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# Nicotinic interactions with antipsychotic drugs, models of schizophrenia and impacts on cognitive function

*Edward D. Levin* *, *Amir H. Rezvani*

*Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, NC 27710, USA*

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ABSTRACT

People with schizophrenia often have substantial cognitive impairments, which may be related to nicotinic receptor deficits, (α7 and α4β2), documented in the brains of people with schizophrenia. The large majority of people with schizophrenia smoke cigarettes. Thus, nicotinic interactions with antipsychotic drugs are widespread. Complementary co-therapies of novel nicotinic ligands are being developed to add to antipsychotic therapy to treat the cognitive impairment of schizophrenia. Thus, it is critical to understand the interaction between nicotinic treatments and antipsychotic drugs. Nicotinic interactions with antipsychotic drugs, are complex since both nicotine and antipsychotics have complex actions. Nicotine stimulates and desensitizes nicotinic receptors of various subtypes and potentiates the release of different neurotransmitters. Antipsychotics also act on a verity of receptor systems. For example, clozapine acts as an antagonist at a variety of neurotransmitter receptors such as those for dopamine, serotonin, norepinepherine and histamine. In a series of studies, we have found that in normally functioning rats, moderate doses of clozapine impair working memory and that clozapine blocks nicotine-induced memory and attentional improvement. Clozapine and nicotine can attenuate each other's beneficial effects in reversing the memory impairment caused by the psychototmimetic drug dizocilpine. A key to the clozapine-induced attenuation of nicotine-induced cognitive improvement appears to be its $5HT_2$ antagonist properties. The selective $5HT_2$ antagonist ketanserin has a similar action of blocking nicotine-induced memory and attentional improvements. It is important to consider the interactions between nicotinic and antipsychotic drugs to develop the most efficacious treatment for cognitive improvement in people with schizophrenia.



## 1. Introduction

Nicotinic receptor systems are important in the neural substrate for a variety of cognitive functions including learning, memory and attention [1]. Nicotinic treatments are promising for reversing the cognitive impairment in a variety of syndromes including Alzheimer's disease, attention deficit hyperactivity disorder (ADHD) and schizophrenia [2–4]. However in the development of nicotinic treatments for cognitive impairment, it is crucial to take into account nicotinic mechanisms of effect in compromised brains as well as interactions of the nicotinic treatments with other medications that are used to treat these disorders. These considerations are particularly important for nicotinic treatments for schizophrenia.

Cognitive impairment in schizophrenia is widespread and can be severe [5]. It ranges from impairment of sensorimotor gating to attentional dysfunction. Cognitive deficits in attention, memory, learning and sensory modulation impair the ability of people with schizophrenia to function well in daily

* *Corresponding author*. Tel.: +1 919 681 6273; fax: +1 919 681 3416.
E-mail address: edlevin@duke.edu (E.D. Levin).
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activities and to successfully function in society. A variety of antipsychotic drugs have been developed which can effectively combat hallucinations. However, for the most part they have no effect of reversing cognitive impairment and can even exacerbate cognitive dysfunction. It is clear that better medications are needed to improve cognitive function in schizophrenia [6].

Among the most promising treatments under development are nicotinic agonists, and in particular nicotinic α7 agonists [7]. For the development of effective nicotinic treatments for schizophrenia, it is important to know both how nicotinic treatments interact with the brain systems compromised by the disease as well as the interactions of nicotinic treatments with the co-administered antipsychotic treatments.

The principal nicotinic receptors which have been characterized with regard to cognitive function are the low affinity α7 and the high affinity α4β2 nicotinic receptors. Although α7 receptors have classically not been considered to be involved in cognition, there are data showing an important role for this class of receptors in cognitive function. For example, the α7 nicotinic agonist ARR-17779 has been shown to cause a significant improvement in learning of the classic win-shift radial-arm maze and also caused a continuing improvement in learning on the repeated acquisition task in the radial-arm maze in which a new problem is presented each session [8]. On this same task, nicotine did not improve accuracy, whereas the atypical nicotinic agonist lobeline did significantly improve accuracy [9]. Some investigators did not find ARR 17779 to effectively improve attention on the 5-choice task [10,11]. However, Young et al. found that mice with α7 knockout had significant impairments on the 5-choice task [12]. The partial α7 agonist GTS 21 significantly improved learning and memory [13] and also attenuated the age-related impairment of classical conditioning in rabbits [14].

