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Medications Development for the Treatment of Nicotine Dependence in Individuals with Schizophrenia

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Abstract

The development of medications for the treatment of nicotine dependence in patients with schizophrenia is a public health priority due to its high prevalence rates, devastating medical consequences, and difficulty to treat. It has been hypothesized that the high prevalence of nicotine dependence among patients with schizophrenia may be due to a shared neurobiological vulnerability. This shared vulnerability has been evidenced in reports showing that nicotine improves neuropsychological deficits associated with schizophrenia such as in the P50 evoked auditory potentials, spatial working memory, and attention. The common pathophysiologic pathways of smoking and schizophrenia may serve as the basis for the pharmacological evaluation of medications for the treatment of these concurrent disorders. Currently, little research of medications for the treatment of this comorbidity has been conducted. Studies have evaluated the efficacy of smoking cessation medications in patients with schizophrenia. These include the nicotine replacement therapy (patch, nasal spray) and sustained release bupropion. Others have evaluated the anti-smoking effect of medications (e.g., clozapine, haloperidol) used for the treatment of schizophrenia. In both cases, the results have not been conclusive. Newer smoking cessation approaches such as varenicline, selegiline, rimonabant, and nicotine vaccine, among others, have yet to be tested in this population. The purpose of this article is to review the results of the studies conducted to date and propose some potential pharmacotherapies based on the current knowledge of the pathophysiology of both disorders.

Keywords

Smoking; nicotine; schizophrenia; treatment; pharmacotherapy; comorbidity

INTRODUCTION

It has been estimated that worldwide the odds ratio of smoking among individuals with schizophrenia is 5.3 higher than in the general population. This association seems independent of the socio-cultural environment. Individuals with schizophrenia who smoke have more smoking-related cardiovascular and respiratory diseases and mortality than the general population, in part due to their more harmful patterns of cigarette use (Curkendall, Mo, Glasser, Rose, & Jones, 2004; Hennekens, Hennekens, Hollar, & Casey, 2005; McCreadie, 2003; Olincy, Young, & Freedman, 1997; Williams et al., 2005). These individuals have about 20%

lower life expectancy than the general population and more than two-thirds of them die of coronary heart disease, compared with approximately one-half in the general population. Unfortunately, the quit rate in this population is very low. It has been estimated that the odds of quitting smoking among individuals with schizophrenia is only 0.16 (CI, 0.14-0.24) as compared with smokers in the general population (de Leon & Diaz, 2005).

Nicotine, the principal psychoactive ingredient of tobacco smoking, can produce complex effects on multiple neurotransmitter systems, considerable individual variability of its behavioral response, and is the main pharmacological agent responsible for tobacco dependence. Nicotine can decrease anxiety, improve attention, decrease appetite, relieve depression, and enhance cognitive performance. Nicotine seems to contribute to maintaining smoking behavior by producing direct reinforcing effects on the brain, establishing paired non-nicotine stimuli as conditioned reinforcers, and more recently it has been hypothesized that by enhancing the reinforcing value of nicotine-conditioned and non-nicotine stimuli (Chaudhri et al., 2006).

Nicotine acts on endogenous nicotinic acetylcholine receptors (nAChRs) located ubiquitously in the nervous system. Nicotinic receptors can modulate multiple systems including dopamine, glutamate, GABA, serotonin, norepinephrine, opioid, and cannabinoid systems. The rewarding and aversive motivational effects of nicotine are mediated by dopamine and non-dopamine brain substrates. The role of dopamine systems in the motivational effects of nicotine is complex, including drug-induced plastic changes at the synapse level. Nicotine produces activation of dopaminergic mesolimbic reward pathways originating in the ventral tegmental area and projecting to the amygdala, hippocampus, nucleus accumbens, striatum, and cortex. Individual differences in the proportion and combination of nicotine receptor subtypes in the different brain regions and genotype variability in the dopamine system explain a significant proportion of the interindividual variability in the nicotine responses and the smoking-induced dopamine release. The nAChRs can also affect inhibitory GABA neurons and modify the activity of dopamine neurons. The initial use of nicotine produces activation of GABA neurons and inhibits dopamine neurons in the VTA. However, the GABA neurons desensitize rapidly and lead to persistent excitation of the dopamine neurons. It has been suggested that the switch from the nicotine's acute effects to the development of dependence may be associated with a change in the balance of dopamine and GABA neurons in the VTA. With the repeated exposure to nicotine, the GABA system becomes desensitized, leading to a shift in the action of nicotine to the DA neurons responsible for the potentiation of the salience of nicotine and its compulsive use. In addition, nAChRs can affect the production of glutamate and acetylcholine which may also modulate effects on VTA neurons transmission. Smoking is also associated with reduced monoamine oxidase A and B activity in the basal ganglia. The effects of the endocannabinoid system on the rewarding properties of nicotine are related to modulation of the extent to which nicotine activates the mesolimbic dopaminergic pathway (Berlin et al., 1995; Brody, 2006; Brody et al., 2006; Corrigall, Franklin, Coen, & Clarke, 1992; Laviolette & van der Kooy, 2004; Maldonado, Valverde, & Berrendero, 2006; Picciotto, 2003; Picciotto & Corrigall, 2002).

