Published in final edited form as:
Prog Neuropsychopharmacol Biol Psychiatry. 2014 July 3; 0: 79–85. doi:10.1016/j.pnpbp.2013.07.010.

Neurocognitive Endophenotypes in Schizophrenia: Modulation by Nicotinic Receptor Systems

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Abstract

Cigarette smoking is the leading preventable cause of death in the Western world, with a considerably higher prevalence observed in schizophrenia compared to the general population. Despite the negative health consequences of smoking heavily, it has been proposed that individuals with schizophrenia may maintain smoking behaviours to remediate symptoms associated with the disorder. Neurocognitive deficits are a core feature of schizophrenia and are present in approximately 80% of patients. Further, these deficits constitute an endophenotype of schizophrenia, as they are stable across disease phases, and heritable. The neurocognitive deficits that are present in schizophrenia are especially debilitating, since they are associated with poor clinical and functional outcomes and community integration. Interestingly, these deficits may also constitute a vulnerability factor towards the initiation and maintenance of tobacco use. Contributing to the potential shared vulnerability between schizophrenia and tobacco dependence is a dysregulation of the nicotinic acetylcholine receptor (nAChR) system. Pre-clinical evidence has shown that nicotine affects several neurotransmitter systems, including dopamine (DA), glutamate, and γ-aminobutyric acid (GABA), and certain neuropsychological deficits associated with these neurotransmitters (reaction time, spatial working memory, sustained attention, and sensory gating) are improved after nicotine administration in patients with schizophrenia. These

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Disclosures: Ms. Mackowick, Ms. Rabin, and Drs. Barr, Ouellet-Plamondon and Wing have nothing to disclose. Dr. George reports that in the past two years he has been a consultant to Novartis and Pfizer, and has had investigator-initiated and multi-site study contract support from Pfizer. We acknowledge the editorial contributions of Ms. Maryam Sharif-Razi and Anushka Talpur to this manuscript.

positive effects on neurocognition appear to be more pronounced in smokers with schizophrenia, and may be an important mechanism that explains the co-morbidity of schizophrenia and tobacco dependence.

Keywords

Tobacco; Mental Illness; Schizophrenia; Cognition; Nicotine; Nicotinic Acetylcholine Receptors; Endophenotype

I. Introduction

Cigarette smoking is the leading preventable cause of death in the Western world (Mokdad et al. 2004), with a considerably higher prevalence seen among those with a psychiatric diagnosis, especially schizophrenia (45–85% versus 17% in the Canadian general population) (Kalman et al. 2005; Lasser et al. 2000). Not only are individuals with schizophrenia more likely to smoke cigarettes, but they smoke more cigarettes per day, are more nicotine dependent, and smoke more intensely (e.g. more puffs per cigarette, greater puff volume, and higher carbon monoxide (CO) boosts) (Tidey et al. 2005). Despite the negative health consequences of smoking heavily, it has been proposed that individuals with schizophrenia may sustain smoking to remediate certain symptoms of the disorder. Specifically, patients with schizophrenia may derive cognitive enhancement by means of cigarette smoking.

Neurocognitive deficits are a core feature of schizophrenia for which there are no satisfactory treatments. Cognitive deficits are present in approximately 80% of patients (Keefe et al. 2005) and affect many domains including attention, social cognition, executive function, and working memory (Heinrichs and Zakzanis, 1998). While positive and negative symptoms of schizophrenia are the most pronounced features of the illness insofar as leading to acute hospitalization and treatment, neurocognitive deficits have been relatively neglected, both in treatment and in research. Cognitive deficits that are present in schizophrenia are especially debilitating, as they lead to poor clinical, social, and functional outcomes. Moreover, these deficits are present throughout the patient's lifetime and are not the result of the positive or negative symptoms of the disorder, or antipsychotic treatment and appear to be stable and heritable features of schizophrenia (Green et al. 2004). As such, neurocognitive deficits are considered an endophenotype associated with this illness (Gottesman and Gould, 2005). These deficits may also constitute a vulnerability factor towards the initiation and maintenance of tobacco use (Sacco et al. 2004; George, 2007; Wing et al., 2012), as several studies have noted transient normalization of several neurophysiological measures of information processing after cigarette smoking or nicotine administration (Adler et al. 1993; Adler et al. 1998; Depatie et al. 2002; George et al. 2006; Olincy et al. 1998; Woznica et al. 2009), as well as further cognitive decline after smoking abstinence (George et al. 2002).