Nicotinic α4β2 receptors also have been implicated in cognitive function. The α4β2 nicotinic agonist metanicotine (RJR 2403 or TC 2403) significantly improved working memory function in rats on the 8-arm radial maze. Interestingly, this effect was evident both one-hour after administration as well as six hours after dosing, long after the compound had been catabolized suggesting a persistent effect of nicotinic stimulation [15]. Thus, it appears that nicotinic receptor subtype selective ligands hold the promise for improving cognitive performance.

## 2. Nicotinic systems and the cognitive impairment of schizophrenia

Nicotinic receptors in the brain appear to play a key role in the manifestation of schizophrenia. Nicotinic receptor deficits in mainly α7 but also α4β2 receptors are seen in the brains of people with schizophrenia who were either taking antipsychotics or not [16,17]. These nicotinic receptor deficits seem to play an important role in the manifestation of cognitive impairment in schizophrenics. Nicotinic co-treatments may hold promise for reducing cognitive dysfunction in schizophrenia. The high rates of tobacco smoking in people with schizophrenia may be a form of self-medication, albeit a very dangerous form, to combat their cognitive impairment [18].

People with schizophrenia without regard to antipsychotic drug use smoke cigarettes more heavily (88%) than almost any other group in the population [18]. A world-wide meta-analysis of smoking and schizophrenia demonstrated three times greater smoking in schizophrenia than in the general population and twice the incidence compared with other major mental illnesses regardless of antipsychotic drug use [19]. It has also been shown that patients with schizophrenia smoke cigarettes much more intensively thereby increasing their nicotine intake with higher antipsychotic doses generally related to greater smoking [20]. Highly dependent smokers are in general those with more severe schizophrenic illness in patients taking antipsychotic drugs [21]. Smoking and nicotine skin patches have a similar effect in improving attentional performance in people with schizophrenia who were taking antipsychotic drugs [22–24]. Interestingly, higher smoking rates appear to precede the onset of schizophrenia [25]. This may be also related to self-medication for cognitive deficits, which are present before the first break into schizophrenia. Antipsychotic drugs which cause greater cognitive impairment such as haloperidol cause increases in smoking while those with less detrimental effects decrease smoking [23,26,27]. Thus, there may be self-medication of people with schizophrenia who smoke tobacco for both cognitive impairments of schizophrenia itself as well as the further cognitive impairments, which can result from antipsychotic drugs.

For the development of new therapeutic avenues for treating the cognitive impairment of schizophrenia is vital to determine the interactions of the candidate drugs with the antipsychotic drugs given to treat the hallucinations of schizophrenia. A series of studies have been conducted to assess the interactions of antipsychotic drugs with nicotinic systems underlying cognitive function. These studies have characterized nicotinic-antipsychotic drug interactions in cognitive functions including pre-pulse inhibition, working and reference memory and selective attention.

Nicotinic α7 and α4β2 receptor dysfunction may underlie both schizophrenia and smoking in schizophrenics [16,28]. Patients with schizophrenia have a deficiency of α7 nicotinic receptors in the hippocampus and frontal cortex [29,30]. In particular, α7 receptors in the hippocampus appear to be important for the cognitive impairment [31–33]. This cognitive impairment may be due to decreased desensitization of hippocampal α7 receptors in schizophrenics [34]. Hippocampal-based deficient auditory sensory gating in patients with schizophrenia has been shown to normalize by nicotine administration via cigarette smoking who were taking antipsychotic drugs [35]. Nicotine patch has been found in our studies and others to significantly improve cognitive function in patients with schizophrenia who were taking antipsychotic drugs [24,31]. It has been shown that nicotine skin patch administration reduces attentional deficits of schizophrenia as well as attenuates cognitive deficits caused by classic neuroleptics [24]. Smoking also has been demonstrated to improve sensory gating in patients with schizophrenia who were either taking antipsychotic medications or not [36]. Therefore, nicotine administered by a safer route than smoking such as nicotine skin patches may provide potential beneficial cognitive effects without the toxic effects of

smoking. New nicotinic subtype selective agonists may be even safer and more effective than the nicotine skin patches.