The first-line and FDA approved medications for the treatment of nicotine dependence are nicotine replacement therapies (NRTs) (gum, patch, nasal spray, inhaler, and lozenge/tablet), bupropion and varenicline. The Agency for Healthcare Research and Quality also recommends clonidine and nortriptyline. Groups of medications under investigation for possible efficacy include monoamine oxidase inhibitors (selegiline), selective serotonin reuptake inhibitors (fluoxetine), opioid receptor antagonists (naltrexone), dopamine agonists (bromocriptine), nicotinic receptor antagonists (mecamylamine), cannabinoid-1 receptor antagonists (e.g., rimonabant), inhibitors of the hepatic P-450 enzyme (e.g., methoxsalen), and nicotine vaccines, among others. Pharmacogenetic studies of NRTs and bupropion have identified candidate

genes for the dopamine D2 receptor and mu opioid receptor that may predict therapeutic response (Berrettini & Lerman, 2005; Foulds, Steinberg, Williams, & Ziedonis, 2006; Frishman, Mitta, Kupersmith, & Ky, 2006; Schnoll & Lerman, 2006).

Schizophrenia is a chronic, deteriorating, and complex disorder that can affect the perception, language and communication, affect, thought processes, volition and drive, attention, and executive function of the individual. Neuropsychological deficits include integrative sensory functions, motor coordination, sequencing of complex motor acts, and primitive reflexes (Bombin, Arango, & Buchanan, 2005). The disorder can greatly affect the quality of life and life expectancy of the individual. The symptoms fall into two broad categories: positive and negative. The positive symptoms include delusions, hallucinations, disorganized speech, and catatonic motor behaviors. The negative symptoms involve affective flattening, alogia, and avolition (Arango, Buchanan, Kirkpatrick, & Carpenter, 2004; Carpenter, 2006; Kirkpatrick, Fenton, Carpenter, Jr., & Marder, 2006).

The symptoms of schizophrenia may be explained by abnormalities in dopaminergic synaptic transmission that seems to produce excessive release of dopamine and leads to overactivity of synapses in the mesolimbic and prefrontal cortex. Post-mortem studies of brains of schizophrenic individuals have shown high-affinity nicotinic binding sites are increased and binding to $\alpha 7$ receptors is reduced in the CA3 region of the hippocampus, suggesting that nicotinic function may be reduced in these individuals (Breese et al., 1997; Breese et al., 2000; Leonard et al., 2000).

Between 15% and 25% of the individuals with schizophrenia have primarily negative symptoms. It has been hypothesized that negative symptoms represent a separate pathologic domain within schizophrenia because of the differences found in the pre-psychotic development; clinical features such as drug abuse, affect, and social functioning, as well as neuroimaging and electrophysiologic findings, and treatment response (Carpenter, 2006). It has been suggested that individuals with primarily negative symptoms are less likely to abuse drugs because their anhedonia may extend to the rewarding properties of drugs of abuse and because their poorer social function makes them less able to obtain them (Kirkpatrick, Messias, & Tek, 2003). To our knowledge, no studies have been conducted to evaluate if this is also the case for tobacco use. If so, the treatment of tobacco dependence in individuals with primary negative symptoms may be different. Recent studies evaluating glutamate modulators, including the NMDA agonists, glycine and D-serine, D-Cycloserine (a partial agonist at the glycine recognition site of the NMDA receptor), acetyl-cholinesterase inhibitors (galantamine, rivastigmine, and Donepezil), have shown some preliminary efficacy for the treatment of negative symptoms (Erhart, Marder, & Carpenter, 2006). However, currently there are no medications approved by the Food and Drug Administration (FDA) for the treatment of negative symptoms and there is no conclusive data of the efficacy of second generation antipsychotics for the treatment of the negative symptoms of schizophrenia (Arango et al., 2004; Kirkpatrick et al., 2006).

Endophenotypes associated with schizophrenia, such as abnormalities in the catechol-O-methyl transferase gene (COMT), seem associated with manifestation of schizophrenia such as cognitive impairments, social withdrawal, and blunted mood. These findings may provide clues to deconstruct the schizophrenic syndrome into biological subcategories with corresponding clinical manifestations. Hopefully in the near future the knowledge of brain functioning and its association with specific clinical manifestations will parallel the current knowledge of cardiovascular functioning and its association with preventable risk and protective factors (Davidson, Caspi, & Noy, 2005).

The treatment of schizophrenia is mostly based on antipsychotic medications and psychosocial interventions. Antipsychotics can be found on a continuum depending on the level of induction of extrapyramidal symptoms (EPS). The first generation (FGA) have, at therapeutic doses, more EPS than the second generation antipsychotics (SGA). However, SGAs can produce disturbances of glucose utilization, lipid metabolism and weight gain. Some of the FGAs include chlorpromazine, flupenthixol, fluphenazine, perazine, perphenazine, pimozide, sulpiride, thioridazine, trifluoperazine, and zuclopenthixol. The SGAs include amisulpride, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and zotepine. Although both types of antipsychotics are superior to placebo for the treatment of schizophrenia, there is still debate as to whether SGAs, as a group, are better than FGAs. SGAs are more efficacious in treating negative symptoms, cognitive disturbances, and depressive symptoms, a clinical profile that is often described as a broader spectrum of clinical efficacy (Falkai et al., 2005; Falkai et al., 2006; Moller, 2000).