Two overarching theories that may explain the high smoking prevalence that is observed among schizophrenia patients are the self-medication hypothesis (SMH) and the addiction vulnerability hypothesis (AVH). The SMH proposes that individuals with schizophrenia

smoke to help ameliorate psychiatric symptomatology associated with the disorder (e.g. positive and negative symptoms, cognitive deficits, anxiety), as well as antipsychotic side effects (Khantzian, 1985; Winterer, 2010). The AVH (Chambers et al. 2001) proposes that there are shared genetic factors and brain abnormalities that underlie both schizophrenia and tobacco addiction (George, 2007; Chambers, 2009). We will focus specifically on nicotinic acetylcholine receptor (nAChR) dysfunction, and how this may contribute both to the cognitive deficits and the high smoking prevalence that is seen in individuals with schizophrenia.

We propose that there is value in treating cognitive deficits and co-morbid tobacco addiction simultaneously in people with schizophrenia. This review will present the most current information about the effects of nAChR dysregulation, as well as exogenous nicotinic agents, on neurocognitive deficits seen in schizophrenia. To this end, a comprehensive picture will be presented, examining different aspects of cognition, as well as including studies from multiple disciplines. Finally, a critical review will be presented to assess the present state of the field, where the gaps are, and to suggest future directions in the way of improving treatment options for those with schizophrenia and co-morbid tobacco dependence.

II. Neurobiology of Nicotinic Acetylcholine Receptors (nAChRs)

An emerging area of research is the potential shared vulnerability between schizophrenia and tobacco dependence, based on putative dysregulation of the nicotinic acetylcholine receptor (nAChR) systems. Nicotine, the main psychoactive constituent in tobacco smoke, acts at the α4β2 nAChR subtype; This receptor is also activated by the endogenous neurotransmitter acetylcholine. nAChRs in the central nervous system (CNS) are pentameric ion channel complexes (Dani et al. 2011) comprised of two α and three β subunits. There are seven α subunits designated α2–α9 and three β subunits designated β2–β4. Thus, there is considerable diversity in subunit combinations, which may explain some of the region-specific and functional selectivity of the effects of nicotinic agents throughout the CNS. Further, the subunits that comprise nAChRs determine whether they are high-affinity or low-affinity: Those that contain the β subunits belong to the high-affinity family while those that contain only α subunits belong to the low-affinity family. These pentameric receptors are either homomerically or heteromerically arranged (e.g. $(\alpha 7)_5$ or $(\alpha 4)_3(\beta 2)_2$). Activation of nAChRs leads to Na^+/Ca^{2+} ion channel fluxes and neuronal firing. Chronic exposure to nicotine results in receptor desensitization (Pidoplichko et al. 1997), inactivation, and upregulation (Gentry & Lukas, 2002). This increase in receptor number is dose-dependent but also reversible in smokers who quit smoking (Breese et al 1997). Due to their wide distribution throughout the CNS, nAChRs are situated on several different neurotransmitter secreting neuron types. Of importance for nicotine addiction are the nAChRs situated on mesolimbic dopamine (DA) neurons that project from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc). Activation of nAChRs on mesolimbic DA neurons leads to DA release in the NAcc, which helps to facilitate the addictive process involved in chronic tobacco use.