## 3. Antipsychotic drug effects on cognitive function

Atypical antipsychotics such as clozapine and risperidone represent a great improvement over classic antipsychotics such as haloperidol in terms of improving cognitive function [37]. Although, attentional function appears to be improved by these drugs [38–42], their effects on memory are more problematic. For instance, clozapine has been found to have adverse effects on working memory in people with schizophrenia and experimental animals [43–45]. In contrast, reference memory [46] was found to be improved by clozapine. Clozapine-induced working memory impairment has been identified in experimental animal models. In monkeys, clozapine impairs the accuracy of delayed response performance [47]. In rats, a similar effect has been seen with clozapine, causing a delayed response choice accuracy impairment [48]. Clozapine has been shown to significantly impair working memory function in normal rats [49]. The clozapine-induced memory impairment is significantly attenuated by nicotine co-administration. Clozapine but not haloperidol improved PPI in DBA/2 mice, which have deficient α7 receptors [50]. This effect was blocked by the α7 antagonist α-bungarotoxin, but not the α4β2 antagonist DHβE. Clozapine, haloperidol and risperidone were also found to impair memory performance in the Morris water maze [51]. Deficits in the delayed response memory task were also seen with haloperidol and risperidone [48]. With the advancement of the therapeutic goal beyond just antipsychotic activity, i.e. to improve cognitive function, it is imperative to determine the mechanisms of cognitive effects of the therapeutic drugs for schizophrenia. In this way, novel approaches for improving cognitive function in schizophrenics can be developed.

The classic neuroleptic haloperidol has been shown in several animal studies to impair working memory as well [52–55]. Olanzapine impairs accuracy in rats, an action that is significantly attenuated by nicotine coadministration [56]. Risperidone attenuates nicotine-induced memory improvement [49].

The hallmark of atypical antipsychotics is that they affect multiple receptor systems. Atypical antipsychotics have been called ''MARTA'' (multi-acting receptor targeted antipsychotics) drugs because they act on a variety of receptor systems [57]. Cozapine for example, has affinity for DA $D_1$, cholinergic muscarinic and serotonergic receptors and relative lack of affinity for DA $D_2$ receptors. It has been shown that drugs with serotonin $5HT_{2A}$-blocking property produce better cognitive function in patients with schizophrenia than drugs with predominantly dopamine $D_2$-blocking activity [58–60]. This may explain the better treatment profile of clozapine over haloperidol. Antipsychotic drug actions blocking $D_2$ receptors have been found to be related to higher rates of smoking in young patients with schizophrenia [61]. Given the efficacy of MARTA drugs and their better treatment profile for schizophrenia, the next step may be to develop combinations of drugs to provide optimal therapy. With drug combinations additional targeted receptor can be achieved without having to devise a novel drug. The selection of the drugs for combination and their relative doses can be adjusted to achieve optimal results to fit the needs of individual patients. Drug combinations can be selected such that the therapeutic effects are complementary and the side effects are offset. Lower doses of each drug can be used in combination to further reduce the problem of undesirable side effects.

The cholinergic nicotinic system is widely distributed throughout the CNS. Thus, it is not surprising to see its complex interactions with antipsychotic drugs. Nicotinic interactions with both DA and glutaminergic systems may be key for their efficacious cognitive effects in combination with antipsychotic drugs. Nicotine has been demonstrated to enhance DA and glutamate release in the frontal cortex [62,63]. Nicotine also plays a protective role in attenuating $D_2$ receptor up-regulation with chronic antipsychotic drug therapy [64]. One critical factor is the background activity of DA systems. Under normal levels of dopamine activity, the antipsychotic clozapine increased firing rate of ventral tegmental area (VTA) DA cells [65]. Dizocilpine reversed this effect, but MLA did not. But under conditions of high DA activity induced by α7 blockade, there was the reverse effect [66]. Nicotinic actions in the VTA may be critically important on DA involvement in frontal cortically based cognitive function.

## 4. Interactions of nicotinic and antipsychotic drugs

Most of the currently used antipsychotic drugs act as antagonists at a variety of neurotransmitter receptors, including those for dopamine, serotonin, norepinepherine and histamine. Nicotine has direct actions at nicotinic cholinergic receptors but also has cascading effects of releasing a variety of transmitters including dopamine, serotonin, norepinepherine and histamine as well as GABA and glutamate [67–69]. Recently, it has been found that at least in vitro clozapine significantly impairs actions of nicotine via an α7 receptor mechanism [70]. The fact that this was seen in hippocampal slices suggests that this clozapine may be relevant for the cognitive function studied in our experiments. Thus, the interactions of nicotinic treatment with antipsychotic drugs are complex.

