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Going up in Smoke? A Review of nAChRs-based Treatment Strategies for Improving Cognition in Schizophrenia

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Abstract

Cognitive impairment is known to be a core deficit in schizophrenia. Existing treatments for schizophrenia have limited efficacy against cognitive impairment. The ubiquitous use of nicotine in this population is thought to reflect an attempt by patients to self-medicate certain symptoms associated with the illness. Concurrently there is evidence that nicotinic receptors that have lower affinity for nicotine are more important in cognition. Therefore, a number of medications that target nicotinic acetylcholine receptors (nAChRs) have been tested or are in development. In this article we summarize the clinical evidence of nAChRs dysfunction in schizophrenia and review clinical studies testing either nicotine or nicotinic medications for the treatment of cognitive impairment in schizophrenia. Some evidence suggests beneficial effects of nAChRs based treatments for the attentional deficits associated with schizophrenia. Standardized cognitive test batteries have failed to capture consistent improvements from drugs acting at nAChRs. However, more proximal measures of brain function, such as ERPs relevant to information processing impairments in schizophrenia, have shown some benefit. Further work is necessary to conclude that nAChRs based treatments are of clinical utility in the treatment of cognitive deficits of schizophrenia.

Keywords

nAChR; nicotine; schizophrenia; cognition

INTRODUCTION

Cognitive deficits, a core feature of schizophrenia [1], include impairments in memory, attention, executive functioning vocabulary, visuospatial skills and old learning [2]. Cognitive deficits predate the onset of psychosis, become more pronounced in the prodrome

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CONFLICT OF INTEREST

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and early years of diagnosis, and tend to plateau thereafter [3]. These deficits are also seen among first-degree relatives of probands with schizophrenia and tend to be stable despite improvements in positive and negative symptoms [4]. Most patients with schizophrenia have cognitive deficits [5] that range from moderate to severe [2], and are strongly correlated with functional outcome [6]. In fact, the degree of cognitive deficits is a better predictor of disability and vocational functioning than positive symptoms [7]. Existing antipsychotic drugs, all of which block dopamine 2 receptors (D_2), continue to be the mainstay of treatment [8]. D_2 receptor antagonists have limited efficacy for negative symptoms and cognitive deficits [9, 10]. There is a need to develop new treatments for schizophrenia including treatments for the cognitive impairments associated with the disorder. Currently strategies that are being developed to target cognitive deficits broadly consist of pharmacological agents and cognitive retraining. The putative pharmacological cognitive enhancers being tested in schizophrenia include drugs with diverse mechanisms of action such as the glutamatergic, dopaminergic and nicotinic systems [11-15]. The focus of this review is the clinical evidence on drugs acting at nicotinic acetylcholine receptors (nAChRs) as cognition enhancers in schizophrenia.

SMOKING AND SCHIZOPHRENIA

One of the most robust lines of evidence supporting the potential use of nAChRs agonists as cognition enhancers in schizophrenia is based on the observation of high rates of tobacco use in schizophrenia. Individuals with schizophrenia have the highest rates of cigarette smoking (58–88%) compared to the general population (~ 23%) [16-19]. The association between schizophrenia and tobacco smoking is stronger even after controlling for confounds such as institutionalization, socioeconomic status and medications [19-21]. Smokers with schizophrenia smoke more cigarettes and favor stronger cigarettes suggesting that they are more dependent on nicotine than other smokers reviewed in [19]. The ubiquitous use of nicotine in people with schizophrenia has led to the hypothesis that cigarette smoking is a form of self-medication to improve cognitive function, reduce primary and/or secondary negative symptoms, enhance antipsychotic response, and ameliorate treatment of side effects from antipsychotics [22]. Nicotine, one of the addictive and reinforcing ingredients in tobacco-smoke, produces its effects via agonist effects at nAChRs.

NICOTINIC RECEPTORS

The nAChRs in the central nervous system are pentameric ligand-gated ion channels that transverse the lipid bilayer to allow influx of cations. The proteins are either heteromeric subunit combinations of α2-α6 and β2-β4 or homomeric subunits. The most common configurations are the heteromeric α4β2 and the homomeric α7 [23]. The α4β2 receptor has higher affinity for nicotine compared to the α7 receptor but a much lower permeability to calcium [24, 25]. The α4β2 has high concentrations in the cortex and thalamus, while concentrations of α7 are higher in the cortex and hippocampus [26, 27]. The α4β2 receptor has about three times higher affinity for acetylcholine compared to α7 [25], but choline acts as a full agonist at the α7 receptor without effect at the α4β2 [28]. The α4β2 receptor also has different pharmacodynamic properties than most receptors. In the presence of an agonist such as nicotine the α4β2 concentrations increase or undergo upregulation [29, 30]. Nicotine

also causes rapid desensitization of the receptor or tachyphylaxis [31]. Based on the current evidence the α4β2 nAChR is thought to regulate the rewarding properties of nicotine [32, 33], while the α7 nAChR is thought to regulate cognitive and sensory gating phenomenon [34, 35]. For a full review of nAChRs see Albuquerue *et al* (2009) and Jenson *et al* (2005) [28, 36].

NICOTINIC RECEPTOR ABNORMALITIES IN SCHIZOPHRENIA

Several lines of evidence have shown nAChRs abnormalities in people with schizophrenia. The postmortem receptor changes, electrophysiological evidence of altered functioning, and neuro-imaging evidence of abnormalities in schizophrenia will now be reviewed.

Postmortem

There are a number of reports of nAChRs analysis in postmortem studies of people with schizophrenia [37-50] (See Table **1**). The methods employed include using a radioactive ligand with affinity to a subunit of the nAChRs to measure the availability of receptors [37-43, 45, 46, 48, 50] or measuring the nAChRs' messenger RNA or proteins to determine the overall concentration of nAChRs both extracellularly and intracellularly [44, 46-49, 51]. All studies tried to control for demographic variables and smoking status. The results of these studies are mixed but support decreased availability of both the high affinity α4β2 and low affinity α7 nAChRs in schizophrenia. mRNA and protein studies have focused on the low affinity α7 nAChR in the dorsal lateral prefrontal cortex (DLPFC) and hippocampus. None of the studies have shown decrease in expression in the DLPFC. However, the hippocampus does not seem to express α7 nAChRs in people with schizophrenia to the same degree as typical individuals, at least in non-smokers [44, 49].

In vivo evidence

Recent nuclear imaging techniques have permitted *in vivo* measurement of human nAChRs. Two recent studies determined availability of β2-containing nAChRs in smokers with schizophrenia and controls [52, 53]. D'Souza *et al*. [52] scanned twelve smokers with schizophrenia and matched controls after a week of abstinence from smoking with a ligand that has high affinity for the β2-containing nAChR. Compared to controls, people with schizophrenia displayed a 21-26% decrease in available receptors in the frontal cortex, parietal cortex and thalamus (in descending order). To our knowledge there are no *in vivo* neuroreceptor imaging studies of α7 nAChRs in schizophrenia.

Besides the receptors themselves, magnetic resonance spectroscopy (MRS) has been used to measure the endogenous α7 nAChR ligand, choline. A recent meta-analysis showed no deficiency for choline in any region of the brain of people with schizophrenia [54], suggesting an alteration in the nAChR system and not the endogenous ligand.