NICOTINE DEPENDENCE AND SCHIZOPHRENIA

Several lines of research have converged to suggest that there are clinical and biological factors that may explain the association between smoking and schizophrenia. It has been suggested that individuals with schizophrenia smoke cigarettes to break the monotony associated with the disorder, attain social contact, experience some pleasure, self-medicate some of the symptoms of schizophrenia or the side-effects of the antipsychotic medication, and/or cope with the nicotine withdrawal. Clinically, the rate of smoking is high prior to the onset of psychotic symptoms (Dalack & Meador-Woodruff, 1996; McEvoy & Brown, 1999).

Smoking may affect more significantly the negative than the positive symptoms of schizophrenia (Smith, Singh, Infante, Khandat, & Kloos, 2002). Individuals with schizophrenia who smoke or are administered nicotine improve on neuropsychological and psychophysiological test measures such as attention and vigilance, spatial organization, and visual-spatial memory, P50 evoked auditory potentials, auditory sensory gating, prepulse inhibition (PPI), smooth pursuit and anti-saccadic eye movement (Depatie et al., 2002; George et al., 2002b; Kumari & Postma, 2005; Levin, Christopher, Briggs, & Rose, 1993; Olincy, Johnson, & Ross, 2003; Smith et al., 2006). Tobacco abstinence among patients with schizophrenia has been associated with slowed motor speed but not with worsening of cognitive performance (Evins et al., 2005b) and some smokers with schizophrenia experience an acute increase in psychotic symptoms during attempts to quit smoking (Punnoose & Belgamwar, 2006). However, there is no clear evidence that early nicotine abstinence can exacerbate psychiatric symptoms (Dalack, Becks, Hill, Pomerleau, & Meador-Woodruff, 1999; Dalack et al., 1996). The clinical observations have led to the development of important research trying to understand the shared biological vulnerability to these disorders.

It is clear that schizophrenics can be motivated to quit or reduce smoking and can be engaged in treatments for nicotine dependence (Addington, El Guebaly, Campbell, Hodgins, & Addington, 1998). It has been reported that according to the Reasons for Quitting Scale, individuals with schizophrenia are more intrinsically than extrinsically motivated to quit smoking. The main reasons for quitting in this population are health concerns, self-control, immediate reinforcement, and social influence (Addington et al., 1998). Behavioral intervention should combine interventions that address the nicotine problems in the context of the schizophrenia disorder (Addington et al., 1998; George et al., 2000; Ziedonis et al., 2005).

Pharmacotherapies for nicotine dependence in individuals with schizophrenia may target the specific clinical symptoms of nicotine dependence or schizophrenia. They may aim at stopping or reducing smoking and/or alleviate the symptoms of nicotine craving or withdrawal.

Pharmacotherapies for schizophrenia may aim at the positive or negative symptoms, cognitive deficits, and/or reduction of extrapyramidal symptoms. Medications may also target the shared neurochemical aspects of both disorders with the expectation that they will produce improvements in psychopathology and nicotine dependence.

NICOTINE REPLACEMENT THERAPY

Nicotine replacement therapy (NRT) is approved by the FDA as a safe and effective aid to quit smoking in the general population. The study of the safety and efficacy of NRTs for the treatment of nicotine dependence among individuals with schizophrenia is of particular interest not only for its public health importance but also for the shared neurobiological mechanisms involved in both disorders. NRT may exert its therapeutic effects by: (1) improving some of the neuropsychological impairments associated with schizophrenia, (2) preventing nicotine withdrawal and craving, (3) preventing the exacerbation of psychotic symptoms associated with nicotine withdrawal, (4) preventing or improving antipsychotic side-effects, and (5) affecting nicotine receptors and their intrinsic role in some of the symptoms of schizophrenia. Table 1 summarizes the current clinical studies of NRTs in individuals with nicotine dependence and schizophrenia, the findings on the outcome of both disorders, as well as the extrapyramidal symptoms.

In preclinical studies in rats and monkeys it has been observed that nicotine administration can induce improvements in animal models of cognitive performance (Elrod, Buccafusco, & Jackson, 1988; Levin, Bettegowda, Weaver, & Christopher, 1998). In clinical studies, nicotine have shown to improve neuropsychological measures in individuals with schizophrenia (Depatie et al., 2002; George et al., 2002b; Kumari et al., 2005; Olincy et al., 2003; Smith et al., 2006). The changes do not seem to extend to all the areas of cognition and some of them may be determined by tachyphylaxis (Harris et al., 2004). In addition, it has been reported that nicotine withdrawal may worsen cognitive performance and psychotic symptoms in this population (Evins et al., 2005b). Smoking abstinence can also produce a significant decrease in visual-spatial working memory (George et al., 2002b). (2) “In schizophrenia, PPI is impaired by smoking abstinence and improved by acute smoking reinstatement, and; (3) enhancement of PPI by cigarette smoking in schizophrenia is mediated by stimulation of central nAChRs” (George et al., 2006). However, other investigators have found that pretreatment with a centrally-acting nAChR antagonist (mecamylamine) did not alter neuropsychological performance in either nonsmoking patients with schizophrenia or controls. They suggest that nAChR dysfunction in schizophrenia and neuropsychological sensitivity to nAChR antagonism may be dissimilar depending on the smoking status of the patient (Sacco et al., 2006).