Clozapine is the prototype of the multi-receptor acting antipsychotic drugs. We have conducted a series of studies of clozapine actions on memory and attention and its interaction with nicotine and nicotinic receptor systems. Clozapine has been shown to significantly impair working memory performance in the radial-arm maze, an effect (Fig. 1), which is significantly attenuated by acute nicotine co-administration [49]. Antipsychotic drugs, such as clozapine, act on a variety of different neurotransmitter receptors, thus it is important to determine which of these effects are responsible for interaction with the nicotinic system in the brain in modulating attentional task. We have begun the pharmacological dissection of antipsychotic drug interactions with nicotine with the examination of the role of $5HT_2$ receptors. There is evidence to suggest that it is the $5HT_2$ antagonistic effect of clozapine that underlies clozapine-induced attenuation of nicotine effects on cognitive function. To support this notion, we have demonstrated that the more selective $5HT_2$ antagonist ketanserin

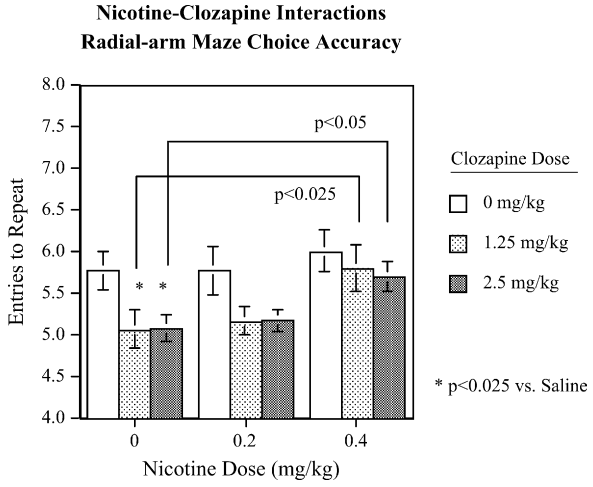


**Fig. 1 – Nicotine interactions with clozapine and working memory performance on the radial-arm maze [49].**

attenuates nicotine-induced radial-arm maze working memory improvement in rats (Fig. 6) [71]. Furthermore, we have shown that ketanserin also blocks the nicotine-induced improvement in attentional performance (Fig. 7) [72]. These findings support the involvement of $5HT_2$ receptors in cognitive functions such as working memory and sustained attention.

Nicotine co-treatment also attenuated the radial-arm maze memory impairment caused by olanzapine [56]. Haloperidol and risperidone both also attenuated the nicotine-induced memory improvement in rats (Fig. 2) [49].

Both clozapine and risperidone (Fig. 3) caused a dose-related impairment in selective attention (lower percent hit) on the visual signal detection operant task [73].

In a series of experiments, we have documented the interactions of nicotine with classic neuroleptic treatment. In