COGNITIVE IMPAIRMENTS IN SCHIZOPHRENIA

Neuropsychiatric Testing

The cognitive deficits in schizophrenia are broad, present in almost every domain, and most likely represent a core symptom of the illness [55]. A recent consortium of experts defined

the areas of cognition that are of most important in schizophrenia [56, 57]. The domains include processing speed, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition. Processing speed is a nonspecific area that relates to the ability to rapidly process information, which is important in many routine activities of daily living and is implicated as the cognitive deficit with the largest effect size [58, 59]. Attention/vigilance includes the ability of people to focus on a task over time. Recent evidence suggests people with schizophrenia have the most difficulty attending to stimuli when broad monitoring is required rather than focused attention [60]. Working memory is the ability to keep relevant information active for short periods of time, such as remembering a phone number to dial and forgetting it after dialing, and has been suggested to be a core deficit in schizophrenia [61]. While learning deficits are common in schizophrenia, analysis of cognitive batteries have found either verbal or visual episodic memory rather than both in almost 50% of patients [62], therefore requiring separate domains for analysis. Reasoning and problem solving is impaired in people with schizophrenia but testing suggests this area of cognition might be persevered more than other areas compared to normal controls [63]. Social cognition represents many of the skills required to successfully interact with individuals. Specific domains of social cognition correlate with functional outcomes in people with schizophrenia [64]. In Fig. **1** show the relative differences better a sample of normal controls and people with schizophrenia in these domains.

A variety of neuropsychiatric tests are used to measure baseline and changes in cognitive function. Subsequently several cognitive batteries have been developed to test several domains including the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [65], the Brief Assessment of Cognition in Schizophrenia (BACS) [66, 67] and the Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (MATRICS) [68]. The MATRICS was initiated to develop a consensus cognitive battery for developing treatments for schizophrenia [57, 68-71]. Computerized cognitive test batteries have received recent attention for both research and clinical application [72] and for use in clinical trials of schizophrenia [73]. The major benefits of computerized tests are automation, efficiency, standardization and additional test measures [74]. The MATRICS and BACS [75, 76] use a combination of paper-pencil and computerized neuropsychological tests whereas the IntegNeuro [77], CogState Schizophrenia battery [78] and the Cambridge Neuropsychological Test Automated Battery (CANTAB) [79] are completely computerized.

INFORMATION PROCESSING DEFICITS (ERPs)

In addition to the deficits in behavioral measures of cognition (attention, memory, executive functions, etc.), patients with schizophrenia also exhibit information processing deficits as indexed by eventrelated potentials (ERPs). An ERP is a stereotyped event-locked deflection (positive or negative) of the scalp potential that is characterized by the amplitude, duration, and after-stimulus latency of its peak [80]. ERPs are a manifestation of the neural activity underlying certain cognitive processes, which makes them an excellent tool for detecting and characterizing anomalies affecting these processes [80].

P50 Gating—Sensory gating refers to the ability of the brain to modulate its sensitivity to incoming sensory information. This automatic function is thought to reflect an inhibitory process that protects against overwhelming higher cortical centers with irrelevant information [81]. Sensory gating can be measured using a paired click paradigm, in which the first auditory stimulus in a pair (conditioning or S1) is followed by an identical stimulus (test or S2) presented in close proximity (500 ms) to S1 [82]. A positive voltage deflection, termed the P50, is evoked approximately fifty milliseconds after the auditory stimuli [82]. When sensory gating is intact, the amplitude of the P50 waveform following the S2 stimulus is diminished relative to the P50 following the S1 stimulus [82].

Meta-analyses support reduced P50 gating in individuals with schizophrenia, despite heterogeneity among studies [51, 83]. This gating deficit has been documented in prodromal individuals and medication-naive recent onset psychosis patients [84].

Mismatch Negativity (MMN)—The MMN is a negatively deflecting ERP component that peaks with a latency of 150-250 milliseconds. It is elicited automatically, irrespective of the direction of the subject's attention, by an infrequent deviant (in pitch, intensity, duration, location, or pattern) auditory stimulus presented randomly in a stream of repetitive standard auditory stimuli [85-87]. It is thought to reflect auditory sensory (echoic) memory because the detection of deviance requires a representation of what has been "standard" in the auditory stream [86].

MMN abnormalities have been consistently reported in schizophrenia [88]. This finding is unlikely a treatment effect since neither typical nor atypical antipsychotics affect the amplitude or latency of this ERP [89-92]. Furthermore, it seems to be specific to schizophrenia since this is one of the few psychiatric disorders that have been consistently associated with specific MMN abnormalities [93, 94]. Most studies show that MMN abnormalities consist of an amplitude reduction to duration and frequency deviants [88, 89, 95-103]. Nevertheless, some evidence suggests that the deviants associated to an anomalous MMN change over the course of the illness. Todd *et al*. [104] showed that schizophrenia patients early in the course of the illness had an amplitude reduction to duration and intensity deviants but not to frequency deviants. However, patients later in the course of the illness showed a reduction to frequency and duration deviants but not to the intensity ones.

P300—The P300 is a positive ERP component arising approximately 300 milliseconds after the presentation of an infrequent (oddball) stimulus during a target detection task [reviewed in 105, 106]. Two main subcomponents of the P300 (P3a and P3b) have been distinguished, which can be evoked separately by specific stimulus and task conditions [107]. P3b is elicited by infrequent task-relevant target stimuli and is believed to reflect the process of context updating and the allocation of attentional resources, and is modulated by "top-down" cognitive processes [reviewed in 105]. The P3a is elicited by infrequent task-irrelevant stimuli. It is believed to reflect "bottom-up" processes involved in the automatic orienting of attention to novel or salient stimuli [reviewed in 105].

Reductions in P300 amplitude and increased latencies have been observed in a number of neuropsychiatric disorders including schizophrenia [reviewed in 106, 108]. Deficits in P300

amplitude are one of the most replicated psychophysiological findings in schizophrenia with effect sizes above 0.8 [105].

ACUTE EFFECTS OF DRUGS ACTING AT nAChRs AND TOBACCO SMOKING IN SCHIZOPHRENIA

Since the 1970's research has suggested a pro-cognitive effect of nicotine, although due to methodological issues the literature primarily indicated that nicotine reverses the cognitive impairing aspects of withdrawal [109]. Since the 1990's many more studies controlling for withdrawal and other possible confounds of nicotine administration have been conducted. A meta-analysis in otherwise healthy individuals suggested procognitive effects of nicotine in several domains of attention, response time to cues, fine motor abilities, short term memory and working memory [110]. However, this study did not review the effects of nicotine in schizophrenia and since there is evidence of an altered nicotinic system in schizophrenia, studies in healthy controls cannot be extrapolated to people with schizophrenia. Given the role of the α7 nAChR in regulating cognitive and sensory gating phenomenon [34, 35], drug development has preferentially focused on this receptor [111].

CLINICAL TRIALS WITH NICOTINE FOR COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA

Many clinical trials have been conducted to study the effects of nicotine and other nAChRs agonists on cognition in both healthy volunteers [110] and people with schizophrenia [112]. However, the degree of nicotine dependence, the state of nicotine satiety, the state of nicotine withdrawal, and method of administration have differed drastically across studies. Nicotine administration studies to enhance cognition in schizophrenia have used gum [113-116], transdermal patch [117-125], nasal and orally inhaled [126-131], and subcutaneous nicotine [132]. In Table **2** we review the studies in which nicotine is given to people with schizophrenia and cognitive outcomes are tested pre and post-delivery to measure effects.