At low concentrations of nicotine, α4β2 nAChR stimulation of afferent GABAergic projections onto mesoaccumbal DA neurons predominates, leading to reduced mesolimbic DA neuron firing and DA release. At higher nicotine concentrations, α4β2 nAChRs desensitize and activation of α7 nAChRs on glutamatergic projections predominates, leading to increased mesolimbic DA neuron firing and DA secretion. Subsequently, nAChRs desensitize within several milliseconds of activation by nicotine. nAChRs then resensitize after overnight abstinence, which presumably explains why most smokers report that the first cigarette in the morning is the most satisfying.

Evidence suggests that individuals with schizophrenia, specifically smokers, show reduced upregulation of high-affinity nAChRs (Breese et al. 2000). Work by D'Souza and colleagues (2012) have demonstrated that smokers with schizophrenia have reduced β2 availability, which also correlated with greater severity of negative symptoms. Further, those with schizophrenia also have fewer α-bungarotoxin (α-BTX) binding sites in the hippocampus, which is indicative of a reduction in α7 nAChRs (Adler et al 1998; Freedman et al. 1995; Leonard et al 1996). This subunit has been genetically linked to schizophrenia, specifically P50 sensory gating deficits, an index of information processing (Freedman et al, 1997), as well as functional polymorphisms of the low-affinity nAChRs that alter sensory physiology (Leonard et al. 2000).

Neuroimaging techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fRMI) could possibly be used to study the effects nicotine has on neurocognition. Recent functional neuroimaging studies (Brody et al. 2006; Esterlis et al.2010) have shown that, after smoking to satiety, nAChR saturation levels are similar to the saturation levels seen after smoking just a few puffs. Therefore, while binding to central nAChRs is an important first step in the effects of nicotine, it is not a complete explanation for continued smoking behaviors. Further, given that nicotine administration improves cognition in patients with schizophrenia, and that smoking just a few puffs from a cigarette results in nAChR saturation, it can be concluded that nAChRs are critical to cognitive function in schizophrenia.

III. Nicotine and Neurocognition in Schizophrenia

Pre-clinical evidence has shown that nicotine alters several neurotransmitter systems, including DA, glutamate, GABA (Mansvelder & McGehee, 2002; Picciotto, 2003), and that certain neurocognitive deficits associated with these neurotransmitters (e.g., reaction time, spatial working memory, sustained attention) are improved after nicotine administration in schizophrenia (Depatie et al. 2002; Levin et al. 1996; Smith et al. 1996). Moreover, smoking abstinence can further impair spatial working memory performance deficits in smokers with schizophrenia (George et al. 2002). However, this effect is reversed once smoking is reinstated (Sacco et al. 2005). Moreover, the administration of the non-selective nAChR antagonist mecamylamine blocks the pro-cognitive effects of smoking reinstatement on visuospatial working memory (VSWM) in schizophrenia. This effect was specific to smokers with schizophrenia (versus healthy controls), and underscores the shared

vulnerability between schizophrenia and tobacco dependence, and implicates nAChR dysregulation in schizophrenia.

It is well-established that, in addition to neuropsychological deficits, there are numerous neurophysiological deficits in schizophrenia, and that nicotine administration can help to reverse these deficits. Prepulse inhibition (PPI), a measure of sensorimotor gating, has been proven to be a stable marker for those with schizophrenia (Grillon et al. 1992). Patients with schizophrenia reliably fail to attenuate their startle responses after being presented with a weak pre-pulse (Braff et al. 2011; Grillon et al 1992). In patients who smoke, PPI is impaired after overnight abstinence (George et al 2006) and is normalized during satiety (George et al. 2006; Woznica et al. 2009). Patients with schizophrenia also have P50 sensory gating deficits, where the second wave (P50 auditory evoked potential) of two paired auditory stimuli is greater than what is observed in healthy individuals (Adler et al. 1982; Judd et al. 1992). In patients who smoke, this deficit is temporarily normalized after cigarette smoking, which is in stark contrast to the P50 impairment that is seen in healthy smokers after cigarette smoking (Adler et al. 1993). A series of studies have shown that working memory deficits in patients with schizophrenia are associated with alterations in brain oscillations in the gamma (30–50 Hz) frequency range (Barr et al. 2010; Basar-Eroglu et al. 2007) and with an index known as theta-gamma coupling (Barr et al. 2013a). However, we recently demonstrated in a small sample of nicotine dependent smokers, that despite excessive gamma power and deficits in theta-gamma coupling, working memory performance was similar to a non-psychiatric control group (Barr et al. 2013b). Though preliminary, these results suggest that smoking may remediate working memory deficits in patients with schizophrenia. Smooth pursuit eye movement (SPEM), initiating and maintaining oculomotor pursuit movements to follow stimuli (Avila et al. 2003; Olincy et al. 2003), is impaired in those with schizophrenia. For example, patients demonstrate an inability to maintain eye velocity to match the moving stimulus and an increase in saccades, among other characteristics. A study by Avila and colleagues (2003) showed that nicotine administration in patients who smoke helped to improve SPEM performance, which further implicates the role of nAChRs in the neurocognitive deficits seen in those with schizophrenia.