In 1991, Hartman et al. found that 8 mg of transdermal nicotine modestly reduced smoking over a 7-h period among 13 psychiatric inpatients, 10 of whom had diagnoses of schizophrenia or schizoaffective disorder. They found that when patients received NRT they smoked significantly fewer cigarettes than when they were receiving placebo (Hartman, Leong, Glynn, Wilkins, & Jarvik, 1991). A human laboratory study reported in 1996 suggests that nicotine patch at doses of 7 mg/day and 14 mg/day produces a dose-related reversal of the memory performance and complex reaction time impairments associated with the administration of haloperidol. The authors conclude that nicotine can reverse some of the side-effects of haloperidol and NRTs have an added beneficial effect by reducing the discomfort of those side-effects (Levin, Wilson, Rose, & McEvoy, 1996).

The first report of a study focusing on a smoking cessation program for smokers with schizophrenia showed it was not only feasible to evaluate the efficacy of smoking cessation in this population but that also NRTs have a therapeutic effect. The authors found that 50% of

the patients completed the 10-week treatment program, 40% decreased their cigarette use by 50%, and 13 % were abstinent at the 6-month follow-up visit. In addition to NRT, the study subjects received behavioral therapy such as motivational enhancement therapy and relapse prevention behavioral therapy and the authors highlight that they were important components of treatment. They also concluded that group therapy was less effective than individual motivational enhancement therapy (Ziedonis & George, 1997).

In 1998, a report evaluating NRT for individuals with schizophrenia in a sample of 50 outpatients who were treated with nicotine patches and group therapy in a smoking cessation program for 7 weeks showed that 42% of the subjects had stopped smoking at the end of the treatment. Follow-up assessments showed that 16% remained abstinent at 3 months, and 12% at 6 months. The NRT was well tolerated. There was no change in the positive or negative symptoms of schizophrenia as well as the extrapyramidal side-effects as measured by the Simpson-Angus Rating Scale score. These results were very encouraging because, as the author points it out, it was feasible to treat nicotine dependence in individuals with schizophrenia using NRT and behavioral group therapy (Addington et al., 1998).

A cross-over study was initiated in 19 patients with schizophrenia or schizoaffective disorder who received 1 day of *ad libitum* smoking followed by 3 days of acute smoking abstinence plus active or placebo transdermal nicotine patches. Then 3 days outpatient followed by the second study condition of the crossover design. There were no group differences in the presentation of schizophrenia or extrapyramidal symptoms (Dalack et al., 1999). Another crossover study by the same author, using transdermal nicotine patch over 32 h in a sample of 10 heavy smokers males with schizophrenia, showed that although NRT was well-tolerated, there was an increase of dyskinesias during the smoking plus active patch portion of the study. There were no changes in psychiatric symptoms and number of cigarettes smoked per day. However, there was a reduction in expired carbon monoxide on the active patch and led to smoking suppression, particularly in the heaviest smokers (Dalack & Meador-Woodruff, 1999). Therefore, it appears that the efficacy of NRT may be independent of its ability to reduce extrapyramidal symptoms in patients receiving antipsychotic medication. Nicotine can also increase pursuit gain in the no-monitoring condition in patients with schizophrenia and controls equally, but did not improve pursuit in the monitoring condition. However, this improvement may be mediated via an effect on attention rather than by an effect on oculomotor function per se. Therefore, it appears that nicotine improves performance on both attention and oculomotor markers of risk for schizophrenia, possibly via common mechanisms (Depatie et al., 2002).

A recent longitudinal study conducted in a sample of 68 nicotine-dependent schizophrenic patients showed a quit rate of 26.9% at 8 weeks and 26.9% at a 3-month follow-up. At the 3-month follow-up, the rate of continuous smoking abstinence in the nicotine-patch group was 23.1% (Chou, Chen, Lee, Ku, & Lu, 2004). An interim report of a cross-over study conducted in 13 subjects with nicotine dependence and schizophrenia who were treated for 1 month with nicotine patch (21 mg/day) or placebo showed a reduction in carbon monoxide (CO) levels during active patch treatment but was not sustained throughout the treatment. The authors confirm their previous findings that NRT does not produce changes in psychiatric symptoms, motor side effects, or untoward effects (Dalack, Ritter, & Meador-Woodruff, 2000). Harris et al. reported that attentional function was increased in nonsmokers, but decreased in nicotine-abstinent smokers after nicotine administration. They suggest that the effects of nicotine in schizophrenia do not extend to all areas of cognition. In addition, the effects on attention may be severely limited by tachyphylaxis (Harris et al., 2004).

