Published in final edited form as:
Neuropharmacology. 2012 March ; 62(3): 1564–1573. doi:10.1016/j.neuropharm.2011.01.044.

Schizophrenia and tobacco smoking comorbidity: nAChR agonists in the treatment of schizophrenia-associated cognitive deficits

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Abstract

Tobacco smoking is a preventable cause of morbidity and mortality throughout the world. Very high rates of tobacco smoking are seen in patients with schizophrenia. Importantly, smokers with schizophrenia generally have higher nicotine dependence scores, experience more severe withdrawal symptoms upon smoking cessation, have lower cessation rates than healthy individuals, and suffer from significant smoking-related morbidity and premature mortality compared with the general population. Interestingly, significant disturbances in cholinergic function are reported in schizophrenia patients. The high smoking-schizophrenia comorbidity observed in schizophrenia patients may be an attempt to compensate for this cholinergic dysfunction. Cholinergic neurotransmission plays an important role in cognition and is hypothesized to play an important role in schizophrenia-associated cognitive deficits. In this review, preclinical evidence highlighting the beneficial effects of nicotine and subtype-selective nicotinic receptor agonists in schizophrenia-associated cognitive deficits, such as working memory and attention, is discussed. Furthermore, some of the challenges involved in the development of procognitive medications, particularly subtype-selective nicotinic receptor agonists, are also discussed. Amelioration of schizophrenia-associated cognitive deficits may help in the treatment of schizophrenia-smoking comorbidity by promoting smoking cessation and thus help in the better management of schizophrenia patients.

1. Introduction

Tobacco dependence in the form of cigarette smoking is often associated with psychiatric comorbidity. Individuals with a psychiatric disorder consume approximately 46% of all cigarettes smoked in the United States (Grant et al., 2004). Exceptionally high smoking rates (60–90%) are reported in patients suffering from schizophrenia (Chapman et al., 2009; de Leon et al., 1995; de Leon and Diaz, 2005; Dome et al., 2010; Hughes et al., 1986; Leonard et al., 2001). Schizophrenia patients also have a higher risk of being current smokers compared with people from the general population (Dome et al., 2010).

Smokers with schizophrenia can be classified as "heavy smokers" and take a greater number of puffs, have shorter interpuff intervals, and consume larger total cigarette puff volumes

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compared with smokers in the general population (Tidey et al., 2005). Furthermore, smokers with schizophrenia had higher blood and saliva nicotine levels compared with control smokers matched for cigarette smoking (Williams et al., 2005). Additionally, smokers with schizophrenia reported greater reinforcing effects from smoking, making them more vulnerable to developing nicotine dependence (Spring et al., 2003). Importantly, withdrawal symptoms upon abstinence from smoking were generally more severe in schizophrenia patients than smokers without schizophrenia (Weinberger et al., 2007). Thus, smoking cessation in these patients poses a significant challenge compared with smokers without schizophrenia. Finally, heavy smoking habits and the inability to abstain from smoking often lead to significant cardiovascular and pulmonary morbidity, resulting in premature deaths in schizophrenia patients (Hennekens, 2007; Shanmugam et al., 2007; de Leon and Diaz, 2005).

To promote smoking cessation in schizophrenia patients, understanding some of the possible reasons for high smoking-schizophrenia comorbidity is critical. In this article, we focus on cholinergic neurotransmission dysfunction reported in schizophrenia patients and its possible role in mediating some of the schizophrenia-associated cognitive deficits. Additionally, some of the procognitive effects of nicotine and subtype-selective nicotinic acetylcholine receptor (nAChR) agonists important for the treatment of schizophrenia-associated cognitive deficits are discussed.

2. Theories explaining the high prevalence of smoking among schizophrenia patients

Several hypotheses have been offered to explain the high prevalence of smoking in patients with schizophrenia. A popular hypothesis is the "self-medication hypothesis," in which smoking may help schizophrenia patients manage their symptoms, such as positive symptoms, negative symptoms, and cognitive symptoms, by compensating for the underlying neurobiological deficits associated with the disorder (Adler et al., 1998b; Dome et al., 2010; Khantzian, 1985; Leonard et al., 2001; Leonard et al., 1998; Markou et al., 1998). An additional or complementary hypothesis is that the high comorbidity may be attributable to the hypothesized beneficial effects of smoking on some of the aversive effects of psychiatric medications (Barr et al., 2008a). For example, smoking is believed to relieve some of the extrapyramidal symptoms caused by classical antipsychotic treatments. Finally, some studies suggest that smoking and psychiatric disorders may have common risk factors (Chambers et al., 2001). The discussion of the merits and evidence supporting each of these hypotheses is beyond the scope of this review. In this review, we tacitly support the "self-medication hypothesis" by implicating deficits in cholinergic neurotransmission (discussed below) reported in schizophrenia patients as a possible cause for the high incidence of smoking-schizophrenia comorbidity.