One of the major confounds of these studies is the interaction of nicotine with antipsychotics. For example, nicotine's cognitive effects have been reported to be modulated differentially by different doses of dopamine D2 antagonists [117]. Smoking status is another important confound as it is established that nicotine can improve/reverse cognitive impairments from nicotine withdrawal [133]. Also, nicotine increases the number of nAChRs and causes receptor desensitization. Finally, unlike long-term cognitive studies, acute administration studies only examine immediate cognitive effects and not long term.

Based on the available studies, nicotine may acutely improve attention. However, the short duration of these studies does not confirm any long-term benefits to attention. Also, the studies examined several cognitive tests with several outcomes but the vast majority failed to control for multiple comparisons. Based on the available evidence nicotine does not enhance general cognitive ability.

Event-related Potentials

P50 Gating—In a study of smokers with schizophrenia who were abstinent overnight, impaired baseline P50 gating transiently normalized upon resumption of smoking [84]. Smokers with schizophrenia, abstinent for at least 1 hour prior to P50 recording displayed gating impairments that were similar to the baseline deficits in nonsmokers with schizophrenia [134]. This gating deficit is also present in up to half of unaffected relatives [135, 136]. Nicotine (6 mg gum) administered to non-smoking unaffected relatives was found to transiently improve the gating deficit [135]. First and second generation antipsychotics did not normalize gating deficits in schizophrenia patients [51, 137, 138]. However, several studies have found that clozapine normalized gating in schizophrenia patients [137, 139, 140].

In the largest study examining P50 in non-psychiatric smokers and non-smokers, Brinkmayer *et al*. found that smokers who had consumed a cigarette within 1-3 hours of the P50 recording had impaired gating–relative to non-smokers [141]. Gating values for light smokers were intermediate between heavy smokers and nonsmokers [141]. Other studies have yielded conflicting results with some publications suggesting enhanced gating in smokers while others have found reduced gating [142-144]. Possible reasons for conflicting results are small sample sizes, variability in P50 technique and analysis, timing of recording in relation to last cigarette smoked and differences in smoking chronicity. In a recent study of healthy non-smokers stratified by baseline P50 gating efficiency, nicotine (6 mg gum) enhanced gating in baseline low P50 suppressors, did not affect gating in baseline medium suppressors, and reduced gating in those with high baseline efficiency [145]. Knott *et al*., [145] suggest that the effect of a drug on gating may differ as a function of this baseline gating efficiency in a manner similar to inverted-U dose-response relationships that have been used to characterize individual variability for other measures, such as nicotine's effect on cognitive performance. Preclinical and clinical evidence implicate the α7 nAChR in auditory gating [146, 147] and furthermore, some α7 nAChR agonists other than nicotine have been shown to enhance sensory gating in schizophrenia (covered in following sections) [38, 148].

Mismatch Negativity (MMN)—Studies on the effect of smoking, nicotine and other nAChRs agonists and modulators in healthy subjects have shown a rather consistent amplitude increase and latency reduction of MMN in both smokers and nonsmokers [149-153]. Studies on the effects of nicotine or nAChRs modulators on MMN in schizophrenia have shown mixed results. Inami *et al*. [121] reported that, in contrast to non-smoking healthy controls, nicotine didn't shorten MMN latencies in non-smoking schizophrenia patients. In turn, Dulude *et al*. [96] reported an increase in MMN amplitude to duration deviants in schizophrenia patients given a high dose (8 mg gum) of nicotine. However, nicotine had no effects on MMN to frequency deviants. A recent study by Fisher *et al*. [154] showed a significant shortening of latency for intensity deviants in schizophrenia patients receiving nicotine (6 mg gum). Interestingly, this study also found a positive correlation between the MMN amplitude to intensity deviants and the subjective clarity of auditory and visual hallucinations. This seems contradictory with reports in the literature showing an inverse relationship between MMN amplitude and symptomatology [155-157].

The variability of these results suggests that, besides the methodological differences of the studies, the course of the illness, the smoking status of individuals, the type of deviant stimuli, and the symptomatology of the sample may influence the effects of nAChRs agonists and modulators on the MMN of schizophrenia patients.

P300—In experienced tobacco users, cigarette smoking or nicotine administration has been shown to increase P300 amplitude [158-160] and/or reduce P300 latency [159, 161, 162]. However, other reports have failed to show such effects [163-166] or have found effects on visual, but not auditory, P300 [162]. In addition, some studies [160, 167, 168], but not others [169], have shown reduced P300 amplitudes in chronic smokers, suggesting a distinction between the effects of acute and chronic exposure to nicotine. A recent study [170] in typical smokers stratified by trait cognitive control found that P3b amplitude was reduced in all abstinent smokers. Greater P3b reductions were associated with higher nicotine dependence. The P3a amplitude was only reduced among the abstinent non-smokers that rated low for trait cognitive control.

The effects of smoking or nAChRs agonists and modulators on the P300 deficits known to be present in schizophrenia have not been well characterized. Using a novel EEG-informed functional magnetic resonance imaging (fMRI) technique, Mobascher *et al*. [171] studied the effects of nicotine (1 mg nasal) on the scalp potential and associated blood-oxygen-level dependence (BOLD) response of a visual P300 in a group of smoking healthy individuals and schizophrenia patients. Despite the fact that no effects of nicotine were found with respect to the amplitude and the latency of the P300 scalp potential, the authors found a nicotine-related increase in the P300-associated BOLD response in the anterior cingulate and the adjacent medial frontal cortex of both groups.

BOLD Response—Several fMRI studies have examined the BOLD response to nicotine in schizophrenia patients [115, 124, 125, 132, 172]. Among control smokers and smokers with schizophrenia, nicotine increased BOLD response in the anterior cingulate and thalamus in people with schizophrenia [125]. Another study showed that while nicotine increased BOLD activity in the anterior cingulate in schizophrenia, it reduced activity in controls [115]. Nicotine also reduced hippocampal activity in both groups but to a significantly greater degree in controls. However, Hong *et al*. [124] found that nicotine induced activation patterns did not differ between controls and people with schizophrenia. Two other studies have reported effects of nicotine on BOLD response in schizophrenia but did not have a control group for comparison [132, 172]. The differences in nicotine-induced activation between controls and people with schizophrenia are not consistent. This may be explained by the use of different tasks during the fMRI studies. Overall though, the literature suggests nicotine induced changes in the cingulate cortex and hippocampus differs among smokers with schizophrenia compared to controls.

EFFECTS OF NICOTINE IN A MODEL OF COGNITIVE DYSFUNCTION

Human pharmacologic models allow for the transient induction of symptoms including cognitive deficits in healthy controls similar to those seen in schizophrenia. Ketamine, an NMDA receptor antagonist, has become one of the most enduring pharmacologic models of

schizophrenia. Ketamine can induce psychotic symptoms and cognitive deficits similar to schizophrenia in normal controls [173, 174] and exacerbates symptoms in people with schizophrenia [175]. Nicotine may reverse the cognitive deficits of ketamine by enhancing glutamatergic transmission in the prefrontal cortex through stimulation of the high affinity $\alpha_4\beta_2$ nAChR [176]. Several studies have examined the interaction of ketamine and nicotine [166, 177-179]. In two of the studies intranasal nicotine and nicotine gum altered either ERP measurements or changes in neuroimaging from ketamine administration [166, 178]. The authors of these studies suggested nicotine mitigation of ketamine-induced effects is evidence that nicotine can improve symptoms of schizophrenia. However, studies using cognitive outcomes have not supported this assertion.