Nicotine nasal spray has also been investigated for the treatment of nicotine dependence in schizophrenics. It may offer some advantages over the patch such as rapid onset of action, intermittent dosing, and more immediate relief from cravings. In addition, the nicotine spray

has been reported to be particularly effective among heavily dependent smokers, such as most schizophrenic patients. A retrospective study of 12 smokers with schizophrenia or schizoaffective disorder treated with nicotine nasal spray plus individual psychosocial support showed that it was well tolerated and had a 42% quit rate at the end of 90 days of treatment. In addition, 30% of the patients substantially reduced the amount of cigarettes that they smoked (Williams, Ziedonis, & Foulds, 2004). In another study using the same formulation, the authors report that there were no effects of active nicotine nasal spray on verbal memory and suggest that nicotine may modestly enhance attention and spatial working memory in schizophrenic patients who are cigarette smokers and have been abstinent overnight (Smith et al., 2006).

A recently published review of all randomized clinical trials comparing nicotine or related products as a sole or adjunctive treatment for people with schizophrenia or other similar serious, non-affective psychotic illness concluded that at this point it is not possible to establish its efficacy and that there is a great need for well-controlled research to study the effects of nicotine on symptoms of schizophrenia as well as on side effects of antipsychotic drugs (Punnoose et al., 2006). In the mean time, treatment of nicotine dependence in individuals with schizophrenia with NRTs may not only help them to quit smoking but also improve some of the symptoms of schizophrenia and better tolerate some of the side-effects of antipsychotic medications (see Tables 2 & 3).

BUPROPION

In 1997 the U.S. Food and Drug Administration approved the use of sustained-release preparation of the antidepressant agent bupropion hydrochloride (bupropion SR; Zyban(r)) for the treatment of nicotine dependence (Hurt et al., 1997; Jorenby et al., 1999). The anti-smoking effects of bupropion may be explained by its dopamine and noradrenalin reuptake inhibitor properties and the recently reported non-competitive antagonist of high affinity nAChRs in the central nervous system (Slemmer, Martin, & Damaj, 2000). The main mechanism of action of bupropion is by preventing and attenuating the nicotine withdrawal symptoms associated with smoking cessation. Because of its action on the nicotine receptor, bupropion may also reduce the reinforcing properties of nicotine. In addition, it has been suggested that some of the metabolites of bupropion may also have an anti-smoking effect (Warner & Shoaib, 2005). In patients with schizophrenia bupropion may have additional therapeutic effects because it can improve some of the symptoms of schizophrenia. For example, bupropion has been associated with improvement of attention, mood, and locomotor activity (Gobbi, Slater, Boucher, Debonnel, & Blier, 2003). Given these properties, bupropion is also being investigated for the treatment of attention deficit hyperactivity disorder (Wilens et al., 2005) and those with comorbid nicotine dependence (Upadhyaya, Brady, & Wang, 2004).

The first report of the use of bupropion in patients with schizophrenia is from 1999. It is a case report of a 41-year-old male patient with schizophrenia receiving treatment with clozapine. He received 150 mg/day of sustained-release bupropion and after one week of treatment he reported that he stopped smoking entirely. He was treated with bupropion for 7 months and remained abstinent at 11 months. The psychotic symptoms were under control and his dose of clozapine was decreased from 550 to 300 mg/day (Evins & Tisdale, 1999). Then in 2001, an open label pilot study of sustained-released bupropion plus group psychotherapy for the treatment of nicotine dependence in patients with schizophrenia was conducted in a sample of 8 patients who received treatment for 14-weeks. The results showed a decrease in carbon monoxide levels that was independent from worsening of neuropsychological symptomatology (Weiner, Ball, Summerfelt, Gold, & Buchanan, 2001).

The first-double blind study of bupropion in smokers with schizophrenia was reported in 2001. The study was conducted in a sample of 19 outpatients with schizophrenia whose symptoms

were stable. They received sustained-release bupropion (150 mg/day) or placebo plus cognitive behavioral therapy for 3 months and then a 3 month follow-up. The results showed that bupropion was associated with significantly greater reduction in smoking (66%) vs. placebo (11%) during the active and follow-up periods. In addition, bupropion was associated with improvement in negative symptoms and stability of psychotic and depressive symptoms in the schizophrenic subjects. These results are important because they demonstrated that bupropion plus CBT not only helped to reduce smoking but also to stabilize psychiatric symptoms (Evins et al., 2001). A 2 year follow-up of 17 of these patients showed that 22% of the subjects were abstinent. The authors found that smoking reduction during the original trial was correlated with smoking reduction at follow-up. These results highlight the importance of the potential long-term benefits of smoking reduction during a clinical trial (Evins et al., 2004).

A placebo-controlled trial of bupropion (150 mg twice daily) conducted by a different group of investigators was reported in 2002. In a sample of 32 subjects with schizophrenia or schizoaffective disorder they found that the abstinence rates in the bupropion-treated group was 50% versus 12.5% in the placebo group. They also reproduced the result that bupropion was well tolerated in this population and could improve the negative symptoms of schizophrenia. They also found that bupropion was more effective in those patients receiving atypical antipsychotic treatment (George et al., 2002a).

In a larger double-blind placebo-controlled trial, a sample of 53 adults with schizophrenia was treated with bupropion 300 mg/day or placebo for 12 weeks. The 7-day point prevalence abstinence at the 4th week of treatment was 36% for the bupropion group and only 7% in the placebo group. The quit rate at week 12 was 16% for the bupropion group and 0% for the placebo group. There was a trend toward improvement in depressive and negative symptoms of schizophrenia with no changes in extrapyramidal symptoms. In addition, the authors found that subjects who receive atypical antipsychotic medications and bupropion had the highest reduction in smoking (Evins et al., 2005a). This investigator also reported that bupropion was able to improve some of the cognitive impairments in this patient group (Evins et al., 2005b).