IV. Treatment Implications

Effects of nicotine administration on cognition

Perhaps the strongest evidence implicating the role of nAChRs in the neurocognitive deficits seen in schizophrenia are smoking cessation treatment trials that focus on the effects nicotine administration has on neurocognitive performance. Preclinical studies have demonstrated that neurocognitive task performance is dependent on prefrontal cortical dopamine levels (Goldman-Rakic, 1999; Knable and Weinberger, 1997). After nicotine administration, dopamine release is enhanced and, conversely, is reduced after nicotine withdrawal (Fung et al. 1996; George et al. 1998; George et al. 2000; Hildebrand et al. 1998; Hildebrand et al. 1999; Vezina et al. 1992). Correspondingly, nicotine administration, in both satiated and abstinent conditions, has been shown to improve many dopamine-linked neurocognitive domains in those with schizophrenia, including verbal and spatial memory,

attention, and reaction time (Depatie et al. 2002; Harris et al. 2004; Jacobsen et al. 2004; Levin et al. 1996; Smith et al. 1996; Smith et al. 2006). Furthermore, additional neurocognitive impairments are seen with smoking abstinence, and remediation of these deficits is observed when smoking is reinstated (Sacco et al. 2005).

Many studies have found that cigarette smoking in schizophrenia improves dopamine-mediated neuropsychological processes. In a study by George and colleagues (George et al. 2002), visuospatial working memory (VSWM) performance was investigated in smokers with schizophrenia who had successfully quit smoking, and those who were current smokers. Results showed that abstinent smokers experienced further VSWM impairment compared to current smokers. Additionally, baseline cognitive data showed that abstinent smokers with schizophrenia had poorer VSWM performance than current smokers with schizophrenia. Subsequently, Sacco et al (2005) investigated the involvement of nicotinic receptor mechanisms in the effects that cigarette smoking has on cognition using a human laboratory paradigm. In this study, overnight smoking abstinence was found to impair VSWM performance, and reinstatement of cigarette smoking helped to reverse these additional impairments. After administration of the nAChR antagonist mecamylamine, the effects of smoking reinstatement were blocked, implicating the role of nAChRs in cognition in schizophrenia. Furthermore, administration of mecamylamine after smoking reinstatement in controls did not modulate VSWM performance. A secondary analysis of this data by Wing and colleagues (2011a), showed a significant positive correlation between plasma nicotine levels and cognitive performance in smokers with schizophrenia, further implicating nAChRs in the pro-cognitive effects seen in smokers with schizophrenia, as well as a specificity of these effects to schizophrenia relative to healthy controls. To further underscore the interaction between cigarette smoking and schizophrenia, Wing and colleagues (2011b) conducted a cross-sectional analysis of current, former, and never smokers with and without schizophrenia. Non-smokers with schizophrenia, and especially never smokers, showed poorer performance than current smokers on tasks that involved sustained attention, executive function, and response inhibition. These data also support the notion that never-smokers may represent a specific subgroup of schizophrenia patients that present with more severe neurocognitive deficits relative to current and past smokers.

