognition	auditory gating	Bitner et al. (2010); Bordia et al. (2015); Radek et al. (2012)
A-582941	α7 full agonist	working memory, social recognition, inhibitory avoidance	sensory gating	Tietje et al. (2008)
AQW051	α7 partial agonist	object and social recognition, spatial reference memory		Feuerbach et al. (2015)
AVL-3288 (Compound 6, CCMI or XY4083)	α7 Type I PAM	object recognition, social recognition, working memory, executive function	auditory gating, conditioned avoidance responding	Ng et al. (2007); Nikiforuk et al. (2015)
BMS-933043	α7 partial agonist	object recognition, working memory, executive function	auditory gating	Bristow et al. (2016)
BMS-902483	α7 partial agonist & 5-HT3 antagonist	object recognition, executive function	auditory gating	Pieschl et al. (2017)
Compound 7z	α7 Type I PAM	object recognition		Hogenkamp et al. (2013)
DMXB-A (GTS-21)	α7 partial agonist & 5-HT3 antagonist	attention, object recognition, spatial reference memory, working memory	sensorimotor gating	Meyer et al. (1997); Callahan et al. (2014); Jones et al. (2014)
EVP-6124 (encenicline)	α7 partial agonist & 5-HT3 antagonist	object recognition		Prickaerts et al. (2012)
EVP-5141	α7 full agonist & 5-HT3 antagonist	object and social recognition, working memory		Boess et al. (2013)
JNJ-39393406	α7 Type I, Type II PAM	object recognition, executive function	auditory gating	Winterer et al. (2013)
Lu AF58801	α7 Type I PAM	object recognition		Eskildsen et al. (2014)
NS1738	α7 Type I PAM	object and social recognition, spatial reference memory		Marcus et al. (2016); Timmermann et al. (2007)
PAM-2	α7 Type II PAM	object recognition, executive function	social interaction model	Potasiewicz et al. (2017)
PNU 120596	α7 Type II PAM	recognition memory, spatial learning, working memory, executive function	auditory gating	Dunlop et al. (2009); Nikiforuk et al. (2015); Stevens et al. (2015)
PNU-282987	α7 full agonist	recognition memory	conditioned avoidance responding	McLean et al. (2016); Marcus et al. (2016)
RG 3487	α7 partial agonist & 5-HT3 antagonist	attention, object recognition, spatial reference memory, executive function	sensorimotor gating	Wallace et al. (2011)
SEN-12333	α7 full agonist & histamine H3 antagonist	object recognition	sensorimotor gating	Roncarati et al. (2009)
SSR-180711	α7 partial agonist	recognition memory, working memory, novelty discrimination	latent inhibition	Pichat et al. (2007); Barak et al. (2009)
TC-5619	α7 full agonist	object recognition	sensorimotor gating	Hauser et al. (2009)
Tropisetron	α7 partial agonist & 5-HT3 antagonist	attention, object recognition, working memory, spatial reference memory	sensorimotor gating	Callahan et al. (2017); Hashimoto et al. (2005), 2006; Kohnomi et al. (2010); Pitsikas and Borsini, 1997

Table 2
α7-nAChR ligands that have been evaluated in human clinical trials for pro-cognitive effects.

Compound Name	α7 nAChR activity & other actions	Clinical Stage	Clinical Endpoints	References
ABT-126	Partial agonist	Phase II	Cognition, Negative Symptomology	Haig et al., 2016a,b; Haig et al. (2018)
AQW051	Partial agonist	Phase II	Cognition, fMRI Brain Activation	Barch et al. (2016)
AVL-3288	PAM	Phase Ib	Cognition, Auditory Sensory Gating, Negative Symptomology	Gee et al. (2017); Kantrowitz et al. (2020)
Cytidine 5′-diphosphocholine (CDP-choline)	Full agonist	Phase II	Cognition, Auditory Sensory Gating	Knott et al., 2015a,b; Aidelbaum et al. (2018); Choueiry et al. (2019)
DMXB-A (GTS-21)	Partial agonist	Phase II	Cognition, Auditory Sensory Gating, Negative Symptomology	Olincy et al. (2006); Freedman et al. (2008)
Encenicline (EVP-6124)	Partial agonist/5-HT3 antagonist	Phase III	Cognition, Negative Symptomology	Keefe et al. (2015)
Galantamine	PAM/acetylcholinesterase inhibitor	Phase II	Cognition, Auditory Sensory Gating, Negative Symptomology	Choueiry et al. (2019); Buchanan et al. (2017)
JNJ-39393406	PAM	Phase Ib	Cognition, Auditory Sensory Gating, Smoking Cessation	Winterer et al. (2013); Perkins et al. (2018)
RG3487	Partial agonist/5-HT3 antagonist	Phase II	Cognition, Negative Symptomology	Umbricht et al. (2014)
Tropisetron	Partial agonist/5-HT3 antagonist	Phase II	Cognition, Auditory Sensory Gating, Negative Symptomology	Shiina et al. (2010); Zhang et al. (2012); Noroozian et al. (2013)
TC-5619	Full agonist	Phase II	Cognition, Negative Symptomology	Lieberman et al. (2013)