3. Dysfunction in cholinergic neurotransmission in schizophrenia: Evidence from clinical and preclinical studies

Postmortem brain analysis of patients with a history of schizophrenia reported elevated levels of choline acetyltransferase, an enzyme involved in the synthesis of acetylcholine, in several brain areas, such as the hippocampus, caudate, putamen, thalamus, and septal areas, compared with controls (McGeer and McGeer, 1977). In contrast, decreased levels of choline acetyltransferase were reported in the nucleus accumbens and pons in schizophrenia patients (Bird et al., 1977; Karson et al., 1993). Furthermore, a postmortem histochemical analysis reported an increase in the number of cholinergic neurons in the pedunculopontine nucleus of the brainstem in patients with a history of schizophrenia compared with controls

(Garcia-Rill et al., 1995). Finally, studies using magnetic resonance spectroscopy revealed increased choline levels in several brain regions, such as the thalamus, anterior cingulate, and caudate nucleus in antipsychotic-naive patients diagnosed with schizophrenia compared with matched healthy volunteers (Bustillo et al., 2002; Theberge et al., 2004). Although the status of schizophrenia patients with respect to smoking was not reported in the aforementioned postmortem and clinical studies, data from a majority of studies support increased acetylcholine levels in the brains of schizophrenia patients. These increased acetylcholine levels are hypothesized to compensate for nAChR dysfunction.

Indeed, disturbances in nAChR expression and function have also been reported after postmortem evaluations of brains of schizophrenia patients compared with brains of subjects without schizophrenia. Decreased expression of α_7 nAChRs was found in several brain regions, such as the hippocampus, reticular nucleus of the thalamus, and prefrontal cortex in schizophrenia patients (Court et al., 1999; Freedman et al., 1995; Guan et al., 1999; Olincy and Stevens, 2007). Furthermore, autoradiographic studies indicated decreased $\alpha_4\beta_2$ nAChR binding in the hippocampus, cortex, and striatum in schizophrenia patients compared with controls (Breese et al., 2000; Durany et al., 2000). Finally, autoantibodies against nAChRs have been found in patients with schizophrenia (Chandley et al., 2009; Margutti et al., 2006).

In addition to changes in the expression or function of nAChRs, evidence from genetic studies links schizophrenia with nAChR genes. Schizophrenia-associated polymorphisms in the neuregulin-1 gene were associated with decreased α_7 nAChR binding and decreased α_7 nAChR mRNA levels in the prefrontal cortex (Mathew et al., 2007). Furthermore, schizophrenia-associated sensory motor gating deficits, measured by P50 evoked potentials for auditory stimuli, have been linked to α_7 subunit gene (*CHRNA7*) polymorphisms (Leonard et al., 1998). Altogether, the above studies suggest decreased cholinergic neurotransmission in schizophrenia patients.

Disturbances in cholinergic neurotransmission are also observed in putative animal models of schizophrenia that involve administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine and phencyclidine (PCP), in the induction of schizophrenia-like behavioral abnormalities. Interestingly, acute and repeated administration of the NMDA receptor antagonists ketamine and PCP resulted in increased release of acetylcholine in several forebrain regions (Kim et al., 1999; Nelson et al., 2002; Sato et al., 1996). In mice, PCP administration was associated with decreased α_7 nAChR expression (Hashimoto et al., 2008).

Interestingly, antipsychotics have anticholinergic properties and affect nAChR expression (Grinevich et al., 2009; Levin and Rezvani, 2007; Singhal et al., 2007; Terry et al., 2003). In unperturbed healthy rats, long-term administration of typical antipsychotic medications, such as haloperidol and chlorpromazine, and atypical antipsychotics, such as risperidone and olanzapine, resulted in decreased density of α_7 nAChRs in the hippocampus, frontal cortex, and basal forebrain (Terry et al., 2005). In contrast, long-term administration of typical (haloperidol and chlorpromazine) and atypical (risperidone and olanzapine) antipsychotics in rats did not affect $\alpha_4\beta_2$ nAChR density in the hippocampus (Terry et al., 2006). Finally, long-term administration of risperidone and haloperidol decreased choline acetyltransferase activity in the hippocampus and striatum. In contrast, long-term administration of clozapine and olanzapine did not affect choline acetyltransferase activity in the striatum and hippocampus. Altogether, the above preclinical data suggest that antipsychotics possibly worsen already decreased cholinergic neurotransmission in schizophrenia patients.