Knott *et al*. [179] tested nicotine gum in 20 smokers and 20 non-smokers with the Rapid Visual Information Processing Task (RVIP) a measure of sustained attention. In the smoking group, nicotine worsened performance on the task in the presence of ketamine. D'Souza *et al*. [177] used ketamine and intravenous nicotine in 37 healthy individuals in a randomized, double-blind, placebo controlled crossover study with a comprehensive cognitive battery and failed to show that nicotine reduced any of the ketamine induced cognitive deficits. In a related study, the N-methyl-D-aspartate (NMDA) antagonist memantine also failed to show an interaction between smoking cigarettes and performance on the RVIP [180].

It is difficult to extrapolate the failure of nicotine to reverse NMDA receptor antagonist induced cognitive deficits to the treatment of cognitive deficits in schizophrenia. Until a medication has shown to have cognitive enhancing effects in schizophrenia it will not be possible to completely validate the ketamine model. However, based on the general negative effects of nicotine in clinical trials, nicotine does not seem appear to improve cognitive function in schizophrenia.

CLINICAL TRIALS WITH nAChRs MEDICATIONS FOR COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA

Several other nAChRs based treatments have been tested as potential therapies for the cognitive deficits associated with schizophrenia (Table **3**). In the following sections we review the published clinical trials assessing the efficacy of nicotinic agents for the cognitive enhancement of schizophrenia.

ACETYLCHOLINESTERASE INHIBITORS

Acetylcholinesterase inhibitors (AChEIs) inhibit the enzyme that breaks down acetylcholine, greatly enhancing the endogenous ligand for nAChRs. Since these medications have proven benefit in delaying the cognitive decline in dementia, they have been tested as potential treatments for the cognitive deficits of schizophrenia. While there are several open label studies and a placebo controlled case report of AChEIs in schizophrenia [181-186], only double-blind, placebo-controlled, randomized studies that evaluated the cognitive effects of AChEIs in schizophrenia/schizoaffective disorder will be reviewed.

DONEPEZIL

Donepezil is a selective AChEI that binds to acetylcholinesterase, but not peripheral butyrylcholinesterase, and is FDA approved for the treatment of mild-severe Alzheimer's disease. Three placebo-controlled randomized studies assessed the cognitive effects of donepezil in schizophrenia [187-189]. In a crossover study over two six-week periods, 5 mg of donepezil failed to show any cognitive enhancement over placebo in a large cognitive battery [187]. Erickson *et al*. [188] gave participants eight-weeks of either donepezil 5 mg or placebo with a two week-washout before starting on the second study medication. Cognitive assessments included the Trails A and B and the RAVLT to assess executive functioning and verbal learning. Both placebo and donepezil improved RAVLT outcomes, but the donepezil group demonstrated statistically greater improvement in the number of words able to be recalled versus placebo. A small crossover study of six participants found no improvement in verbal fluency after 12 weeks of donepezil 10 mg versus placebo [189]. However, the study found that subjects with schizophrenia had an increased BOLD response in the frontal regions including the anterior cingulate when treated with donepezil. While one of the crossover studies reported some improvement with donepezil, all had 15 or fewer participants in the studies. Also, as shown with the one positive study, carryover effects were seen in crossover studies. The first published randomized placebo controlled parallel group study of donepezil consisted of 36 participants all on stable doses of risperidone randomized to donepezil 5 mg, 10 mg, or placebo over 12-weeks [190]. A large cognitive battery was administered at weeks 4 and 12 and showed no significant cognitive effects of either dose of donepezil versus placebo. The only positive study for the use of donepezil was also a 12-week study that used 5 mg of donepezil [191]. Lee *et al*. [192] studied 24 participants all stabilized on haloperidol with a large cognitive battery. After 12-weeks the donepezil arm showed significantly greater immediate recall and recognition on the HVLT (verbal memory) compared to placebo. A greater trend of improvement was also seen in the donepezil treated group on the MMSE (general cognition), the RAVLT, and DS tasks. Many other studies randomized participants with schizophrenia to donepezil 10 mg and failed to demonstrate cognitive improvement versus placebo over time periods ranging from 8-16 weeks of treatment [193-195]. Another 16-week study also reported no improvements in cognition with donepezil 10 mg but failed to report placebo response [195]. Interestingly one small study (n=11) found participants stabilized on ziprasidone showed deterioration in some aspects of cognition including planning and verbal learning after 16 weeks of treatment of donepezil compared to placebo [196]. Akhondzadeh *et al*. [197] studied the effects of donepezil in 30 participants stabilized on long-acting injectable risperidone. Subjects were randomized to placebo or donepezil over 12 weeks. No improvements in neurocognitive symptoms were detected.

In what is by far the largest study of the neurocognitive effects of any of the AChEIs in schizophrenia, Keefe *et al*. [198] randomized 245 people with schizophrenia who were stabilized on a second generation antipsychotic (excluding clozapine), to 12 weeks of donepezil titrated up to 10 mg daily. Assessments for cognition were done at weeks 6 and 12 using the CATIE neurocognitive battery [199, 200]. Almost 60% of the participants were current cigarette smokers and equally distributed between the placebo and donepezil

treatment arms. A total of 195 participants completed the study with approximately the same attrition rate of around 20% in both arms. In the intent to treat sample there was no significant difference between placebo and donepezil on the CATIE Neurocognitive Battery Composite score. But the observed completers analysis showed a significant improvement in placebo greater than the donepezil arm, (cognitive improvement effect sizes for placebo, 0.45 and donepezil, 0.29; p = 0.04). At week 12 the Controlled Oral Word Association Test and the Category Instances tests were significantly more improved with placebo, no other cognitive tasks were significantly different between placebo and donepezil. A subgroup analysis found smoking status did not affect cognitive outcomes in either group.

In summary, donepezil does not seem to be an effective agent for cognitive deficits in schizophrenia. In fact, it may even interfere with learning in schizophrenia [196, 198], although it may be indicated in those with comorbid schizophrenia and dementia [181].

RIVASTIGMINE

Rivastigmine is an AChEI also approved for the treatment of mild-severe Alzheimer's disease and for mild-moderate dementia of Parkinson's type. Unlike donepezil, rivastigmine has affinity for both acetylcholinesterase and butyrylcholinesterase, but it is not known if this is clinically relevant.

One of the first published randomized placebo controlled studies of rivastigmine was a 12-week fMRI study [201]. After the 12-week treatment of 20 participants there was a trend for the group treated with rivastigmine 12 mg toward improved attention in one condition (p=0.075) compared to placebo. In another 24 week study of participants stabilized on risperidone, olanzapine, or quetiapine, after 12-weeks the rivastigmine treated group showed no significant improvement in an n-back task but showed some enhanced BOLD response in the visual cortex [202]. In a 24-week evaluation, the same group demonstrated no improvement in cognitive test performance [203]. The only other placebo-controlled study with rivastigmine found no cognitive enhancing effects on the CANTAB after 24-weeks with participants on either first or second generation antipsychotics [204].

One non-placebo controlled study found ERP changes elicited during a memory task that suggested rivastigmine induced information-processing benefits in people with schizophrenia [205]. In summary the results of clinical trials with rivastigmine have been disappointing. However, much larger studies would need to be conducted to conclusively determine whether rivastigmine has utility as a cognitive enhancer in schizophrenia.