agonists, partial agonists, and positive allosteric modulators (PAMs), a summary of some of the positive behavioral properties associated with each compound, and representative references.

3. Clinical trial failures

Despite extensive preclinical evidence to support the pro-cognitive effects of α7-nAChR ligands noted above (and summarized in Table 1) and positive results in some early (Phase I and II) clinical trials, to date, no compound has met the primary objective of cognitive improvement in schizophrenic patients in a large phase III, double blind, placebo controlled clinical trial or unanticipated side effects emerged (see review, Tregellas and Wylie, 2019). The failure of pro-cognitive agents in schizophrenia clinical trials have reduced the enthusiasm of pharmaceutical companies and, unfortunately, many have abandoned this line of research. While it is possible that the lack of robust (pro-cognitive) efficacy or side effect burden may represent real limitations of α7-nAChR ligands, it should be noted, that given the number of compounds that have been developed, only one agent have been evaluated in a large scale Phase III clinical trial in schizophrenia patients (Encenicline-EVP-6124, see Table 2). Moreover, there is an increasing amount of discussion about possible limitations of both the preclinical and clinical studies conducted to date that may have resulted in the so-called "treatment failures" of pro-cognitive agents. Some of these potential limitations are listed in Table 3. See also several recent reviews (Bertrand and Terry, 2018; Terry and Callahan, 2019; Tregellas and Wylie, 2019) on this subject.

4. Translational gaps and overreliance on rodent models

The unfavorable results of clinical trials for pro-cognitive agents in schizophrenia described above have led to questions about the "translational validity" of animal models used in preclinical studies (see Lewis et al., 2018). In drug discovery research for schizophrenia and other neuropsychiatric disorders, addressing the translational elements, face, construct, and predictive validity in animal models is particularly challenging. In this context, multiple challenges include the subjective nature of many of the human symptoms, the lack of biomarkers and objective diagnostic tests, and our relatively poor understanding of the neurobiology and genetics of neuropsychiatric disorders (see review Nestler and Hyman, 2010; Monteggia et al., 2018). One of the goals of the Research Domain Criteria (RDoC) paradigm launched in 2010 by the National Institute of Mental Health (NIMH) was to improve translation between animal experiments and clinical studies in psychiatry research. The basic concept in the preclinical realm was to encourage basic scientists to identify molecular or neural mechanisms (or neural circuitry) that contributes to specific domains of a mental function rather than creating animal models of diseases. In the clinical realm, researchers were encouraged to conceptualize normal human behavior, emotion, and cognition as dimensional, with mental illnesses as dimensional extremes as opposed to being restricted by DSM diagnostic categories (see Morris and Cuthbert, 2012; Ross and Margolis, 2019). However, more that 10 years after the introduction of the RDoC paradigm, it is unclear if it has improved research progress in psychiatry especially in the drug discovery arena and its clinical relevance is increasingly being questioned (see Carpenter, 2016; Ross and Margolis, 2019).

Regarding translational validity, rodent models are undoubtedly important in basic research for testing disease-related hypotheses and the early evaluations of novel therapeutic agents, however, it is likely they have been relied upon too much in neuropsychiatric drug discovery especially at the later preclinical stages of drug development. Compared to humans, the behavioral repertoire of rodents is quite limited and, while debated (see, Laubach et al., 2018), there are major anatomical differences in their brains, most notably, the development of cortical regions of the forebrain, particularly the dorsolateral

Table 3
Limitations of Preclinical and Clinical Studies of pro-cognitive agents to date.