4. Cholinergic system and cognition

Schizophrenia is a complex, chronic multisymptom disorder associated with positive, negative, and cognitive symptoms that result in severe disability and often lead to social isolation and economic instability. Although disturbances in cholinergic transmission are seen in schizophrenia, it Is not clear what role this dysfunction plays in the pathophysiology of schizophrenia.

Optimal functioning of the cholinergic system is essential for normal cognitive function. The frontal cortex and hippocampus are two brain regions critically involved in cognitive function, and these two brain areas are tightly regulated by extensive cholinergic projections from several forebrain regions (Hasselmo and Sarter, 2010; Lysakowski et al., 1989; Mesulam, 2004; Rye et al., 1984; Sarter et al., 2005). Disruption of cholinergic system function, both in humans and animals via administration of cholinergic receptor blockers, resulted in cognitive impairment in tasks involving working memory and attention (Levin, 1988; Liljequist and Mattila, 1979; Nuotto, 1983). Furthermore, forebrain cholinergic neurons are activated in animals during the performance of tasks that assess attention and working memory (Masuda et al., 1997; Pepeu and Giovannini, 2004). Finally, pharmacological enhancement of cholinergic neurotransmission facilitated working memory in both humans and animals (Baratti et al., 1979; Cox and Tye, 1973; Davis and Mohs, 1982; Drachman, 1977). These studies highlight the critical role of cholinergic neurotransmission in cognitive function, including memory and attention.

5. Schizophrenia-associated cognitive impairment and smoking

Cognitive impairments are present in the majority of schizophrenia patients. However, the degree of severity of schizophrenia-associated cognitive deficits varies between individuals (Gold and Harvey, 1993). Importantly, these cognitive deficits often lead to an inability to perform day-to-day functions. Schizophrenia-associated cognitive deficits affect several domains, such as verbal learning and memory, attention, speed of processing, problem solving, visual learning and memory, social cognition, and working memory (Nuechterlein et al., 2004). Schizophrenia-associated cognitive deficits are a major problem because current schizophrenia treatments mainly target the positive symptoms (classical and atypical antipsychotics) and negative symptoms (atypical antipsychotics) with either no or limited procognitive effects (Velligan and Miller, 1999). Unfortunately, classical antipsychotics are known to worsen schizophrenia-associated cognitive deficits (Kasper and Resinger, 2003). Treatment of schizophrenia-associated cognitive deficits is critical because, as mentioned above, these deficits correlate greatly with day-to-day functioning, and attenuation or reversal of these cognitive deficits may improve functional outcomes and social rehabilitation in schizophrenia patients.

Interestingly, nicotine administration in both smoking and nonsmoking patients with schizophrenia resulted in the alleviation of cognitive deficits. For example, nicotine administration via nasal spray resulted in improvements in spatial organization and memory in patients suffering from schizophrenia (Barr et al., 2008b; Sacco et al., 2005; Smith et al., 2006). Furthermore, administration of nicotine in the form of nicotine gum or transdermal patch improved attention in schizophrenia patients (Barr et al., 2008b; Harris et al., 2004). Finally, abstinence from smoking in smokers with schizophrenia worsened deficits in spatial working memory and attention, which were alleviated by smoking (Sacco et al., 2005). Furthermore, alleviation of the aforementioned cognitive deficits upon resumption of smoking was blocked by administration of the nAChR antagonist mecamylamine (Sacco et al., 2005). The above studies suggest that tobacco smoking has beneficial procognitive effects in schizophrenia patients.

In summary, deficits in cholinergic function seen in schizophrenia patients may play a critical role in mediating impaired working memory, spatial organization, and attention in schizophrenia patients. Furthermore, tobacco smoking or nicotine administration alleviated schizophrenia-associated deficits in attention and memory. Thus, treatment of schizophrenia-associated cognitive deficits may promote smoking cessation in schizophrenia patients and significantly improve the health of schizophrenia patients.

4. Effects of nicotine and subtype-selective nAChR agonists on cognitive function

As discussed above, several cognitive domains are impaired in schizophrenia. Because of the limited literature on the beneficial effects of nicotine on cognitive domains other than attention and memory, this review is limited to preclinical studies that evaluated the effects of nicotine and subtype-selective nAChR agonists on attention and working memory in both unperturbed animals and putative animal models of schizophrenia. The available clinical studies that support a role of nicotine and subtype-selective nAChR agonists in attention and memory tasks are presented. Preclinical tasks used to assess the beneficial effects of nicotine and subtype-selective nAChR agonists on attention and memory are briefly described in Table 1.