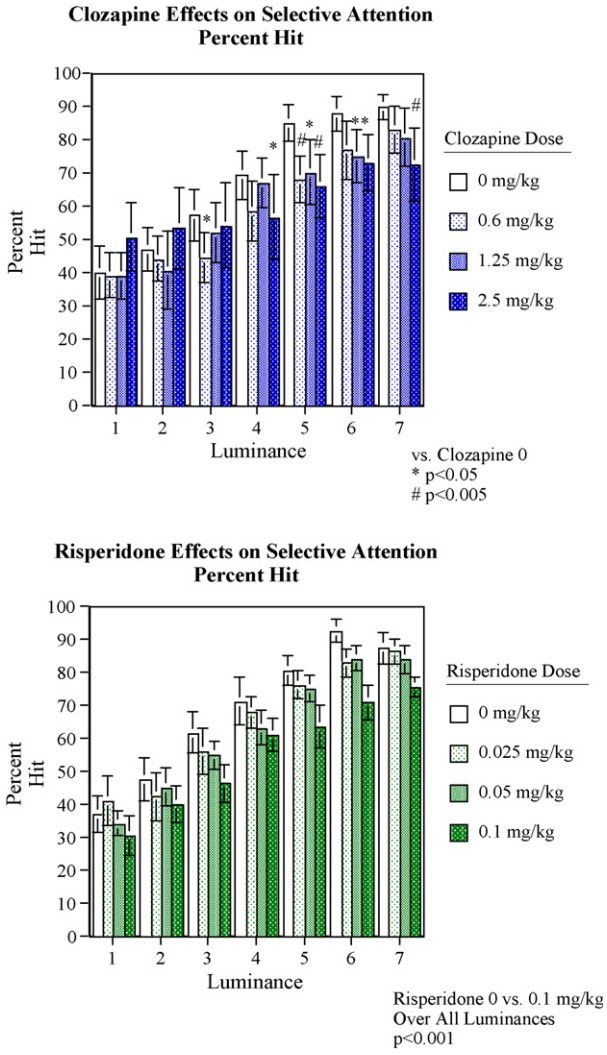


**Fig. 3 – Clozapine and risperidone induced impairments on sustained attention [73].**

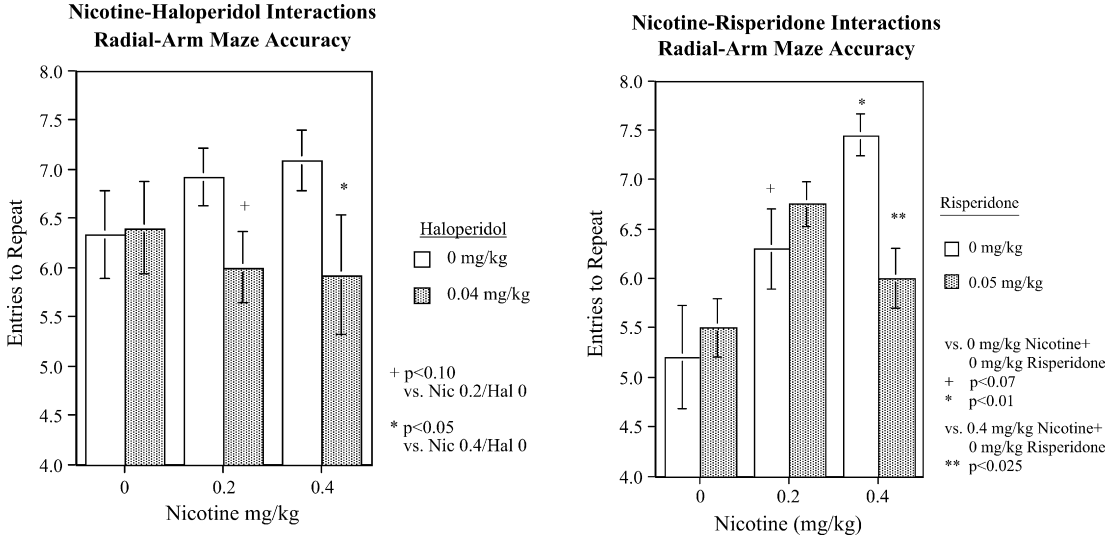


**Fig. 2 – Nicotine interactions with haloperidol and risperidone and working memory performance on the radial-arm maze [49].**

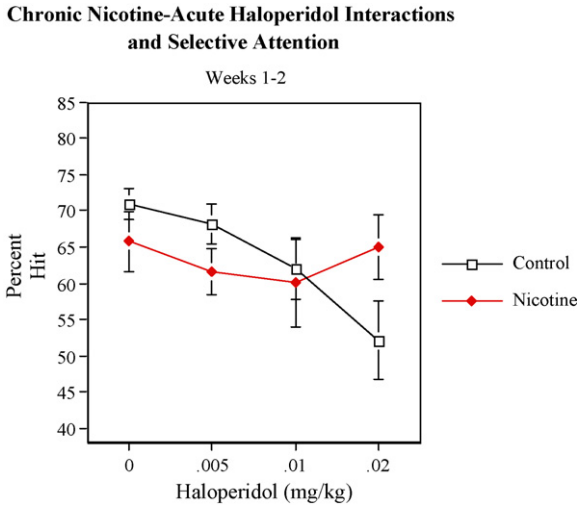


**Fig. 4 – Chronic nicotine interactions with haloperidol and sustained attention [73].**

parallel clinical and experimental animal studies, we have determined nicotine-haloperidol interactions with regard to cognitive function. In the clinical studies, we found that nicotine-induced cognitive improvement is not blocked by haloperidol, but rather nicotine is effective in reversing haloperidol-induced deficits in cognitive functions. Nicotine administered via skin patches attenuated the working memory impairment caused by moderate and high doses of haloperidol [24]. The haloperidol-induced decrease in mental processing speed was also reduced by nicotine patch treatment. Interestingly, the consistency of attentional response is improved by nicotine in a dose-related fashion regardless of the dose of haloperidol. In parallel basic studies in laboratory rats, we have demonstrated that nicotine-induced memory improvements were not blocked by haloperidol [55]. Haloperidol (Fig. 4) also caused a significant impairment in attentional performance, an effect, which was attenuated by chronic nicotine (5 mg/kg/day) infusion for the first two weeks of treatment. Chronic nicotine infusion at the same dose level also attenuated the attentional cognitive impairment induced by acute administration of clozapine or risperidone treatment in female rats [74].