GALANTAMINE

Galantamine is another AChEI that is indicated for the treatment of mild-moderate Alzheimer's disease. However, unlike the other available AChEIs, it is also an allosteric modulator of the $\alpha 4\beta 2$ and $\alpha 7$ nAChRs [206-209]. Interestingly, it does not cause desensitization of nicotinic receptors.

The first published randomized placebo controlled study of galantamine was an 8-week parallel group study in participants stabilized on risperidone (n = 14) [210]. After titrating up

to 24 mg per day, the galantamine treated arm showed significant improvement on the RBANS total score and on subtests measuring attention and delayed memory. Lee *et al*. [192] found after 12 weeks of treatment with galantamine 16 mg/day participants stabilized on their first generation antipsychotic had improved visuospatial abilities on the Rey Complex Figure Task compared to placebo but not on the other cognitive tasks administered. Dyer *et al*. [211] used a higher dose of galantamine than any other study (32 mg/day) in 18 non-smoking participants stabilized on a second generation antipsychotic. After 8 weeks galantamine treated participants showed deterioration on a continuous performance task, Stroop task, and Letter-Number Span Task from the Weschler Adult Intelligence Scale compared to placebo treated participants. A low dose study of galantamine (8 mg/day) demonstrated no cognitive improvement compared to placebo (n = 21) [212]. A crossover study of 35 people with schizophrenia and tardive dyskinesia found no improvement on the MMSE with galantamine, but the MMSE is not meant to assess subtle cognitive changes [213]. In the longest trial (24 weeks) with galantamine in participants receiving long-acting injectable risperidone [214], there were no beneficial effects of galantamine on cognitive test performance.

Buchanan *et al*. [215] conducted the largest placebo-controlled randomized clinical trial with galantamine. Participants on a second-generation (excluding clozapine) or low dose first-generation antipsychotic were randomized to galantamine 24 mg/day over a 12-week period. A total of 86 participants were randomized and 73 finished the study, approximately 42% of the participants were cigarette smokers [215]. After controlling for multiple comparisons there was a significant benefit of galantamine on the Weschler Adult Intelligence Scale (WAIS) digit symbol substitution task ($p = 0.02$) but placebo treated individuals showed significant improvement on a continuous performance task ($p = 0.05$).

In summary, the effects for galantamine have been more impressive than the other AChEIs, but the effects seem small at best. Larger studies need to be conducted to conclusively determine whether galantamine has utility as a cognitive enhancer in schizophrenia.

Overall, AChEIs may have beneficial effects in several domains of cognition including attention, visual memory, verbal memory and language, and executive function [216], but the effects are small and of dubious clinical significance.

α4β2 nAChR MEDICATIONS

Varenicline is a partial agonist at α4β2 and full agonist at α7 nAChRs [217] that was developed as a treatment for nicotine dependence. Clinical trials have shown it is one of the most effective treatments for nicotine addiction [218], however significant psychiatric effects have been reported with its use [219]. Most studies of varenicline in schizophrenia have focused on smoking outcomes [220-224]. In a small (n=6) pilot study varenicline did not appear to enhance P50 gating [223]. In a small (n=12) open label study of schizophrenia patients who smoked, RBANS total score and visuospatial working memory did not change significantly, but improvements in verbal learning and memory were noted [221].

Two placebo-controlled clinical trials have been conducted with varenicline in people with schizophrenia [220, 222]. Shim *et al*. [220] randomized approximately 120 patients to either

placebo or varenicline over an 8-week period. Half of the patients in each arm were current smokers. The primary analysis showed no statistical improvement with varenicline versus placebo on several cognitive tasks including a Continuous Performance Task (CPT), the Digit Symbol Substitution Task (DSST), a Digit Span Task (DST), a Visual Span Task (VST), the Stroop Word Color Task (SWCT), and the Wisconsin Card Sorting Task (WCST), however secondary analysis looking at improvement over time found varenicline significantly improved scores on the DSST and decreased nonperseverative errors on the WCST. Smoking status also contributed to some cognitive differences, varenicline showed a significantly greater improvement in CPT reaction time in smokers but greater improvement in SWCT in non-smokers. Hong *et al*. [222] studied approximately 60 smoking and non-smoking people with schizophrenia over 8-weeks. After two weeks a series of biomarkers were tested and varenicline was found to reduce P50 auditory sensory gating in non-smokers and reduced startle response and antisaccadic error regardless of smoking status. However, other biomarkers including prepulse inhibition and memory saccadic error were not significantly different. After 8 weeks the varenicline treated group did not show significant improvement on the DSST or a CPT task.

None of the participants in the varenicline studies reported had adverse events related to worsening of psychosis. But some of the adverse reports of varenicline induced worsening of psychosis are in people with schizophrenia treated with an antipsychotic [219]. Therefore, the limited effects seen in cognitive enhancement along with the potential for adverse side effects will most likely limit future uses of varenicline as a cognitive enhancer. Another experimental α4β2 nAChR agonist, AZD3480, showed no cognitive enhancing effects in a study of 410 people with schizophrenia who smoke, but the medication was well tolerated [225].

ALPHA7 nAChR MEDICATIONS

Several medications that target α7 nAChR agonists have been in development as cognitive enhancers for schizophrenia, for review see Wallace, T. L. and Bertrand, D. [111]. To date few of the compounds have made it to market or published in peer-reviewed journals, although a few medication trials have been published. DMXB-A, an α7 nAChR agonist, has had many studies published [226-229]. Only two of the studies assessed changes in cognitive function in people with schizophrenia. In a three-day crossover study comparing 2 doses of DMXB-A and placebo, the lower dose of DMXB-A had statistically greater improvement on the total RBANS score than placebo [226]. A four-week crossover study of the same doses used in the proof-of-concept study showed no significant changes in cognition between placebo and DMXB-A. Practice effects were seen in the cognitive battery and a reanalysis of only the first randomization showed DMXB-A improved attention/vigilance with both doses and working memory with the low dose. Both DMXB-A studies excluded smokers from participation in the study. P50 gating was improved in non-smoking schizophrenia patients on the lower dose of DMXB-A [100]. Tropisetron, another α7 nAChR agonist, was tested in an eight-week randomized double-blind placebo controlled trial in 33 participants with schizophrenia stabilized on risperidone [230]. The primary analysis found no cognitive improvements with tropisetron but among nonsmokers sustained visual attention and P50 gating was improved compared to placebo. Lieberman *et al*. [231]

reported on a 12-week randomized double-blind placebo controlled trial of 154 people with schizophrenia treated with TC-5619 while stabilized on risperidone or quetiapine, almost half of the participants were cigarette smokers. TC-5619 did not show any cognitive improvement in cognitive abilities on any of the cognitive tasks but a subanalysis found smokers have significant improvement in working memory and executive function. A recently published study, which did not have a cognitive battery, found that the positive α7 nAChR allosteric modulator JNJ-393934 did not affect P50, MMN or P300 [147].