4.1. Effects of nicotine on memory and attention

Both acute and chronic nicotine administration enhanced working memory in the radial-arm maze in young adult and aged rats (Levin et al., 1993; Levin et al., 1990; Levin and Rose, 1990, 1991; Levin and Torry, 1996). The ventral hippocampus plays a critical role in the memory-enhancing effects of chronic nicotine. Ibotenic acid-induced lesion of the ventral hippocampus attenuated the memory-enhancing effect of chronic nicotine (Levin et al., 1999). Furthermore, nicotine administration enhanced working memory in delayed matching-to-sample tasks in aged nonhuman primates (Buccafusco and Jackson, 1991). Importantly, nicotine administration reversed the memory-impairing effects of some antipsychotic medications, such as clozapine and olanzapine, in the radial arm maze task in rats (Addy and Levin, 2002; Levin et al., 2005). Nicotine has also been shown to attenuate NMDA antagonist-induced impairments in working memory in the radial-maze task (Levin et al., 1998).

N-methyl-D-aspartate receptor dysfunction is hypothesized to be a key player in mediating the pathophysiology of schizophrenia, particularly schizophrenia-associated cognitive deficits (Goff and Coyle, 2001; Konradi and Heckers, 2003). Indeed, administration of the NMDA receptor antagonists PCP and ketamine produced a schizophrenia-like state in healthy humans and worsened existing symptoms in schizophrenia patients (Allen and Young, 1978; Bubenikova-Valesova et al., 2008; Malhotra et al., 1997; Steinpreis, 1996). Importantly, NMDA receptor antagonists, such as PCP and ketamine, profoundly disrupted cognitive function in both healthy subjects and schizophrenia patients (Krystal et al., 2000; Krystal et al., 1994; Malhotra et al., 1996), including disruptions in attention and working memory (Adler et al., 1998a; Krystal et al., 1994; Malhotra et al., 1996; Morgan et al., 2004). Consistent with this finding, NMDA receptor antagonists also disrupted performance in attention and working memory tasks in experimental animals (Amitai et al., 2007; Greco et al., 2005; Handelmann et al., 1987; Kesner and Dakis, 1993; Rezvani et al., 2008). Thus, NMDA receptor antagonist administration is often used as an inducing condition to model schizophrenia-like cognitive deficits in humans and animals (e.g., Amitai and Markou, 2010).

Nicotine also enhanced attention in several experimental animal procedures that assess attention. The 5-choice serial reaction time task (5-CSRTT) is extensively used to assess attention in animals (for review, see Chudasama and Robbins, 2004; Robbins, 2002; Young et al., 2009). The enhancement of attention by acute nicotine in unperturbed rats and mice, measured in the 5-CSRTT, is not very robust and can be best described as inconsistent (Blondel et al., 2000; Grottick and Higgins, 2000; Mirza and Bright, 2001; Muir et al., 1995; Semenova et al., 2007; Young et al., 2004). Importantly, however, the attention-enhancing effects of acute nicotine in the 5-CSRTT in unperturbed rats have been reported under challenge conditions, such as reducing the length of the visual stimulus, decreasing the intertrial interval, and other similar manipulations that increase attentional load (Hahn et al., 2002; Stolerman et al., 2000). In contrast to findings in unperturbed rats, acute nicotine administration enhanced performance in the 5-CSRTT in rats with lesions of cholinergic neurons in the basal nucleus of Meynert (Muir et al., 1995). Attention in rodents has also been evaluated using the sustained attention task, which is also sometimes referred to as the lateralized visual signal detection task (Bushnell, 1998; McGaughy and Sarter, 1995). The effects of acute nicotine on attention in this task in rats have also been mixed, with some studies reporting beneficial effects (Grilly, 2000; Rezvani et al., 2002) and others reporting no effects of nicotine (Bushnell et al., 1997; Turchi et al., 1995).

Several hypotheses have been proposed to explain the inconsistent effects of nicotine on attention in unperturbed animals. One hypothesis is that the cholinergic system is maximally activated in unperturbed animals. Therefore, nicotine administration cannot further improve performance (Turchi et al., 1995). Another hypothesis states that acute nicotine can produce dysphoric effects that may interfere with performance on attentional tasks (Heishman et al., 1993). Furthermore, repeated administration of nicotine is hypothesized to result in the development of tolerance to these dysphoric effects and consequently improve performance on attentional tasks. Indeed, chronic nicotine administration via subcutaneous osmotic minipumps in rats increased attention in the 5-CSRTT (Semenova et al., 2007). An earlier study also reported beneficial effects of chronic nicotine in rats in a go/no go task that had an attentional component (Nelsen and Goldstein, 1972). In summary, although chronic nicotine improved attentional performance, the effects of acute nicotine on attention are inconsistent, with studies reporting either pro-attentional or no effects on attention. Clearly, further work is required to fully understand the effects of nicotine on attentional processes.