In summary, bupropion seems safe to administer to individuals with schizophrenia as an anti-smoking aid. So far, none of the studies reviewed reported any significant side-effects. Although the efficacy of bupropion widely varied among the studies, the consensus is that bupropion is not only feasible to be administered to this population but is also efficacious. The highest rate of smoking cessation (50%) was achieved when bupropion was administered at a dose of 300 mg/day in the context of a structured psychosocial intervention. Although there is no consensus about the type of psychosocial intervention, a combination of supportive individual and group therapy may be more efficacious but it still needs to be empirically demonstrated.

The efficacy of bupropion in this population may be enhanced by the concomitant administration of nicotine replacement therapies. However, no formal assessment of the efficacy of the combination of these treatments has been reported. In all the studies the relapse rates are very high. Therefore, it is possible that longer treatment with bupropion may reduce relapse rates.

Because most patients with schizophrenia are treated with antipsychotic medication, the interaction of bupropion with this class of medications and their effect on smoking has needs to be studied. Given bupropion's action as an inhibitor of the cytochrome P450 2D6, the possibility of drug-drug interaction with antipsychotic medications should be kept in mind when prescribing both medications. Future research should include prospective measurement of antipsychotic plasma levels.

Based on secondary data analysis, the atypical antipsychotics combined with bupropion seem to produce better smoking cessation rates. This effect may be due to improvements in cognitive performance, particularly in patients with negative symptoms of schizophrenia. This effect may also help to improve the therapeutic alliance with the patient, his/her permeability to the psychosocial treatment, retention in treatment, and the smoking cessation rates. The effect of bupropion on the extrapyramidal side-effects of antipsychotic medications was reported in few studies. The preliminary results suggest that either bupropion does not seem to exacerbate them or they are so infrequent with the use of new atypical antipsychotics that no significant effect was observed in the small samples that were reported.

ANTIPSYCHOTICS

Antipsychotics are the medication of choice for the treatment of schizophrenia. They have been divided in typical and atypical. The typicals can produce more extrapyramidal symptoms than the atypical ones. Some of the typical antipsychotic medications include chlorpromazine, perphenazine, thioridazine, trifluoperazine, and haloperidol. The atypicals include clozapine, olanzapine, and risperidone. Clozapine binds to the D4 DA receptor subtype 10 times as strongly as it binds to D2 receptors and has high affinity for the 5-HT₂ receptors. Risperidone also has a higher affinity for the 5-HT₂ receptor than for the D2 receptor (Hertel, Nomikos, Iurlo, & Svensson, 1996; Sumiyoshi et al., 1994). The atypicals are considered more efficacious in treating the negative symptoms, cognitive disturbances, and depressive symptoms of schizophrenia (Falkai et al., 2005; Falkai et al., 2006; Moller, 2000).

Antipsychotic medications have been investigated for the treatment of the comorbidity of nicotine dependence and schizophrenia because they (1) can improve the symptoms of schizophrenia and therefore reduce the rate of smoking associated with some of the symptoms of schizophrenia, (2) can improve the cognitive functions of schizophrenic patients and facilitate the compliance with the prescribed medications and psychotherapy, and (3) exert a direct effect on the rewarding system via the nicotinic and dopamine systems that will reduce the patients' nicotine craving and withdrawal.

The interactions between antipsychotics and nicotine have long been observed. In 1985 it was reported that individuals who smoked required higher doses of antipsychotic medications (Ereshefsky et al., 1985; Jann et al., 1986). Also, heavy smoking has been associated with lack of response to treatment with haloperidol (McEvoy, Schooler, & Wilson, 1991). In a study reported in 1995, 10 patients with schizophrenia who were treated with haloperidol showed an increase in smoking confirmed with the expired air CO and plasma nicotine and cotinine levels (McEvoy, Freudenreich, Levin, & Rose, 1995b). To evaluate if the increase in smoking is associated with the dopamine system a study was conducted comparing the effect of haloperidol (dopamine antagonist) and bromocriptine (dopamine agonist) on smoking behavior. The results showed that the smoking rate was significantly lower with bromocriptine (Caskey, Jarvik, & Wirshing, 1999). Therefore, it has then been hypothesized that the increase in smoking may be a compensatory increase to try to overcome the D2 blockade produced by haloperidol and obtain the usual nicotine reward (Dawe, Gerada, Russell, & Gray, 1995).

Preclinical studies have shown that the effect level of the antipsychotic medications on the dopamine D2 receptors may influence the efficacy of the antipsychotic for the treatment of nicotine dependence. The administration to rats of nicotine in combination with haloperidol or risperidone produces induced greater memory impairment than the administration in combination with clozapine. This difference may be due to the greater dopamine D2 antagonist effect of risperidone and haloperidol compared with clozapine (Addy & Levin, 2002).