Preclinical	Clinical
Translational challenges due to the poor understanding of the etiology and pathophysiology of schizophrenia	Studies often underpowered due to the inclusion of cognitively "normal" patients
Overreliance on rodent models	Polypharmacy and drug exposure history not properly addressed
Overreliance on acute dose-effect analyses	Unanticipated practice effects masking a positive outcomes
Pro-cognitive agents not evaluated in test subjects that have been chronically treated with antipsychotic.	Chronicity of the illness not taken into account. Recently diagnosed and first episode patients should be evaluated.
Pro-cognitive agents not evaluated in test subjects that have been chronically treated with nicotine or nicotine plus antipsychotics	Inclusion of inexperienced trial sites and focus on volume of patients enrolled as opposed to the quality of the recruitment sites

prefrontal cortex (DLPFC). This portion of the brain of humans and more advanced non-human primates (e.g., macaques) has been implicated specifically in the most complex cognitive processes such as working memory, sustained attention, decision taking, and executive function (reviewed, Barbey et al., 2013).

Regarding, α7-nAChRs, there are also significant differences in the genetics, pharmacology, biophysical properties, and neuronal localization of α7-nAChRs between rodents and humans that could underlie different outcomes in preclinical and clinical trial evaluations of α7-nAChRs ligands (reviewed Bertrand and Terry, 2018). From a genetics standpoint, the recent findings of Yin et al. (2017) are particularly notable. In humans with 15q13.3 microdeletion syndrome, caused by heterozygous deletions involving the CHRNA7 gene, behavioral abnormalities often observed in neuropsychiatric conditions such as schizophrenia and autism were observed, whereas Chrna7 knockout mice did not exhibit similar neurobehavioral phenotypes. From a pharmacological perspective, the effects of specific agonists in vitro differ between human and rodent sequences coding for α7-nAChRs. For example, the partial agonist DMXB-A (GTS-21) activates the rat α7-nAChR to a maximal response greater than twice that of the human α7-nAChR, and the Ki of GTS-21 at the rat receptor is roughly an order of magnitude less than at the human receptor (Meyer et al., 1998), suggesting that similar serum levels might have disparate effects between the species. Finally, differences in the synaptic receptor expression between rodents and humans may be relevant as suggested by a recent study in nonhuman primates where postsynaptic localization of α7-nAChRs on spines were demonstrated in glutamatergic synapses of layer III dorsolateral prefrontal cortex (Yang et al., 2013). Most physiological studies in rodent frontal cortex, in contrast, have demonstrated presynaptic α7-nAChR actions and it has been suggested that spine α7-nAChRs are not prevalent or only have subtle effects on neuronal physiology in rodents compared to primates. Collectively, the information discussed here would appear to justify a renewed interest in the use of nonhuman primate species (see Monteggia et al., 2018) in neuropsychiatry and drug discovery research, given their richer behavioral repertoire and more homologous brain anatomy with humans compared to rodents.

5. Polypharmacy and drug exposure history

In both preclinical and clinical evaluations of α7-nAChR ligands, it is uncommon for the subject of polypharmacy and chronic antipsychotic drug history to be adequately addressed. Clearly, there are practical limitations in clinical trials, but the patient's treatment history (which in many cases consists of multiple years of antipsychotic treatment) should be more carefully considered, not just concomitant antipsychotic treatment at the time of the clinical trial. Antipsychotics are well documented to have a variety of chronic effects on the mammalian brain including alterations of neurotransmitter receptor expression and neural plasticity (reviewed, Morrison and Murray, 2018), i.e., effects that could influence the response to a novel α7-nAChR ligand. Interestingly, guidelines related to polypharmacy and concomitant drug exposure have been developed for studies designed to evaluate potential pro-cognitive agents in schizophrenia trials. For example, a workshop on clinical trial design for evaluating cognitive enhancing drugs for schizophrenia was held in 2004 and it included experts from the FDA, NIMH, and scientists from academia and the pharmaceutical industry (see Buchanan et al., 2005). Among the various guidelines developed, it was recommended that polypharmacy (treatment with multiple antipsychotics) and combining a putative cognitive-enhancing agent with an antipsychotic with high affinity for the targeted receptor be avoided. However, it is unclear how closely such policies have been followed.

In preclinical evaluations of potential pro-cognitive agents for potential use in schizophrenia, the concomitant administration of antipsychotics has only rarely been done and when it has, the antipsychotic has most commonly been administered acutely (e.g., Marquis et al., 2011). We recently conducted a series of experiments in rats where the α7-nAChR partial agonist tropisetron was administered to rats that had been exposed to either risperidone or quetiapine for 30 or 90 days then tested them in a novel object recognition task (Poddar et al., 2018). Tropisetron markedly improved NOR performance in rats treated with either antipsychotic for 30 or 90 days indicating that in this particular case, the antipsychotic treatment history did not interfere with the pro-cognitive effect of tropisetron. Thus, α7-nAChR ligands like tropisetron may have potential as adjunctive medications in schizophrenia since the pro-cognitive effect was maintained in the presence of chronic antipsychotic treatment. However, in this study, tropisetron was administered acutely and future studies would need to be conducted to determine if this pro-cognitive effect of tropisetron is lasting.