Very few studies have assessed the effects of nicotine in putative animal models of schizophrenia. Chronic nicotine treatment did not improve PCP-induced cognitive deficits in the 5-CSRTT in rats (Amitai and Markou, 2009). In contrast, nicotine attenuated memory and attentional impairments induced by another NMDA receptor antagonist, dizocilpine, in the lateralized visual signal detection task in rats (Rezvani et al., 2008). The differences in the effects of nicotine on attention in these two studies could be attributable to subtle differences in the pharmacological profiles of the two NMDA receptor antagonists, phencyclidine and dizocilpine, that induce cognitive deficits in animals that resemble those seen in schizophrenia. Alternatively, the differential effects of nicotine could also be attributable to the cognitive tasks (5-CSRTT *vs*. lateralized visual detection task) used in the two studies. Both tasks assess attention, but the lateralized visual detection task may be more able to detect the proattention effects of nicotine than the 5-CSRTT. In summary, the above data suggest that acute and chronic nicotine enhanced attention in both unperturbed animals and putative animal models of schizophrenia.

4.2. Effects of subtype-selective nicotinic receptor agonists on memory and attention

$\alpha_4\beta_2$ and α_7 nAChRs play a critical role in mediating the memory-enhancing effect of nicotine. Nicotine-induced memory enhancement in the radial-arm maze task was blocked by the nAChR antagonists dihydro-β-erythroidine and methyllycaconitine, which exhibit

relative selectivity for these two receptors, respectively (Levin et al., 2002). Furthermore, the α_7 nAChR agonists *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide (ABBF) and GTS-21 enhanced working memory in the radial arm maze and the Morris water maze in aged rats (Arendash et al., 1995; Boess et al., 2007).

In addition to working memory, several α_7 and $\alpha_4\beta_2$ nAChR ligands have shown procognitive effects in recognition-based memory tasks, such as the social recognition memory and novel object recognition tasks. For example, administration of the α_7 nAChR agonists ABBF and AR-R17779 enhanced novel object and social recognition memory in unperturbed rats (Boess et al., 2007; Van Kampen et al., 2004). The α_7 nAChR agonists ABT-089, GTS-21, and A-582941 also improved working memory in the delayed matching-to-sample task in nonhuman primates (Briggs et al., 1997; Buccafusco et al., 2007). In a transgenic th(tk-)/th(tk-) mouse model that shares many of the anatomical and biochemical dysfunctions seen in schizophrenia, administration of the α_7 nAChR agonist TC-5619 improved novel object recognition memory (Hauser et al., 2009). Finally, the $\alpha_4\beta_2$ receptor agonist varenicline enhanced memory in a novel object recognition task in unperturbed rats (Rollema et al., 2009).

The role of α_7 nAChRs in attention is debatable because opposite findings have been reported in pharmacological and genetic studies. For example, the selective α_7 nAChR agonist AR-R17779 did not have beneficial effects on attention in the 5-CSRTT (Grottick and Higgins, 2000; Hahn et al., 2003), suggesting that α_7 nAChRs have possibly no role or a limited role in attention. In contrast, impairments in attention have been reported in α_7 nAChR knockout mice in the 5-CSRTT (Hoyle et al., 2006; Young et al., 2007; Young et al., 2004). However, compensatory neurobiological mechanisms occurring in α_7 nAChR knockout mice could be responsible for some of the attention-impairing effects in these mice. Additionally, differences in species (rats *vs*. mice) could also contribute to the different results between these two studies. Altogether, these findings suggest that α_7 nAChRs may be required for attention, but activation of these receptors in unperturbed animals by agonists may not enhance attention beyond a certain optimal level. Importantly, α_7 nAChRs are permeable to calcium and play an important role as heteroreceptors that modulate the release of several neurotransmitters (Dani, 2001). A small proof-of-concept trial showed beneficial effects of the α_7 nAChR partial agonist 3-[(2,4-dimethoxy)benzylidene]anabaseine (DMXB-A) on attention in nonsmoking patients with schizophrenia (Olincy et al., 2006). However, a larger clinical study in nonsmoking schizophrenia patients did not show beneficial effects of the same α_7 nAChR partial agonist (Freedman et al., 2008). The effects of α_7 nAChR agonists on attention need further evaluation in putative animal models of schizophrenia and smoking and nonsmoking schizophrenia patients.