Clozapine is the prototypic atypical antipsychotic. It can reduce the psychotic symptoms while producing few extrapyramidal side-effects. It can also reduce the cognitive impairment

associated with schizophrenia and normalize the auditory sensory gating deficit frequently found in patients with schizophrenia. This last deficit is associated with the inability of schizophrenic patients to filter out unimportant sounds, which in turn can distract, confuse, and perhaps provide them a substrate for delusional misinterpretations. Repeated doses of clozapine can reverse auditory sensory gating impairment, probably through an alpha(7) nicotinic receptor mechanism (Nagamoto et al., 1996; Oranje, Van Oel, Gispen-De Wied, Verbaten, & Kahn, 2002). Clinically, the evidence of the efficacy of clozapine for the treatment of nicotine dependence in patients with schizophrenia is mounting. A study conducted in a group of patients with schizophrenia who were switched from haloperidol to clozapine showed that patients who achieved a clozapine plasma level greater than 200 ng/ml had a decline in smoking between 25% and 35% (McEvoy et al., 1995a). In a survey of 30 schizophrenic outpatients who had been treated with typical neuroleptics and were switched to received clozapine, the patients reported a decrease in reported daily cigarette use during clozapine treatment (George, Sernyak, Ziedonis, & Woods, 1995). A comparison of three groups of chronic, hospitalized, schizophrenic patients, receiving either a typical antipsychotic, clozapine, or another atypical antipsychotic showed that clozapine was associated with a significantly lower incidence of smoking than either typical or other atypical antipsychotics (Combs & Advokat, 2000). In another study of 70 patients with schizophrenia receiving conventional antipsychotics were switched to clozapine the results showed that patients smoked less when they received clozapine (McEvoy, Freudenreich, & Wilson, 1999).

It appears that when patients are switched to receive clozapine there is a removal of the D2 blockade produced by the typical antipsychotics which has been considered responsible for the high rate of smoking in patients receiving those medications (Dawe et al., 1995; McEvoy et al., 1995b). Interestingly, this last study also showed that smokers had a better response to the antipsychotic effects of clozapine than non-smokers. The authors hypothesize that there may be some synergistic effects between nicotine or clozapine or that perhaps there is a subgroup of patients with schizophrenia whose pathophysiologic mechanisms (e.g., sensory gating deficit) make them respond more favorably to either nicotine or clozapine (McEvoy et al., 1999).

A comparison of patients receiving typical versus atypical antipsychotics with both groups receiving structured group therapy and nicotine replacement therapy showed that the group who received atypical antipsychotic agents had significantly higher smoking cessation rates. There were no differences in the levels of dyskinesic and extrapyramidal symptoms between patients who quit and those who continued to smoke. The dose of adjunctive anticholinergic medication was higher in the group prescribed with typical antipsychotic. This study suggest that atypical antipsychotics are not only more effective for the treatment of nicotine dependence but also that they cause less side-effects, independent of the smoking status (George et al., 2000).

Reduction or discontinuation of antipsychotic treatment in schizophrenics who smoke may have different effects depending upon whether they are receiving typical or atypical ones. Discontinuation of typical antipsychotics does not appear to induce more deterioration in smokers versus non-smokers. Perhaps the dopaminergic effect of smoking keeps the psychotic symptoms under relative control (Apud, Egan, & Wyatt, 2000). With typical antipsychotics the results seem different. Clozapine is metabolized in the liver to demethylclozapine (norclozapine) and clozapine N-oxide by the cytochrome 1A2 and 3A4 enzymes. Because cigarette smoking can induce cytochrome 1A2, it has been reported that smoking can reduce the blood concentrations of clozapine (Haring et al., 1989; Wetzel et al., 1998). However, one study does not support this finding (Hasegawa, Gutierrez-Esteinou, Way, & Meltzer, 1993). It has been reported that the concentration of clozapine and demethylclozapine can be 40% lower in smokers than in non-smokers. Furthermore, there are some case reports of a patients

receiving clozapine who develop severe side-effects after abrupt smoking cessation. This may be due to a sudden rise in plasma concentrations of clozapine and/or its metabolites as a result of stopping the smoking-related cytochrome 1A2 enzyme induction (Oyewumi, 1998; Skogh, Bengtsson, & Nordin, 1999). Therefore, it is recommended to adjust the dose of clozapine in patients with schizophrenia who smoke or quit smoking (Haring et al., 1989; Seppala, Leinonen, Lehtonen, & Kivisto, 1999; Skogh et al., 1999; Wetzel et al., 1998).

Clozapine has shown to be superior to other atypical antipsychotics for the treatment of nicotine dependence. A pilot study examined the smoking behaviors of patients treated with either risperidone alone or in combination with clozapine and showed that patients co-prescribed clozapine with risperidone smoke significantly less than patients treated with risperidone alone (Procyshyn, Tse, Sin, & Flynn, 2002). Although olanzapine can attenuate cue-elicited craving for tobacco, it can produce significant working memory impairment (Hutchison et al., 2004). This impairment can improve with nicotinic co-treatment (Levin, Petro, & Beatty, 2005). It appears that antipsychotic medications that block the 5HT₂ receptor, such as clozapine, may limit the cognitive enhancement associated with nicotine co-treatment (Levin & Rezvani, 2006). Therefore, the treatment with olanzapine may not be ideal because it may also require the co-administration of nicotine.