Other factors related to polypharmacy and drug exposure history that have not been adequately addressed are how chronic nicotine exposure or the combination of chronic nicotine exposure and antipsychotic treatment might affect the efficacy of a pro-cognitive agent. Given the well-documented chronic effects of nicotine on nAChR expression (see Lewis and Picciotto, 2013 for review), and the aforementioned high smoking rates in schizophrenia, this could certainly be an important consideration when evaluating an α7-nAChR ligand for pro-cognitive effects. Levin and colleagues (see review, Levin and Rezvani, 2007) have performed some experiments in rodents to investigate nicotinic interactions with antipsychotic drugs and cognitive function. For example, they have shown that nicotine and some nicotine agonists can reduce cognitive impairments caused by some antipsychotic drugs. In other studies, they have shown that nicotine-induced cognitive improvements were attenuated by the some antipsychotics (e.g., clozapine). However, the specific questions raised above (i.e., how chronic nicotine exposure or the combination of chronic nicotine exposure and antipsychotic treatment might affect the efficacy of a pro-cognitive agent including an α7-nAChR ligand) have not been rigorously investigated either in animal models or in clinical studies.

6. Pro-cognitive drug dose, frequency of administration, and duration of treatment

Another potential limitation of many clinical studies conducted to

date to evaluate novel pro-cognitive agents was the choice of dose, the frequency of administration, and the duration of treatment. Most of the rodent studies (where robust cognitive effects were observed) have employed acute or sub-acute dosing of α7-nAChR ligands, which contrasts with most of the clinical trials that were conducted over several weeks or months. All neuronal nAChRs (including α7-nAChRs) become temporarily inactive after prolonged exposure to an agonist (Quick and Lester, 2002), thus the repeated administration of α7-nAChR agonists in the clinical studies may have resulted in receptor desensitization, or potentially even functional antagonism. To support this argument are the disparate effects of the immediate and slow-release versions of DMXB-A (GTS-21) observed in clinical trials. Whereas, the immediate release formulation (which was rapidly absorbed, but quickly cleared) improved cognition and P50 sensory gating in schizophrenic patients, the slow-release version was not effective (Olincy et al., 2006; Freedman et al., 2008; Kem et al., 2018). Another emerging hypothesis is that low concentrations of α7-nAChR ligands may be more effective than higher concentrations, as the latter will maintain receptors in a desensitized and unresponsive state (see Tregellas and Wylie, 2019). In many of the more recent animal studies, the greatest response to a nAChR agonist was observed with a low drug dose and increasing the dose often produced a decreasing effect, in an inverted U-shaped response curve, which is thought to be due to receptor desensitization. A particularly notable example was a non-human primate study where, a low dose of an α7-nAChR agonist (PHA543613) facilitated neuronal activity in the prefrontal cortex and improved performance of a spatial working memory task, whereas higher doses were not effective (Yang et al., 2013).

The ability to select the proper dose and frequency of administration of an α7-nAChR ligand for optimal target engagement could possibly be improved if functional biomarkers were identified for use in both preclinical and clinical studies. Noninvasive neuroimaging methods such as functional magnetic resonance imaging (fMRI) may be able to facilitate the identification of biomarkers since they can be used to investigate neural circuitry alterations that underlie symptoms of schizophrenia as well as how medications affect this neural circuitry. Here, a biomarker that can be linked to a disease mechanism is categorized as a type I biomarker and a biomarker that can be linked to a treatment response is categorized as a type II biomarker (see Wylie et al., 2016 for review). Interestingly, Tregellas and colleagues, using fMRI, linked hippocampal hyperactivity to smooth pursuit eye movement (SPEM) deficits in schizophrenia patients. The findings revealed a link between eye-tracking abnormalities and a hypothesized disease mechanism, thereby potentially qualifying hippocampal hyperactivity during SPEM as a type I biomarker. Additional studies in schizophrenia patients demonstrated that nicotine and the α7-nAChR partial agonist DMXB-A could normalize hippocampal hyperactivity during SPEM, suggesting that SPEM during fMRI could also represent a potential type II biomarker of treatment response (see Wylie et al., 2016; Tregellas and Wylie, 2019). In summary, while the use of fMRI for the development of biomarkers for schizophrenia and other neuropsychiatric disorders is in the early stages, it has the potential to facilitate drug development by improving the translation from animal models to the clinical realm as well to inform investigators as to the best dosing strategies to optimize target engagement.