$\alpha_4\beta_2$ nAChRs are also reported to play a role in attention, and ligands activating these receptors have shown beneficial effects on attention. Administration of the $\alpha_4\beta_2$ nAChR agonist ABT-418 enhanced attention in the 5-CSRTT in unperturbed rats (Hahn et al., 2003). In clinical studies, repeated administration of the $\alpha_4\beta_2$-selective agonist TC-1734 improved attention in healthy adults compared with placebo (Dunbar et al., 2007). Two small proof-of-concept clinical studies demonstrated improvement in attention after administration of the $\alpha_4\beta_2$-selective agonist ABT-089 and ABT-418 in adults with attention deficit disorder (Wilens et al., 1999; Wilens et al., 2006). Furthermore, selective $\alpha_4\beta_2$ receptor agonists may be hypothesized to have superior pro-attentional efficacy compared with nicotine (Howe et al., 2010). Further studies that evaluate $\alpha_4\beta_2$ nAChRs in animal models of schizophrenia and schizophrenia patients are warranted.

In summary, nAChR agonists, especially those acting at $\alpha_4\beta_2$ and α_7 nAChRs, have great potential to alleviate attentional and working memory deficits seen in schizophrenia. Currently, very few studies have evaluated compounds acting on these receptors in animal models of schizophrenia or schizophrenia patients. More importantly, these compounds need to be evaluated in smokers with schizophrenia. Several clinical studies are currently ongoing that assess the procognitive effects of $\alpha_4\beta_2$ and α_7 nAChR agonists in schizophrenia patients (http://www.clinicaltrials.gov).

5. nAChR agonists as procognitive medications for schizophrenia-associated cognitive dysfunction: Potential challenges and future directions

The use of nicotine for the treatment of schizophrenia-associated cognitive deficits is limited by its aversive effects seen at high doses and tachyphylaxis upon prolonged treatment (Buchanan et al., 2007). Recently, several subtype-selective positive allosteric modulators targeting the different nAChRs have been identified (Taly et al., 2009). These subtype-selective nAChR positive modulators/agonists may provide more tolerable and efficacious alternatives to nicotine (Taly et al., 2009). However, several challenges exist in the discovery and development of nAChR agonists as procognitive medications for schizophrenia-associated cognitive deficits. Cognition is a broad term that encompasses several domains. To perform tasks involved with daily living, either all domains or a combination of certain domains is required. A major challenge for the development of nAChR agonists as procognitive agents is identifying agents that are effective in improving several cognitive domains. Evidence currently suggests that subtype-selective nAChR agonists may enhance certain domains, while not being effective in others. Specifically, preclinical evidence suggests that $\alpha_4\beta_2$ and α_7 nAChR agonists have beneficial effects on memory and attention in preclinical animal models and clinical studies. Thus, compounds that positively target a large number of cognitive domains need to be identified. Interestingly, nAChRs undergo desensitization upon activation. Thus, activation of nAChRs may have very short-lasting effects. In this respect, identifying compounds that activate nAChRs without desensitization may prove to be extremely useful in the clinical development of these nAChR agonists as procognitive compounds. Finally, preclinical studies have shown that repeated administration of nicotine upregulates nAChRs (Flores et al., 1992; Schwartz and Kellar, 1983; Yates et al., 1995). Therefore, determining the effects of chronic administration of nAChR agonists on receptor expression and function and how these changes might alter the beneficial effects of these compounds on cognition is important.

Furthermore, novel nAChR-based cognitive enhancers may have interactions with currently used and under-development antipsychotic medications, resulting in unanticipated adverse effects in schizophrenia patients. Identifying possible interactions between nAChR compounds and antipsychotic medications using preclinical animal models will help limit the adverse effects or diminished efficacy resulting from the combined administration of nAChR-based procognitive medications and antipsychotic drugs. One way to overcome the problem of antipsychotic-nAChR interactions is to look for dual-use medications, such as nAChR-based cognitive enhancers with potential antipsychotic activity or antipsychotic compounds that will have potential procognitive effects. Recently, several allosteric modulators of muscarinic cholinergic receptors have been identified that have antipsychotic-like activity in preclinical animal models and procognitive properties (Bridges et al., 2010; Jones et al., 2008; Maehara et al., 2008). Muscarinic cholinergic receptors also play an important role in cognition and may be used as potential treatments for schizophrenia-associated cognitive deficits (Sellin et al., 2008), but the present review is limited to the

discussion of nAChRs. Finally, interactions between nAChR agonists and medications other than antipsychotic treatments that schizophrenia patients may be taking need to be determined. For example, a preclinical study reported a possible interaction between nicotine and the α_2 adrenergic receptor antagonist idazoxan. Specifically, repeated administration of nicotine and idazoxan in rats with dizocilpine-induced cognitive deficits resulted in the development of seizures in some rats (Timofeeva and Levin, 2008). Although idazoxan is not used in humans, α_2 adrenergic receptor antagonists are used in the treatment of hypertension in humans. Whether the interaction between nicotine and idazoxan was specific to idazoxan or would be seen with other α_2 adrenergic receptor antagonists remains to be determined.