CONCLUSION

Reducing the cognitive impairments associated with schizophrenia and increasing functioning remains an important goal of treatment. Several lines of evidence suggest alterations in the nAChRs system in people with schizophrenia. While nicotine use is relatively ubiquitous in people with schizophrenia, there is little evidence to support the notion that nicotine and other nAChRs-based treatments have profound cognitive enhancing qualities. Tasks measuring attention generally improve with nicotine administration and nAChRs-based treatments in schizophrenia, but the published reports often use large batteries with multiple outcomes and fail to account for multiple comparisons. The reported improvements are normally from secondary analysis and not robust signals of general cognitive improvement. Although more traditional cognitive test batteries have failed to capture consistent improvements with drugs acting at nAChRs, more proximal measures of information processing indexed by ERPs, have demonstrated some benefit.

The lack of beneficial effects of nicotine led to clinical trials with AChEIs. These drugs have also failed to show consistent, replicable, significant and clinically meaningful benefits. Larger ongoing studies for the allosteric modulator galantamine will hopefully provide more conclusive results (Clinicaltrials.gov identifier NCT01012167). Varenicline, also shows limited cognitive benefits unlike its utility as a treatment for smoking cessation in schizophrenia [232]. Initial studies with another α4β2 nAChR agonist have also been disappointing [225]. Selective α7 nAChR agonists have been tried in schizophrenia although the results are preliminary. Other α7 nAChR based drugs, such as positive allosteric modulators, are being investigated but are still early in development.

A number of factors need to be considered in developing nAChR based drugs. It is important to determine the influence of smoking status on the response to nAChRs-based medications, since the majority of people with schizophrenia smoke [16-19] and nicotine causes desensitization of nAChRs [31]. The current studies with nAChRs agonists have had varying degrees of allowance for cigarette smokers. The published studies with α7 nAChR agonist DMXB-A [226, 227] did not include any smokers in their studies while in the large study with TC-5619 [231] almost 50% of the sample were current smokers. Interestingly for TC-5619, cigarette smokers had slightly greater response to the medication than nonsmokers. This begs the question of whether nAChRs-based medications that are effective only in nonsmokers will be commercial viable given that most schizophrenia patients smoke? Furthermore, these medications are prescribed in the backdrop of antipsychotic medications that are dopamine D2 receptor antagonists and some which are potent anticholinergics [233]. Since dopamine and cholinergic signaling are important in

cognition [234], it is important that we determine if nAChRs agonists work with a variety of antipsychotic medications.

A greater understanding of the nicotinic system is needed to determine if it is a therapeutic target for cognitive enhancement. But the continued perseverance in preclinical and clinical testing with new medications may lead to nAChR based treatment strategies that improve clinical outcomes in schizophrenia by enhancing cognition.

FUTURE DIRECTIONS: NICOTINIC ALLOSTERIC MODULATORS

One of the challenges in activating nAChRs is their propensity to desensitize. Ongoing work is developing compounds that bind to the α7 nAChR at alternative sites than acetylcholine, and enhance transmission without inducing desensitization, such as positive allosteric modulators [111]. While several of these compounds are in the pipeline, clinical evidence is still awaiting publication. The development and testing of these compounds may usher in clinically relevant medications for the treatment of schizophrenia.

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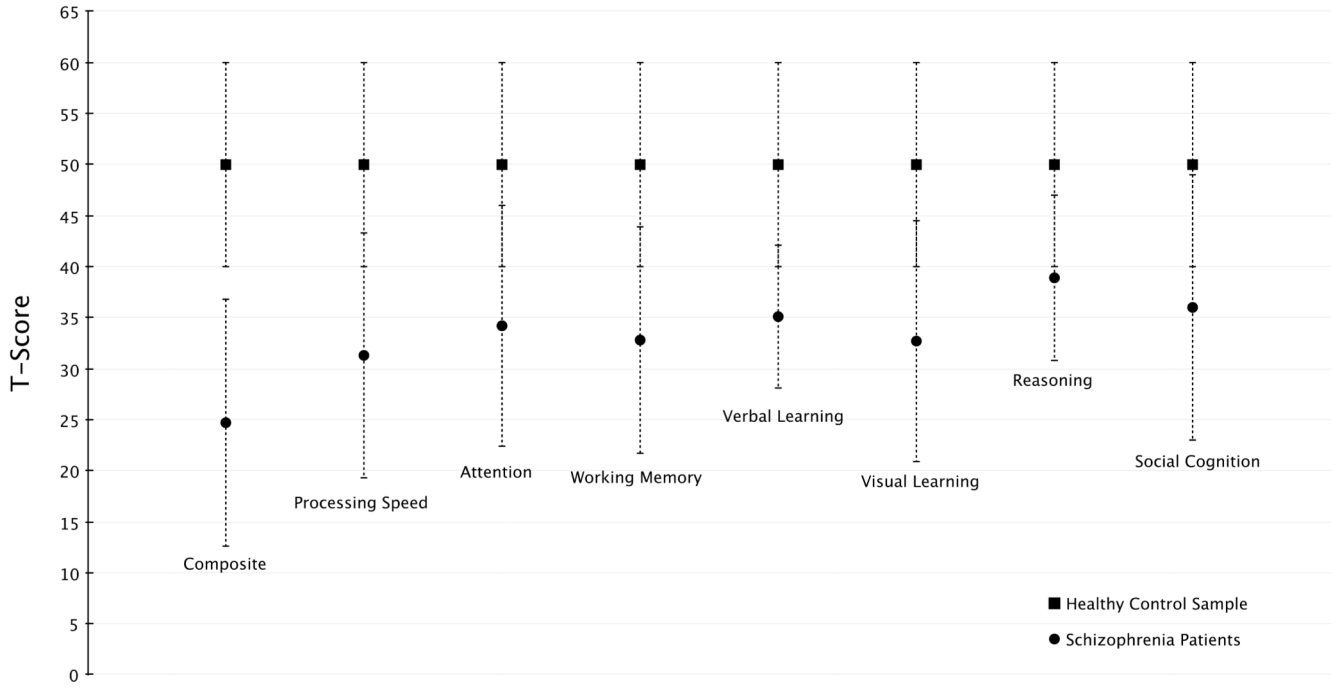

Fig. (1).

Comparison of cognitive scoring on the MATRICS consensus cognitive battery in schizophrenia patients (n=323) and a sample of healthy controls (n=300). Data shown as mean T-score ± SD from reference 57.

Table 1

Postmortem finding in people with schizophrenia versus healthy controls among nicotinic receptors either from ligand binding studies or messenger RNA/proteins

Reference	α7 Binding Ligand	α7 mRNA or Proteins	α4β2 Binding Ligand	α4β2 mRNA or Proteins
Freedman *et al* 1995	↓ Hipp		↓ Hipp	
Leonard *et al* 1998	↓ Hipp		↓ Hipp*	
Court *et al* 1999	↓ Thalamus		ND in many areas	
Guan *et al* 1999	↓PFC, ND PC			
Breese *et al* 2000 **			↓ Hipp, Thalamus, Cau	
Court *et al* 2000			↑ Striatum	
Durany *et al* 2000			↓ Striatum	
Leonard *et al* 2001		↓ Hipp		
Martutle *et al* 2001	↓ CC		↑ CC and OFC	
Martin-Ruiz *et al* 2003		ND DLPFC	↑ DLPFC	ND DLPFC
De Luca *et al* 2006		ND DLPFC		
Mathew *et al* 2007	ND DLPFC, Hipp	ND DLPFC and Hipp		
Mexal *et al* 2010		↓ Hipp***		
Thomsen *et al* 2011	ND Hipp			