In addition to studies examining the effects of cigarette smoking on neurocognition, several studies also employ nicotine replacement therapy (NRT), specifically the transdermal nicotine patch, to investigate the acute role of nAChRs in cognition. However, there are relatively few of these studies available as most NRTs are used in combination with other therapies such as Cognitive Behavioral Therapy or other cognitive therapies. For the purposes of focusing specifically on nicotine and nAChR mechanisms, only studies utilizing NRT monotherapy were considered. In a study by Barr and colleagues (2008), the effects of transdermal nicotine on cognition were investigated in nonsmoking patients and controls. Participants received either transdermal nicotine (14 mg) or placebo patch in a randomized, crossover design, and were administered a cognitive battery before and after patch application. As observed with cigarette smoking, nicotine significantly improved cognitive performance, specifically on a continuous performance task. Other measures (e.g., Stroop task) were only improved in patients relative to controls. These results underline the fact that nicotine, as opposed to the other constituents in tobacco smoke, improves cognition. In a

study by AhnAllen et al. (2008), three different nicotine conditions (baseline, 8 hours overnight withdrawal, 21mg transdermal nicotine) were employed to examine cognitive performance (the Attention Network Test [ANT]) in smokers with and without schizophrenia. While results showed that the groups did not differ in performance on ANT alertness, orienting, or executive functioning across all nicotine conditions, participants with schizophrenia did show faster reaction times with transdermal nicotine as compared to baseline. In comparison to controls, participants with schizophrenia also showed reduced accuracy after overnight smoking deprivation.

Effects of nAChR agonists and antagonists on cognition in schizophrenia

Due to less than optimal quit rates among smokers with mental illness (Lasser et al. 2000), particularly in schizophrenia, many smoking cessation pharmacotherapies are being investigated not only for their potential to aid in a successful quit attempt, but also for their ability to help ameliorate the symptoms associated with nAChR dysfunction. In fact, all three approved treatments for nicotine dependence (nicotine replacement therapies, bupropion and varenicline) act on central high-affinity nAChRs to some extent (George and O'Malley, 2004). However, to date, there are very few published, well-controlled trials that examine the efficacy of smoking cessation pharmacotherapies in treating cognitive impairments in schizophrenia.

One such pharmacotherapy that is receiving increasing attention in the schizophrenia literature is varenicline. Varenicline is a partial agonist at the α4β2 nAChR, and a low-affinity full agonist at the α7 receptor (Coe et al. 2005; Mihalak et al. 2006). This may be relevant to schizophrenia, as the α7 receptor has been implicated in the amelioration of P50 deficits by nicotine in schizophrenia patients (Adler et al. 1996; Adler et al. 1998; Freedman et al. 1997). Varenicline binds to the α4β2 nAChR and stimulates DA release from the nucleus accumbens (NAcc), which mirrors the DA release that is seen after nicotine administration, but to a lesser extent (Coe et al. 2005). While varenicline has been shown to be an effective anti-smoking pharmacotherapy (Gonzales et al. 2006; Oncken et al. 2006; Tonstad et al. 2006), including in smokers with schizophrenia (Williams et al. 2012), its pro-cognitive effects have not been widely studied. One of the first studies to examine the cognitive effects of varenicline in patients with schizophrenia was done by Smith et al (2009). Fourteen smokers with schizophrenia were enrolled in an open-label study that measured effects on cognitive function, cigarette smoking, and psychopathology. While varenicline did produce significant improvements in some scores associated with verbal learning and memory, there were no improvements in measures of attention or visual-spatial learning and memory. As this study was relatively small and lacked a placebo-control condition, subsequent studies on varenicline were needed. In a recent study by Shim and colleagues (2012), the effects of varenicline treatment on cognitive impairments in individuals with schizophrenia were examined. This study included 120 outpatients with schizophrenia, 60 smokers and 60 non-smokers. Participants were randomly assigned to receive either varenicline or placebo, and underwent a neurocognitive test battery at baseline and weeks 1, 2, 4, and 8. Results showed that varenicline improved performance on the Digital Symbol Substitution Test and the Wisconsin Card Sorting Test non-perseverative errors relative to placebo. In smokers, Continuous Performance Test reaction time and