In a pharmacological animal model of schizophrenia, NMDA glutamate receptor blockade with dizocilpine (MK-801), we have found that nicotine effectively attenuates the memory impairment [75] as well as aspects of the attentional impairment [76]. Recently, we found that although nicotine and the antipsychotic drug clozapine each individually significantly attenuated the attenuated the attentional impairment caused by dizocilpine, when given together nicotine and clozapine significantly attenuated each other's therapeutic effects [77] (Fig. 5).

## 5. The potential of nicotinic treatment for the cognitive impairments of schizophrenia

The usefulness of nicotinic treatments for a variety of neuropsychiatric indications including schizophrenia has been suggested [78–82]. Attentional improvement by nicotinic agents may be a key therapeutic effect for these psychiatric disorders [83,84]. It has been demonstrated that smoking withdrawal induced deficits in both attentional performance and spatial working memory in patients with schizophrenia [85]. Interestingly, these deficits are reversed with smoking and the smoking effect can be blocked by the nicotinic

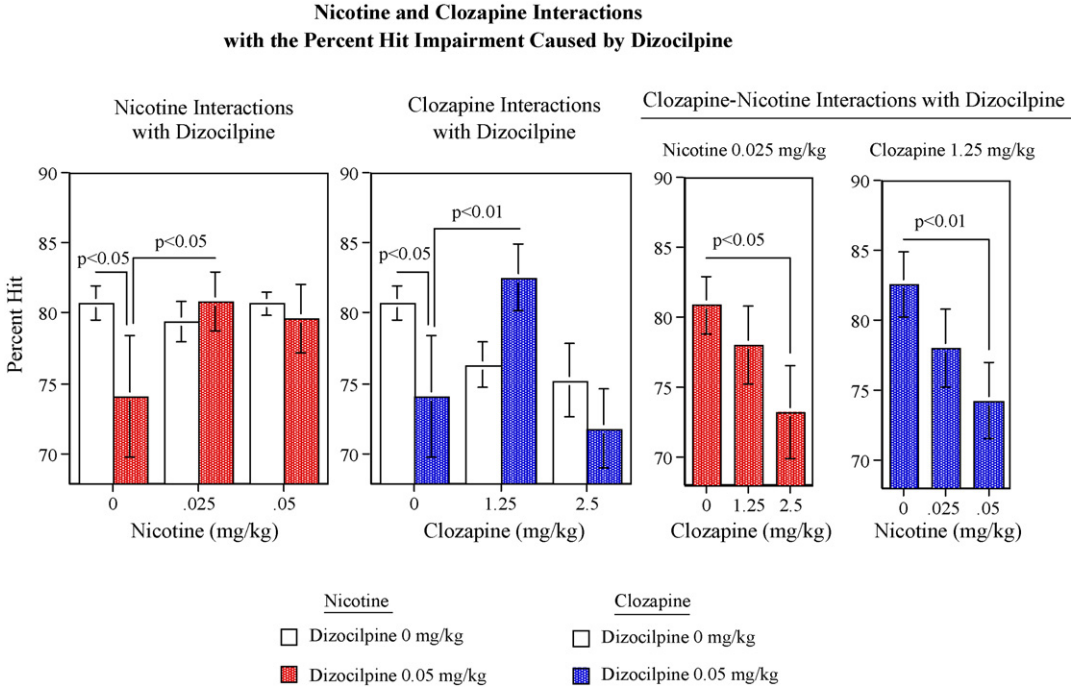


**Fig. 5 – Nicotine interactions with clozapine and selective attention [77].**

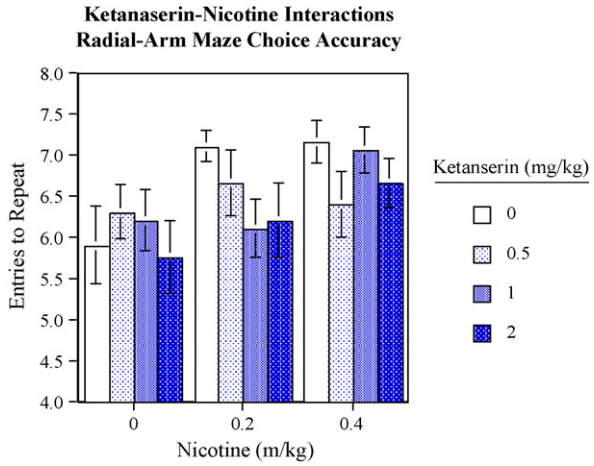


**Fig. 6 – Nicotine interactions with ketanserin and working memory on the radial-arm maze [71].**

antagonist mecamylamine. Nicotine also normalizes smooth pursuit eye movements in people with schizophrenia, an effect, which is accompanied by increased activity in the cingulate gyrus and lowered activity in the hippocampus [86]. Nicotine improves antisaccade and eye tracking performance in patients with schizophrenia [87–89]. Nicotine skin patches have been shown to improve N-back memory test performance in withdrawn smokers with schizophrenia [90]. This was accompanied by enhanced activation in the cingulate cortex and thalamic nuclei. In a complementary fashion, nicotinic blockade caused significant deficits in the N-back task [91]. Nicotine nasal spray has been shown