Cau = Caudate, CC = cingulate cortex, DLPFC = dorsal lateral prefrontal cortex, Hipp = hippocampus, OFC = orbital frontal cortex, PC = parietal cortex, PFC = Prefrontal cortex, →= decrease, ↓= increase ND = no difference

* did not increase with nicotine use as seen in normal controls

** all comparisons smoking controls versus schizophrenia smokers

*** Only in non-smokers with schizophrenia

Table 2
Nicotine administration studies in people with schizophrenia that measure cognition

	Nicotine Administration	Dose (mg) or Administration	Duration	Design	Smokers	Antipsychotics	Enrolled	Cognitive Battery	Results of Nicotine (N) Compared to Placebo (P) or Control (C) Condition
Levin 1996	Patch	7, 14, 21	4 days	Placebo Crossover	100%	Haloperidol (titrated to low, medium, and how doses)	15	ANAM (DMS, RT, SMT, SPRT), CPT	SPRT: N > P, DMS: N > P, CPT: N > P (On all tasks interaction with nicotine dose and haloperidol dose)
Smith 2002	Cigarettes/Nasal	3-6 cigarettes / 50% 6 sprays (L) 50% 12 sprays (H)	4 days	Placebo Crossover	100%	1st and 2nd Generation	31	ANAM (DMS, RT, SMT, SPRT), RMT (5-items, DS, PW, SS), VF	SPRT: Cigarettes, Nasal > P RT: H Nasal > P PW, SS: Nasal > P
*Sherr 2002	Nasal	2 sprays	2 days	Crossover	52%	1st and 2nd Generation	29	CPT	N = C
*Depatie 2002	Patch	14	2 days	Placebo Crossover	100%	1st and 2nd Generation	15	CPT	CPT: N > P
*Myers 2004	Nasal	6 sprays	2 days	Crossover	52%	1st and 2nd Generation	29	DMS, DRT	DRT: (Smokers) N > control
*Jacobson 2004	Patch	28 or 35 Weight based	2 days	Placebo Crossover	100%	1st and 2nd Generation	13	SAL, VWM	VWM: N > P
Harris 2004	Gum	6	2 days	Placebo Crossover	50%	1st and 2nd Generation	20	RBANS	Attention: (Non-Smokers) N > control
Smith 2005	Nasal	8 sprays	4 days	Placebo Crossover	100%	1st and 2nd Generation	27	ANAM (SPRT), CPT, DMT, RANDT MS	CPT, DMT: N > P
*Barr 2007	Patch	14	2 days	Placebo Crossover	0%	1st and 2nd Generation	28	CPT, GP, LNS, ST	CPT, ST: N > P
*Jubelt 2008	Patch	14	2 days	Placebo Crossover	0%	1st and 2nd Generation	10	EMP	EMP: N > P
*Hong 2011	Patch	21 or 35 based on cigarette use	2 days	Placebo Crossover	100%	1st and 2nd Generation	20	RVIP	RVIP: N > P

	Nicotine Administration	Dose (mg) or Administration	Duration	Design	Smokers	Antipsychotics	Enrolled	Cognitive Battery	Results of Nicotine (N) Compared to Placebo (P) or Control (C) Condition
Hahn 2013	Cigarettes/Patch	Ad libitum/14	3 days	Placebo Crossover	100%	1st and 2nd Generation	17	SARAT, SDT	SARAT: Patch > P SDT: Patch, Cigarettes > P

ANAM: Neuropsychological Assessment Metrics, **CPT**: Continuous Performance Test, **CRT**: Complex Reaction Time, **DMS**: Delayed Matching to Sample, **DMT**: Dot Memory Test, **DRT**: Delayed Recognition, **DS**: Digit Span, **EMP**: Episodic Memory Paradigm, **GP**: Grooved Pegboard, **LNS**: Letter Number Sequence, **MS**: Memory Scale, **N**: Nicotine, **P**: Placebo, **PW**: Paired Words, **RBANS**: Repeatable Battery for the Assessment of Neuropsychological Status, **RMT**: Randt Memory test, **RT**: Reaction Time, **RVIP**: Rapid Visual Information Processing, **SAL**: Selective Attention Load, **SARAT**: Spatial Attentional Resource Allocation Task, **SDT**: Singleton Detection Task, **SMT**: Sternberg Memory Test, **SPRT**: Spatial Rotation Task, **SS**: Short Story, **ST**: Stroop Test, **VSWM**: Visuospatial Working Memory, **VWM**: Verbal Working Memory, **WCST**: Wisconsin Card Sorting Test, **WSPT**: Word Serial Position Test

* Healthy controls enrolled but results only on schizophrenia cohort

Table 3

Randomized double-blinded placebo-controlled studies of nicotinic medications measuring cognition in schizophrenia

	Experimental Medication	Target Dose (mg/day)	Duration (Weeks)	Design	Smokers	Antipsychotics	Randomized/ Completers	Cognitive Battery	Results Compared to Placebo
Friedman 2002	Donepezil	5 and 10	12	Parallel	78%	risperidone	36/34	CPT, DS, RAVLT, SSWMT, TMTA and B, VF, WCST	placebo = donepezil 10 = donepezil 5
Nahas 2003	Donepezil	10	12 each	Cross-over	NA	olanzapine or risperidone	6/6	COWAT	placebo = donepezil
Tuğa 2004	Donepezil	5	6 each	Cross-over	NA	fluphenazine or pimozide	12/12	TMTA and B, VF, WAIS (BD), WCST, WMS-R (DS, FG, LM, VePA, ViPA, ViR)	placebo = donepezil
Freudenreich 2005	Donepezil	10	8	Parallel	80%	Mostly olanzapine or risperidone	36/32	BOWA, GP, HVLT, TMTA and B, WMS-R (DS)	placebo = donepezil
Erickson 2005	Donepezil	5	8 each	Cross-over	NA	1st or 2nd generation	24/15	RAVLT, TMTA and B	RAVLT: donepezil > placebo
Mazeh 2006	Donepezil	10	12	Parallel	NA	1st or 2nd generation	20/17	ADAS-cog	placebo = donepezil
Lee 2007	Donepezil	5	12	Parallel	58%	haloperidol	24/23	BNT, DS, DSST, HVLT, MMSE, RVLT, ST, TMTA and B, VF	HVLT: donepezil > placebo MMSE, RVLT, DS: (trend) donepezil > placebo
Fagerlund 2007	Donepezil	10	16	Parallel	64%	ziprasidone	21/11	BSRT, CANTAB (IED, SOC, SSP), DS, RCFT, TMTB, VF	BSRT: placebo > donepezil SOC: (trend) placebo > donepezil
Kohler 2007	Donepezil	10	16	Parallel	46%	2nd generation (no clozapine)	26/22	BDAE (AN, Reading), CPT,CVLT, DS, DSST, FT, JOLO, LNNB, MEA (Token Task, COWAT, VNT), SR, WAIS (BD), WCST, WMS-R (LM, VR)	placebo = donepezil
Keefe 2008	Donepezil	10	12	Parallel	59%	2nd generation (no clozapine)	245/195	CATIE Battery: CI, COWAT, CPT, GP, HVLT, LNTAWM, VWMT, WISC-III Mazes, WCST, WAIS (DSST)	CI, COWAT: placebo > donepezil
Akhindzadeh 2008	Donepezil	10	12	Parallel	NA	Risperidone	30/30	WAIS (BD), WCST,	placebo = donepezil