Stroop interference were reduced after varenicline administration compared to placebo. In another study by Hong and colleagues (2011), varenicline was administered to both smoking and non-smoking patients and assessed its short and long-term effects on cognitive measures and biomarkers. Additionally, they employed a slow titration method and moderate dosing (half the recommended dose used for smoking cessation) so that α4β2-specific effects could be retained while simultaneously minimizing any adverse side effects. Regardless of smoking status, varenicline (1 mg/day) was shown to reduce the startle response (PPI) and improve executive function via reduction of anti-saccade error rates. In nonsmokers, the P50 sensory gating deficit was reduced after long-term varenicline treatment. While varenicline cannot fully mimic the robust effects of nicotine (as it is a nAChR partial agonist), it may be safe and effective to help ameliorate cognitive deficits, especially in nonsmokers with schizophrenia. It is also possible, given the effects on various biomarkers, that varenicline treatment could be used to target different subgroups of patients that present with different or more pervasive biological abnormalities. While these results suggest some beneficial effects of varenicline treatment for improving cognitive function, especially in smokers, further study is still needed.

In addition to laboratory studies, the effectiveness of varenicline for smoking cessation in schizophrenia has also been evaluated in clinical trials. In an open label trial by Pachas et al (2012) evaluated the effectiveness of 12 weeks of varenicline treatment with weekly group cognitive behavioral therapy on smoking outcomes in smokers with schizophrenia. Participants took varenicline for 4 weeks before attempting cessation. Patients showed improved psychotic symptoms, depressive symptoms, and nicotine withdrawal symptoms. Additionally, 14- and 28-day abstinence rates were 47.3% and 34%. For those who did not achieve abstinence, expired CO declined greatly, reflecting a decrease in smoking behavior. Williams et al (2012) evaluated the efficacy of varenicline, not in combination with CBT, for smoking cessation in patients with schizophrenia or schizoaffective disorder. At end of treatment (12 weeks) 19.0% of patients met criteria for smoking cessation versus 4.7% for placebo. Additionally, varenicline treatment was well-tolerated, and there was no evidence of psychotic or mood symptom exacerbation. Taken together, for those with schizophrenia, varenicline is a suitable and effective smoking cessation aid, especially in combination with CBT.

While much of the research concerning smoking cessation pharmacotherapy is focused on varenicline, there are other available compounds that act on nicotinic receptors. Bupropion is a commonly used non-nicotine pharmacotherapy that likely involves dopamine and norepinephrine blockade as its primary mechanism of action (Ascher et al. 1995), as well as antagonism of high-affinity nAChRs (Slemmer et al. 2000). The cognitive effects of bupropion in schizophrenia, as well as the effects of tobacco abstinence, were investigated in a study by Evins and colleagues (2005). After controlling for abstinent status, bupropion was associated with a reduction in reaction time on a continuous performance task (AX-CPT), as well as a reduction in perseverative errors on a task of verbal learning and memory (California Verbal Learning Test). While this study does show promise for the utilization of bupropion for ameliorating cognitive deficits, the need for replication is great.