to improve spatial organization and also improve memory in people with schizophrenia [92,93]. Nicotine also improves eye tracking, memory and attentional function in schizophrenia [84,85,88,92]. Nicotine skin patch treatment in healthy volunteers significantly improved the speed of pre-attentive sensory processing as indexed by mismatch negativity to auditory stimuli in an oddball paradigm [94].

Specific nicotinic receptors may be more promising for the improving aspects of cognition in people with schizophrenia. For example, nicotinic α7 receptors offer a promising avenue for novel drug development for treatment of the cognitive impairments of schizophrenia [7]. Abnormal α7 genotype is significantly associated with schizophrenia, smoking in schizophrenia and deficient sensory gating [95–97]. Because of the findings of α7 receptor deficits in schizophrenia and its involvement in the cognitive impairment of schizophrenia, a variety of promising new α7 agonists, which penetrate the blood brain barrier and are bioavailable with oral administration, have been developed [98,99]. Tropisetron, a partial agonist at α7 receptors, has been reported to improve sensory gating (P50 inhibition) in patients with schizophrenia [100]. However, the $5HT_3$ actions of this drug may also underly its effectiveness [101]. A selective α7 nicotinic acetylcholine receptor agonist, PNU-282987, has been found to reverse sensory gating deficits caused by amphetamine in the rat and to stimulate whole cell currents in hippocampal cells [102]. The α7 agonist DMXB has been shown to enhance sensory gating likely through α7 receptors in the hippocampus [103,104]. Anabasine, an α7 agonist, reversed the ''popping'' behavior, which is a model for schizophrenia in mice given dizocilpine [103]. The PPI deficit caused by isolation rearing is also reversed by the α7 agonist (*R*)-*N*-(1-azabicyclo[2.2.2]oct-3-yl)(5-(2-pyridyl)thiophene-2-carboxamide [105]. Thus, nicotinic α7 agonists appear to hold promise for further development to reverse at least some aspects of cognitive impairment in people with schizophrenia.