Additionally, some general challenges exist in the discovery of procognitive medications. One of these challenges is the lack of translational tests across species to assess the procognitive benefits of compounds (Markou et al., 2009; Young et al., 2009). The development of procognitive medications is also hampered by the lack of animal models of cognitive deficits that have predictive validity (Markou et al., 2009). The establishment of predictive validity in terms of pharmacological isomorphism (Geyer and Markou, 1995) is hampered by the lack of an effective treatment for schizophrenia-associated cognitive deficits as a positive control. To improve the identification and development of new procognitive medications, the United States National Institute of Mental Health has so sponsored three initiatives, namely the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), and Treatment Units for Research on Neurocognition and Schizophrenia (TURNS) (Buchanan et al., 2007; Carter et al., 2008; Marder and Fenton, 2004). These initiatives have attempted to bring together academic, industrial, and government bodies to help in the development of new medications for the treatment of schizophrenia-associated cognitive deficits. Efforts are increasingly underway to develop tests for assessing cognitive function across species. These efforts may eventually help identify novel medications that target schizophrenia-associated cognitive deficits. Such medications may also ultimately help reduce schizophrenia-smoking comorbidity and improve the overall health of schizophrenia patients.

6. Negative symptoms in schizophrenia and the beneficial effects of nicotine

This review has largely focused on the beneficial role of tobacco smoking in schizophrenia-associated cognitive deficits. However, schizophrenia patients also suffer from significant negative symptoms, such as decreased motivation, anhedonia, altered expression of emotions, and a decreased amount or content of speech. The reinforcing effects of nicotine are well documented in both humans and animals (Corrigall and Coen, 1989; Goldberg and Henningfield, 1988). Therefore, high levels of smoking in schizophrenia patients could be an attempt to ameliorate the negative symptoms associated with schizophrenia. Supporting this hypothesis, a recent clinical study involving the α_7 receptor agonist DMXB-A showed considerable improvement in anhedonia and alogia (i.e., poverty of speech) in patients with schizophrenia (Freedman et al., 2008). However, a complete review of the beneficial effects of nicotine and nAChRs on the negative symptoms of schizophrenia is beyond the scope of this review.

7. Conclusion

A high degree of comorbidity exists between smoking and schizophrenia. Over the years, research has highlighted significant disturbances in the expression of nAChRs, especially α_7 and $\alpha_4\beta_2$ nAChRs, in both schizophrenia patients and putative animal models of

schizophrenia. Furthermore, the data suggest that administration of nicotine or nAChR subtype-selective agonists results in beneficial cognitive effects on attention and working memory in preclinical animal models. Because of the limitations of chronic tobacco use, α_7 and $\alpha_4\beta_2$ nAChR-based strategies are currently being evaluated as possible therapies for schizophrenia-associated cognitive deficits. Finally, although this review has focused primarily on nAChR-based strategies for the amelioration of schizophrenia-associated cognitive deficits, it must be understood that nAChRs are widely distributed as heteroreceptors on presynaptic nerve terminals and can influence the release of several different neurotransmitters.

In conclusion, addressing the problem of tobacco smoking in smokers with schizophrenia is critical for decreasing smoking-associated morbidity in schizophrenia patients. The treatment of symptoms not alleviated by antipsychotics, such as cognitive and negative symptoms, may be useful in promoting abstinence in schizophrenia patients. More work is clearly required to identify the neurobiological substrates mediating schizophrenia-smoking comorbidity. A better understanding of this comorbidity will help provide alternative and better treatments for smoking cessation, schizophrenia, and the comorbidity of these two disorders.

Acknowledgments

This work was supported by NIH research grants 2R01MH62527, 1R01DA11946, 2R01DA232090, and 2U19DA026838 to AM. MSD was supported by fellowship 19FT-0045 from the Tobacco-Related Disease Research Program (TRDRP) of the State of California. The authors would like to thank Mr. Michael Arends for outstanding editorial assistance.