Mecamylamine is a non-competitive antagonist for many nAChRs, both centrally and peripherally (Martin et al. 1990; Martin-Ruiz et al. 1989). In order to evaluate the effects of nAChR blockade on cognitive performance in schizophrenia, Sacco et al (2005) designed a within-subjects study to compare neuropsychological performance in smokers with and without schizophrenia after administration of mecamylamine. Subjects were treated with placebo, 5.0 and 10.0 mg/day of mecamylamine, and then performed a cognitive battery that included tests of visuospatial working memory, attention, verbal memory, and executive function. This cognitive battery was completed at baseline, after overnight smoking abstinence, and after smoking reinstatement. In patients, visuospatial working memory was significantly impaired following overnight abstinence, and this was remediated after smoking reinstatement. However, after administration of mecamylamine, the pro-cognitive effects of nicotine were blocked. In a separate study by this group performed in non-smokers (Sacco et al. 2006), mecamylamine had no effect on performance in either the patients or the controls. While mecamylamine has no pro-cognitive effects, evidenced by the absence of an effect on performance in non-smokers, the fact that it blocks the pro-cognitive effects of nicotine emphasize that amelioration of cognitive deficits in schizophrenia largely depend on nAChR stimulation.

Galantamine is a cholinesterase inhibitor and a potent modulator of central nAChRs (Coyle and Kershaw, 2001), and several trials have shown that galantamine may be effective in treating cognitive impairments (Schubert et al. 2006; Buchanan et al. 2008). Sacco and colleagues (2008) examined the effects of acute doses of galantamine in satiated and abstinent smokers and non-smokers with schizophrenia. No neurocognitive improvements were seen after any of the acute galantamine doses, regardless of smoking status, indicating that galantamine may not be useful for treating cognitive deficits in schizophrenia.

In addition to the many readily-available pharmacotherapies, there are also a number of experimental nicotinic agents in development. Several α7 agonists are currently being investigated for potential cognitive enhancement in schizophrenia. This is especially important because the α7 receptor has been specifically implicated in schizophrenia, as it is linked to P50 gating deficits (Freedman et al. 1997). Olincy and Freedman (2012) found that an alternative nicotinic agent, 3-[2,4-dimethoxybenzylidene]anabaseine (DMXB-A), improved attention, working memory, and negative symptoms in nonsmokers with schizophrenia. An exploratory, placebo-controlled trial of the Targacept compound TC-5619 by Lieberman et al (2013) was conducted to test the effects of the aforementioned α7 agonist on cognitive dysfunction and negative symptoms in schizophrenia. Working memory was the only cognitive measure that was significantly improved in those patients who were smokers. Due to the exploratory nature of both of these studies, additional research is needed to explore the full range of possible benefits of α7 agonism in schizophrenia patients, especially in smokers.

V. Conclusions and Recommendations for Future Studies

While treatment of tobacco dependence and pervasive cognitive deficits remain formidable challenges in schizophrenia, the amelioration of cognitive deficits after nicotine (or nicotinic agent) administration may provide some insight into the pathophysiology of schizophrenia.

As schizophrenia patients do indeed derive some cognitive benefit from smoking and other forms of nicotinic stimulation, it is of utmost importance to target drug development towards the nAChR system. Moreover, it is important to consider the heterogeneity in schizophrenia, especially in terms of smoking status and cognitive endophenotypes, as differential responses to nicotine administration may reflect underlying neurobiological differences within the overarching disorder of schizophrenia. For example, there is considerable inter-individual variability in P50 gating dysfunction in schizophrenia patients (Patterson et al., 2008), and in healthy controls acute nicotine administration appears to benefit only those with marked gating dysfucntion, and can even impair gating in good P50 suppressors (Knott, Fisher, & Miller, 2010; Knott et al., 2013; de la Salle et al., 2013). Accordingly, P50 gating may be one method to select more homogeneous patient groups in future clinical trials.

While the majority of schizophrenia patients are smokers, there are some who have successfully quit, and some who have never been smokers. In order to gain insight into what factors may protect some patients from becoming smokers, more controlled studies using never smokers and former smokers should be conducted. Additionally, genetic and imaging studies could help elucidate differences in nAChR expression and function between these groups.

In addition to schizophrenia, bipolar disorder (BD) and major depressive disorder (MDD) are also associated with a high smoking prevalence and neurocognitive impairments. Unlike schizophrenia, however, smoking is not associated with modulation of neurocognitive dysfunction in smokers with BD or MDD (Morisano et al., 2013). Due to the specificity of cigarette-smoking modulation of neurocognition in schizophrenia, as well as the need for improvement of smoking cessation outcomes (Wing et al., 2012), developing treatments that target the nAChR system, both to benefit neurocognition and other psychiatric outcome measures, is of utmost importance.