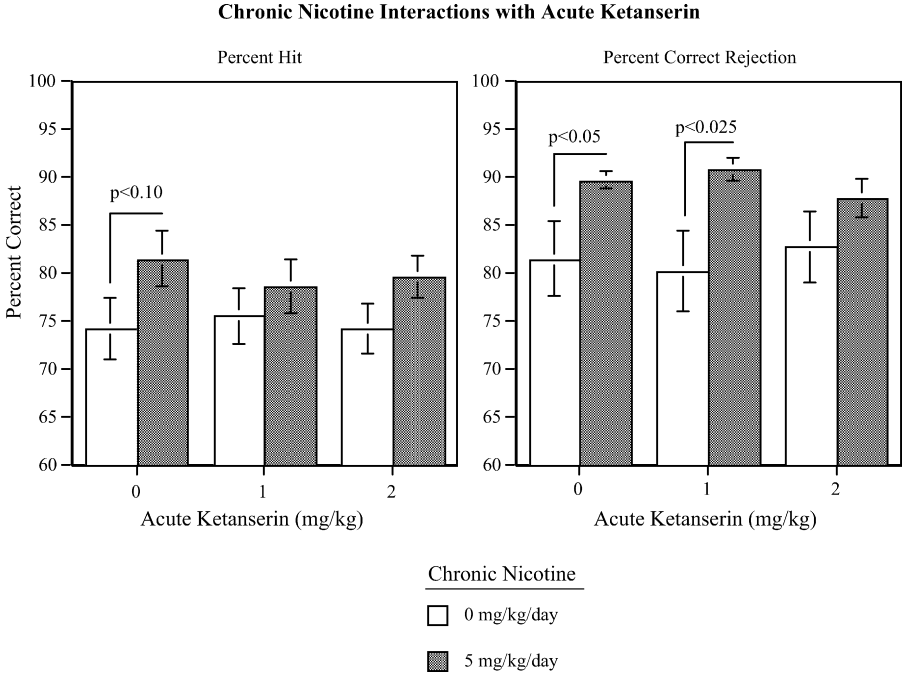


**Fig. 7 – Chronic nicotine interactions with ketanserin and attentional performance [72].**

Future research should investigate more closely the interactions of chronic exposure to nicotinic agonists and antipsychotic drugs. This would more closely mimic the real world co-administration of these drugs. Given the nicotinic receptor number increases [106,107] and other effects of chronic nicotine such as upregulation of cyclic AMP pathway [108] that could interact with antipsychotic drug action. Also, pharmacological specificity of drug actions needs to be more closely examined. For example, there is much cross-reactivity of drugs affecting ligand-gated ion channels especially nicotinic and $5HT_3$ receptors. Actions of ''nicotinic'' drugs at $5HT_3$ receptors may explain some therapeutic drug effects. For example Alder and co-workers have shown that odansetron, a selective $5HT_3$ ligand, significantly improves auditory gaiting deficits in patients with schizophrenia [101].

## 6. Conclusions

Nicotinic receptor systems in the brain are important for a variety of aspects of cognitive function impaired in schizophrenia and aggravated by antipsychotic drugs. Nicotine and selective nicotinic α7 and α4β2 agonists can significantly improve learning, memory and attention. Nicotine and nicotine agonists can reduce some of the cognitive impairments caused by some antipsychotic drugs as well as reduce cognitive impairments seen in the NMDA glutamate blockade animal model of schizophrenia.

Interestingly, nicotine-induced cognitive improvement was found to be significantly attenuated by the antipsychotic drug clozapine. One of the principal effects of clozapine is to block $5HT_2$ receptors. Thus, the limitation of antipsychotic drug treatment in blocking nicotine-induced cognitive improvement may result from their actions at serotonin receptors as we have shown that $5HT_2$ antagonist ketanserin significantly attenuated nicotine-induced improvements in memory and sustained attention in rats.

Hippocampal α7 and α4β2 nicotinic receptor systems play an important role in the neural basis of nicotinic antipsychotic drug interactions. Local acute and chronic hippocampal infusions of either nicotinic α7 and α4β2 antagonists significantly impair spatial working memory. Chronic hippocampal nicotinic antagonist infusions have serve as a model of persistent decreases in nicotinic receptor level seen in schizophrenia and Alzheimer's disease.

Nicotinic co-treatment may be a useful adjunctive treatment to attenuate cognitive impairment of schizophrenia. There are a variety of nicotinic agonists under development for this purpose. Both α7 and α4b2 nicotinic receptor subtype drugs may be effective. Development of nicotinic treatments for schizophrenia should attend to possible limiting factors rising from interactions with antipsychotic drugs. Clinical trials need to keep track of the antipsychotic drug regimen and stratify the outcome analysis by antipsychotic regimen. Also, given that the great majority of people with schizophrenia are tobacco smokers already taking in nicotine, the degree to which they may decrease smoking in response to novel nicotinic agonist administration it may be difficult to differentiate cognitive performance of those receiving the novel nicotinic medication and smoking less from those receiving placebo and continuing to smoke at higher levels. Novel nicotinic agonist treatment for the cognitive impairments of schizophrenia and antipsychotic medication hold great promise as therapeutic treatments to improve the lives of people who suffer from schizophrenia.

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