7. Optimizing α7-nAChR activity

A large-scale effort to overcome the challenges related to nAChR desensitization and the administration of orthosteric agonists and partial agonists has been the development of positive allosteric modulators (PAMs). PAMs are thought to bind to sites that are distinct from the well-conserved (orthosteric) agonist binding domains and they require the presence of the endogenous ligand to increase receptor activity. Two date, two types of PAMs have been developed, designated Type I and Type II. Type I PAMs are defined as molecules that predominately affect the apparent peak current, agonist sensitivity, and Hill coefficient, but not the receptor desensitization profile. Type II PAMs possess the aforementioned properties described for Type I PAMs as well as the ability to modify the desensitization profile of agonist responses (see Bertrand and Gopalakrishnan, 2007). It has been argued that Type II PAMs (compared to Type I PAMs) are less likely to induce tolerance, which may occur after the chronic administration of nAChR agonists, whereas, Type I PAMs, may have the advantage (compared to Type II PAMs) of minimizing the potential for calcium induced cytotoxicity (Ng et al., 2007, see also Nikiforuk et al., 2015). A large number of PAMs from both classes have been developed with pro-cognitive properties in animal models (see Table 1); however, to date only a few clinical trials have been conducted (or are underway) with α7-nAChR PAMs (i.e., AVL-3288, galantamine, JNJ-39393406).

Finally, the classical view that nAChR stimulation is the key action responsible for the pro-cognitive effects of α7-nAChRs ligands may require additional consideration given the observations that low doses of the selective α7-nAChR antagonist methyllycaconitine (MLA) can (in some cases) improve cognition in animal models (Hahn et al., 2011; Burke et al., 2014). and facilitate LTP induction in hippocampal region CA1 in rats (Fujii et al., 2000). More recently, low concentrations/doses of MLA exerted surprising (positive) effects in several model systems. Specifically, in electrophysiological experiments, low concentrations of MLA potentiated receptor responses to acetylcholine in human α7-nAChR-transfected oocytes, enhanced long term potentiation (LTP) in rat hippocampal slices, increased hippocampal glutamate efflux in microdialysis experiments in rats, and improved the acquisition of a novel object recognition task in rats (van Goethem et al., 2019). Interestingly, the nonselective nAChR antagonist mecamylamine (in some cases) has also been found to exert pro-cognitive effects in working memory tasks in both rodents and monkeys as well as a recognition memory task in humans with attention deficit hyperactivity disorder (ADHD). For details of these studies, see Buccafusco et al. (2009); Bertrand and Terry (2018).

8. Additional clinical trial design issues

There is growing evidence that schizophrenia patients whose cognitive performance is comparable to healthy controls (i.e., up to 25% of patients) may not benefit from pro-cognitive agents (Granger et al., 2018; DeTore et al., 2019). Therefore, the inclusion of such individuals in a clinical trial designed to determine a compound's pro-cognitive efficacy may limit the power of the study. Unfortunately, a recent analysis of 87 randomized, double-blind, placebo-controlled, clinical trials listed on ClinicalTrials.gov indicated that the vast majority of such clinical trials may have been underpowered due to the inclusion of cognitively “normal” patients (Cotter et al., 2019).

The argument that pro-cognitive strategies (specifically α7-nAChR-based approaches) should target subgroups of individuals who exhibit lower levels of cognitive function is supported by recent clinical studies with the selective α7-nAChR agonist CDP-choline in both healthy subjects and patients with schizophrenia. In healthy study participants showing relatively lower cognitive and sensory gating scores at baseline, CDP-choline was found to enhance multiple domains of cognition (Knott et al., 2015a, 2015b) and to improve sensory gating (Knott et al., 2014b). The same laboratory also reported CDP-choline-mediated improvements of P50 sensory gating scores in schizophrenia patients who exhibited impaired gating (Aidelbaum et al., 2018). They also demonstrated that combining CDP-choline with galantamine (an acetylcholinesterase inhibitor and nAChR PAM) improved sensory gating to speech stimuli in schizophrenia patients who expressed low baseline suppression (Choueiry et al., 2019).