Taken together, there is increasing evidence to suggest that nicotine and nicotinic agents can ameliorate neurocognitive deficits in schizophrenia patients. More specifically, nAChR mechanisms play a critical role both in the pathophysiology of schizophrenia, as well the vulnerability of these patients to co-morbid nicotine and tobacco dependence. With this knowledge, and an absence of available cognitive-enhancing therapies, nicotine and nAChR agonists may be a beneficial pharmacological treatment strategy to target neurocognitive dysfunction and tobacco dependence in schizophrenia.

Acknowledgments

This work was supported in part by grants from the Canadian Institutes for Health Research (CIHR MOP#115145 to Dr. George), the Canada Foundation for Innovation (CFI-LOF#19229) and Ontario Mental Health Foundation (to Drs. George and Barr), the Chair in Addiction Psychiatry at the University of Toronto (to Dr. George), the Institute of Medical Sciences (Ms. Mackowick) and NIDA grant K02-DA-016611 (Dr. George).

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Table 1

Summary of Studies of Neurocognition and Nicotinic Pharmacotherapies for Tobacco Addiction in Schizophrenia

Intervention	Finding	Reference
NRT	Transdermal nicotine (14 mg) administered to non-smoking patients and controls significantly improved cognitive performance; some measures were only increased in patients relative to controls	Barr et al., 2008
	Smokers with SCZ showed faster reaction times while on 21 mg transdermal patch relative to baseline; SCZ also showed reduced accuracy after overnight smoking deprivation relative to controls	AhnAllen et al., 2008
Varenicline	In smokers with SCZ, varenicline produced significant improvements in some scores associated with verbal learning and memory, but no improvements in attention or visuo-spatial learning and memory	Smith et al., 2009
	In smokers and non-smokers with SCZ, varenicline improved DSST and WCST non-perseverative errors relative to placebo; CPT RT and Stroop interference was reduced after varenicline administration in smokers	Shim et al., 2012
	Regardless of smoking status, varenicline reduced PPI and antisaccade error rates (improvement of executive function) in SCZ; non-smokers had reduction of P50 gating deficit after long-term varenicline treatment	Hong et al., 2011
	Varenicline + CBT improved psychotic symptoms, depressive symptoms, and nicotine withdrawal symptoms in smokers with SCZ; 14- and 28-day abstinence rates were 47.3% and 24%, respectively	Pachas et al., 2012
	Varenicline alone did not produce symptom exacerbations or other safety concerns; 19% of patients on varenicline met criteria for cessation vs 4.7% for placebo	Williams et al., 2012
Bupropion	Bupropion reduced RT on a continuous performance task (AX-CPT) and perseverative errors on a verbal learning and memory task (CVLT)	Evins et al., 2005
Mecamylamine	VSWM was significantly impaired in patients after overnight smoking abstinence. This effect was reversed after smoking reinstatement. Administration of mecamylamine blocked the pro-cognitive effects of nicotine.	Sacco et al., 2005
	In non-smokers, mecamylamine administration showed no effect on cognitive performance in either patients or controls.	Sacco et al., 2006
Galantamine	In patients, galantamine may have benefits for processing speed and verbal memory.	Buchanan et al., 2008
	Adjunctive galantamine treatment with risperidone improves memory and attention in patients with schizophrenia.	Schubert et al., 2006
	Acute doses of galantamine had no effect on neurocognition in satiated and abstinent smokers and non-smokers with schizophrenia.	Sacco et al., 2008
DMXB-A (GTS-21)	In non-smokers with SCZ, DMXB-A improved attention, working memory, and negative symptoms	Olincy & Freedman, 2012
TC-5619	In patients who smoked, working memory was significantly improved after TC-5619 administration; No other cognitive measures were affected.	Lieberman et al., 2013