Abbreviations

nAChR	nicotinic acetylcholine receptor
NMDA	*N*-methyl-D-aspartate
PCP	phencyclidine
5-CSRTT	5-choice serial reaction time task
ABBF	*N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide
DMXB-A	3-[(2,4-dimethoxy)benzylidene]anabaseine

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Table 1

Preclinical tasks assessing memory and attention.

Cognitive function	Task	Description	Reference
Memory	Radial arm maze	The radial arm maze consisted of an octagonal central chamber with eight attached arms. Each of the arms was baited with food, and the animal was expected to retrieve the reward (food) from each arm without revisiting a previously visited arm. Spatial working memory was measured by the number of baited arms entered prior to entering a previously visited arm. Chronic nicotine administration using subcutaneously implanted glass and silastic pellets (12 mg/kg salt) improved working memory 1 week after pellet implantation compared with saline controls. Subjects were female Sprague Dawley rats.	Levin et al., 1990
	Morris water maze task	In this task, animals were placed in the Morris water maze at different starting locations during multiple trials. The animals were expected to escape from drowning by locating a platform submerged under the water. The average distance traveled by the animal to locate the submerged platform from various start locations over multiple trials was used as a measure of working memory. The α_7 agonist ABBF (1 mg/kg, per oral [p.o.]) improved working memory in aged rats in the Morris water maze task.	Boess et al., 2007
	Novel object recognition task	This task was performed over two trials separated by 24 h. In the first trial, the subject was allowed to explore two objects. The second trial, conducted 24 h after the first trial, consisted of presentation of an object from the previous trial and a novel object. The discrimination index, defined as the difference in time spent exploring the novel object minus the time spent exploring the familiar object divided by the total time spent exploring the two objects, was used to assess novel object recognition memory. The α_7 agonist ABBF (0.3–1 mg/kg, p.o.) improved object recognition memory in mice.	Boess et al., 2007
	Social memory task	This task was performed over two trials separated by 24 h. On day 1, the adult rat being assessed was presented with a juvenile rat for a period of 2 min. Social investigation in the form of sniffing, grooming of body parts, anogenital sniffing, and close following was scored over the period of 2 min to build a composite social investigation score. On the following day (i.e., after 24 h), the adult rat was again presented with the same juvenile rat. A decreased social investigation score was indicative of social memory. The α_7 agonist ABBF (0.3–1 mg/kg, p.o.) improved social recognition memory in rats.	Boess et al., 2007
	Delayed matching-to-sample task	This computerized task was designed to assess memory in nonhuman primates. The task involved presentation of a stimulus of a specific color on the computer screen. The subject was allowed to respond after a delay of up to120 s by pressing one of two illuminated keys. One of the two illuminated keys was of the same color as the stimulus presented on the screen. Selection of the key matching the color of the stimulus presented was considered a correct response. The percentage of correct responses was used as a measure of attention. The percentage of correct responses after the longest delay was significantly greater after nicotine (7.5 μg/kg, intramuscular injection) administration in aged monkeys compared with saline controls.	Buccafusco and Jackson, 1991
Attention	5-Choice serial reaction time task	The experimental subject was expected to monitor a light stimulus that was presented in one of the five equidistant located apertures. The animal signaled the detection of the light stimulus by nosepoking in the aperture where the light stimulus appeared. Correct responses were rewarded, and incorrect responses were punished with a timeout period. Accuracy, a measure of attention, was defined as the total number of correct responses divided by the total number of correct and incorrect responses. Chronic nicotine administration (9 mg/kg/day, salt) via minipumps improved accuracy 4–6 days after minipump implantation compared with saline controls in Wistar rats.	Semenova et al., 2007
	Sustained attention task	In this task, experimental animals were required to detect a light "signal" that varied in intensity. In a given trial, the signal may or may not have been presented prior to presentation of two levers in the chamber. The animal was expected to respond by responding on one of the two levers, and the correct lever was determined based on where the light signal was presented prior to the introduction of the levers in the chamber. Attention was assessed by determining the correct number of hits (i.e., responding	Rezvani et al., 2002

Cognitive function	Task	Description	Reference
		on the correct lever when the signal was presented, defined as the total number of correct detections/total number of signal trials) or false alarms (i.e., animal incorrectly pressed the signal lever when no signal had been presented; number of false alarms/number of blank trials). Low doses of nicotine (0.0125, 0.025, and 0.05 mg/kg, salt; administered subcutaneously) dose-dependently increased the percent correct rejection in adult female Sprague Dawley rats. The same nicotine doses did not affect correct detections of the signal (i.e., percent hits).	