Another factor that may be important to consider in the evaluation of pro-cognitive agents in schizophrenia is the chronicity of the illness. The duration of the disease and the efficacy of antipsychotics has been the subject of several reviews (e.g., Leucht et al., 2008), but the concept

could also certainly apply to pro-cognitive drug evaluations. Most participants in antipsychotic clinical trials have been chronically ill having experienced multiple episodes and hospitalizations. While these patients may represent the "typical" cases of schizophrenia, there is increasing interest in the effects of medications on patients who have been recently diagnosed (e.g., first episode patients). As reviewed by Leucht et al. (2008), there are multiple differences between recent onset and chronic schizophrenic patients that could result in different outcomes in clinical trials. These differences include the level of cognitive impairment, the level of treatment compliance, the sensitivity to treatment side effects, and changes in brain morphology (Molina et al., 2005; Rabinowitz et al., 2006; Mori et al., 2007). Thus, studies explicitly recruiting recent onset or first episode patients should be conducted and in large clinical trials, these patients could be included along with chronically ill patients and the study outcomes stratified by group.

Another observation that has been commonly made in failed studies of pro-cognitive agents in neuropsychiatric patients is an improvement in symptoms across all treatment arms once patients are randomized, suggesting that being in a study itself may have a powerful therapeutic effect. It has been suggested that efforts to simplify the studies by reducing the number of interactions of patients with study staff prior to the drug evaluation phase be considered. Alternatively, efforts to ensure that all study procedures, staff interactions, and assessments are included in any run-in period prior to actual randomization of patients might also help to reduce this apparent practice or placebo effect (Marder et al., 2017).

From a meta-analytic review of placebo-controlled trials of antidepressant drugs, Undurraga and Baldessarini (2012) argued that when drug evaluations progress to Phase III and additional testing sites are recruited to increase the number of study subjects, an unanticipated result is that the quality of the sites diminish (a factor that may contribute to the study failure). Thus, new policies should be developed for neuropsychiatric drug evaluations to focus more on the quality of the recruitment and site conduct rather than on the volume of patients enrolled, which may result in fewer but more productive study sites. Such policies would necessitate continual monitoring of the conduct of the study sites and contract research organizations and the termination of sites that do not perform properly (Marder et al., 2017).

9. Conclusions and future directions

There are now decades of preclinical evidence to support the argument that α7-nAChRs should be viable therapeutic targets for schizophrenia and other disorders of cognition. A wide variety of molecules developed to modulate α7-nAChRs exhibited pro-cognitive activity in animals and some have shown positive effects in early (Phase I and II) clinical trials. However, to date, there has been no large phase III clinical trial in schizophrenia where an α7-nAChR ligand has shown clear efficacy as pro-cognitive agent without untoward side effects. A thorough review of the literature indicates that multiple factors can potentially affect the success of pro-cognitive agents in schizophrenia (including α_7-nAChR ligands) such as the translational value of the animal models used, clinical trial design limitations, confounding effects of polypharmacy, and complex dose-effect and dose frequency considerations.

From the preclinical perspective, more studies should be conducted where the pro-cognitive agent is evaluated in animals that have chronically been treated with an antipsychotic drug. Moreover, the number of chronic dosing paradigms in animal studies should be increased to parallel chronic administration in clinical populations. In both the preclinical and clinical evaluations of α7-nAChR ligands, a wider dose range (to include low doses) and the frequency of administration (repeated versus intermittent administration) should be evaluated. In the later phases of preclinical drug discovery, a greater emphasis should be placed on non-human primates (as opposed to rodents) given their more complex behavioral repertoire and brain homology with humans. From the clinical perspective, patients whose cognitive performance is comparable to healthy controls should be excluded and efforts should be made to reduce apparent practice or placebo effects associated with multiple interactions of patients with study staff prior to the drug evaluation. Recent onset or first episode patients should be included along with chronically ill patients and the study outcomes stratified by group. Finally, new policies should also be developed to focus more on the quality of recruitment sites rather than on volume of patients enrolled.

CRediT authorship contribution statement

Alvin V. Terry: Conceptualization, Writing - review & editing. **Patrick M. Callahan:** Conceptualization, Writing - review & editing.

Declaration of competing interest

The authors do not declare any conflict of interest.

Acknowledgements

The authors would like to thank Ms. Ashley Davis for her administrative assistance in preparing this manuscript. The author's laboratories and/or salary are supported in part by the following funding sources, National Institutes of Health grants, MH097695, MH083317, and NS099455, and Prime Behavior Testing Laboratories, Evans, Georgia.

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