	Experimental Medication	Target Dose (mg/day)	Duration (Weeks)	Design	Smokers	Antipsychotics	Randomized/ Completers	Cognitive Battery	Results Compared to Placebo
								WMS-R (DS, FG, LM, VePA, ViPA, ViR)	
Sharma 2006	Rivastigmine	12	24	Parallel	81%	Olanzapine, quetiapine, or risperidone	40/21	CPT, CVLT, DTS, FT, TMTA and B, VF, WCST, WAIS (DS, LNS)	placebo = rivastigmine
Kumari 2006	Rivastigmine	12	12	Parallel	81%	Olanzapine, quetiapine, or risperidone	36/21	n-back	placebo = rivastigmine
Chouinard 2007	Rivastigmine	9	24	Parallel	70%	1st or 2nd generation	24/20	CANTAB (PAL, RTI, RVIP, SOC, SWM)	placebo = rivastigmine
Schubert 2006	Galantamine	24	8	Parallel	94%	risperidone	17/14	CPT, OMMT, RBANS, TOT, UOA	RBANS (Total score, attention and delayed memory items): galantamine > placebo
Lee 2007a	Galantamine	16	12	Parallel	NA	1st generation	24/22	BNT, DS, DSST, HVLT, MMSE, RCFT, ST, TMTA, VF	RCFT: donepezil > placebo
Caroff 2007	Galantamine	8-24	12 each	Cross-over	NA	1st and 2nd generation	38/35	MMSE	placebo = galantamine
Dyer 2008	Galantamine	32	8	Parallel	0%	2nd generation	20/18	CPT,GP, ST, WAIS (LNS)	CPT, ST, LNS: placebo > galantamine
Sacco 2008	Galantamine	4 and 8	3 days	Cross-over	57%	NA	21/21	CPT, DS, ST, TMTB, VSWM	placebo = galantamine
Buchanan 2008	Galantamine	24	12	Parallel	42%	2nd generation (no clozapine), low dose 1st generation	86/73	BACS-NS, BVSMT, CPT, CVLT, GP, WAIS (DSST, LNS)	DSST: galantamine > placebo CVLT: (trend) galantamine > placebo CPT: placebo > galantamine
Lindenmayer 2011	Galantamine	24	24	Parallel	NA	long acting injectable risperidone	38/32	CPT, FT, OWMT, PEAT, SST, STDT, WLMT	placebo = galantamine
Hong 2011	Varenicline	2	8	Parallel	68%	1st and 2nd generation	69/59	CPT, MCCB, WAIS (DSST)	placebo = varenicline
Shim 2012	Varenicline	2	8	Parallel	52%	1st and 2nd generation	120/91	CPT, DS, ST, VST, WAIS (DSST), WCST	placebo = varenicline (smoking status had significant effects)
Velligan 2012	AZD3480	5,	12	Parallel	100%	Olanzapine, quetiapine, or risperidone	440/308	IntegNeuro, WAIS(SS), BACS-SC	placebo = AZD3480
Olincy 2006	DMXB-A	150/75 or 75/37.5	3 days	Cross-over	0%	1st and 2nd generation	13/12	RBANS	Total Score: 75/37.5 > placebo
Freedman 2008	DMXB-A	300 or 150	4	Cross-over	0%	1st and 2nd generation	31/31	MCCB	Attention/Vigilance: 300 and 150 > placebo Working Memory: 300 > placebo, (trend) 150 > placebo Verbal Learning: placebo > 300 and 150

	Experimental Medication	Target Dose (mg/day)	Duration (Weeks)	Design	Smokers	Antipsychotics	Randomized/ Completers	Cognitive Battery	Results Compared to Placebo
Shiina 2010	Tropisetror	10	8	Parallel	28%	risperidone	40/33	CANTAB (DMS, IED, PRM, RVIP, SOC, SRM, SSP, SWM)	RVIP (non-smokers): tropisetror > placebo
Lieberman 2013	TC-5619	25	12	Parallel	46%	quetiapine or risperidone	185/154	CSB, DSST, TMTA and B	1-back, GMLT, SCI-Cog: (trend) TC-5619 > placebo 1-back, GMLT (smokers): TC-5619 > placebo

ADAS-Cog: Alzheimer Disease Assessment Scale – Cognitive subscale, **AN**: Animal naming, **BACS-NS**: Brief Assessment of Cognition in Schizophrenia, **BD**: Block Design, **BDAE**: Boston Diagnostic Aphasia Exam, **BNT**: Boston Naming Task, **BOWA**: Benton Oral Word Association Test, **BSRT**: Buschke Selective Reminding Test, **BVSMT**: Brief Visuospatial Memory Test, **CI**: Category Instances, **COWAT**: Controlled Oral Word Association Test, **CPT**: Continuous Performance Test, **CSB**: CogState Schizophrenia Battery, **CVLT**: California Verbal Learning Task, **DMS**: Delayed Matching to Sample, **DS**: Digit Span, **DSST**: Digit Symbol Substitution Test, **DTS**: Dot Test Score, **FG**: Figural memory, **FT**: Finger Tapping, **GMLT**: Groton Maze Learning Task, **GP**: Grooved Pegboard, **HVLT**: Hopkins Verbal Learning Task, **IED**: Intra-Extra Dimensional Set Shifting, **JOLO**: Judgment of Line Orientation, **LM**: Logical Memory, **LNNB**: Luria-Nebraska Neuropsychological Battery (stereognosis), **LNS**: Letter Number Sequence, **LNTAWM**: Letter-Number Test of Auditory Working Memory, **MAE**: Multilingual Aphasia Exam, **MCCB**: MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) Consensus Cognitive Battery, **MMSE**: Mini-Mental State Examination, **NS**: Number Sequencing, **OMMT**: Object Matching Memory Test, **OWMT**: Object Working Memory Test, **PAL**: Paired Associates Learning, **PEAT**: Penn Emotional Acuity Test, **PRM**: Pattern Recognition Memory, **RAVLT**: Rey Auditory Verbal Learning Test, **RBANS**: Repeatable Battery for the Assessment of Neuropsychological Status, **RCFT**: Rey Complex Figure Test, **RTI**: Reaction Time, **RVIP**: Rapid Visual Information Processing, **RVLT**: Rey Visual Learning Test, **SC**: Symbol Coding, **SGI-Cog**: Subject Global Impression-Cognition, **SOC**: Stocking of Cambridge, **SR**: Seashore Rhythm, **SRM**: Spatial Recognition Memory, **SSP**: Spatial Span, **SST**: Set Shifting Test, **SSWMT**: Simple Spatial Working Memory Test, **ST**: Stroop Test, **STDT**: Strategic Target Detection Test, **SWM**: Spatial Working Memory, **TMTA and B**: Trail Making Test Part A and B, **TOT**: Tower of Toronto, **UOA**: Unirhinal Olfactory Acuity Test, **VePA**: Verbal Paired Associates, **VF**: Verbal Fluency, **ViPA**: Visual Paired Associates, **ViR**: Visual Reproduction, **VNT**: Visual Naming Task, **VST**: Visual Span Test, **VSWM**: Visuospatial working memory, **VWMT**: Visuospatial Working Memory Test, **WAIS**: Weschler Adult Intelligence Scale, **WCST**: Wisconsin Card Sorting Test, **WISC-III**: Wechsler Intelligence Scale for Children-Third Edition, **WLMT**: Word List Memory Test, **WMS-R**: Weschler Memory Scale-Revised