In summary, the prescription of antipsychotic medication is necessary for most patients with schizophrenia. Although smoking is associated with lower severity of the akathisia associated with the administration of antipsychotic medications (Barnes et al., 2006), clinicians should not be prevented from trying to help their schizophrenic patients quit smoking because of fear of worsening their schizophrenia or the side-effects of the prescribed antipsychotic medications. Current research in this field is shedding light about the choice of antipsychotic medication for schizophrenics who smoke. So far, it is not recommended to use typical antipsychotics, particularly haloperidol, because they may worsen the smoking problem and increase extrapyramidal side-effects. Among the atypical antipsychotics, the first choice is clozapine. Other medications in this group may help but may require the use of additional medications. The use of clozapine in individuals who smoke requires a close monitoring of their smoking behavior and modifications of the clozapine dose if they quit smoking or other nicotine product is provided.

VARENICLINE

Varenicline is a partial agonist at the $\alpha 4\beta 2$ nicotinic receptors and was recently approved by the FDA for the treatment of nicotine dependence. It mimics the effects of nicotine on dopamine (DA) release in the nucleus accumbens and reduces nicotine self-administration (Fagerstrom & Balfour, 2006). Its use for the treatment of nicotine dependence in schizophrenic patients has not been investigated. However, it may be a promising medication. In two phase III trials, varenicline was associated with significantly higher short- and long-term abstinence rates than placebo or bupropion sustained-release (SR). In addition, varenicline appears to attenuate the urge to smoke, negative affect withdrawal symptoms, and the reinforcing effects of smoking (Gonzales et al., 2006; Oncken et al., 2006). It has been suggested that given the agonist effect of varenicline on the 7 receptor, it may also be useful for the treatment of schizophrenia and Alzheimer's disease (Mihalak, Carroll, & Luetje, 2006). To our knowledge, no studies have been conducted testing the safety and efficacy of varenicline for the treatment of nicotine dependence in individuals with schizophrenia.

DMXBA

Recently it has been reported that 3-2,4 dimethoxybenzylidene anabaseine (DMXBA), a weak partial agonist of $\alpha 7$ nAChRs, can enhance auditory sensory gating in animal models. In humans, DMXBA has been well tolerated and have shown to improve several cognitive

measures. Another $\alpha 7$ -selective partial agonist, tropisetron also improves the auditory gating deficit in mouse models and in humans with schizophrenia (Hogg & Bertrand, 2004; Koike et al., 2005). Their effect on cognitive improvement may be due to the nicotinic agonist effect which appears to mediate the release of gamma-aminobutyric acid (GABA) by hippocampal interneurons. Alpha-7 nicotinic receptor agonists appear to be reasonable candidates for the treatment of cognitive and perceptual disturbances in schizophrenia (George et al., 2006; Hogg et al., 2004; Hogg & Bertrand, 2006; Martin, Kem, & Freedman, 2004).

RIMONABANT

Rimonabant is a cannabinoid CB1 receptor antagonist. CB1 receptors appear to be involved in the mechanisms of nicotine dependence, as well as other drug dependencies. They may modulate dopamine release and affect the rewarding processes associated with nicotine dependence. Preclinical studies have shown that rimonabant reduces nicotine self administration and attenuates reinstatement of nicotine-seeking behavior. Preliminary results from clinical studies suggest that patients treated with rimonabant have higher odds of quitting smoking than those treated with placebo. Furthermore, rimonabant may prevent the weight gain associated with smoking cessation. However, the final results of some clinical trials are not yet available (Fagerstrom et al., 2006; Maldonado et al., 2006; Schnoll et al., 2006).

CB1 mediate attentional performance impairments and may contribute to the pathophysiological substrates of cognitive dysfunction in schizophrenia. Moreover, there is increasing evidence of the anatomical, pharmacological, behavioral association between the cannabinoid and dopamine receptor systems in the pathophysiology of addiction and schizophrenia. The association between these may explain the emotional processing and sensory perception deficits underlying addiction and schizophrenia (Arguello & Jentsch, 2004; Laviolette & Grace, 2006a; Laviolette & Grace, 2006b). Therefore, CB1 receptor antagonists may offer a therapeutic window for patients with nicotine dependence and schizophrenia.

ANTIDEPRESSANTS

Antidepressants have been investigated for the treatment of nicotine dependence. The serotonin reuptake inhibitors paroxetine, fluoxetine, and sertraline, and the serotonin and noradrenaline re-uptake inhibitor venlafaxine are potential treatments for nicotine addiction. This is due to the hypothesized role of 5-hydroxytryptamine in mediating the addictive potential of nicotine, although a pooled analysis from five clinical trials with SSRIs showed no significant treatment effects. It has been suggested that SSRIs may be effective for subgroups of smokers. For example, fluoxetine appears more efficacious for smoking cessation in patients with high baseline levels of depressive symptoms (Hitsman et al., 1999). Also, venlafaxine may be more efficacious among lighter smokers (Cinciripini et al., 2005).

A recent review of the use of SSRI augmentation of antipsychotics in the treatment of negative symptoms in schizophrenia suggests that fluvoxamine and fluoxetine can ameliorate primary negative symptoms in chronic schizophrenic patients treated with first-generation antipsychotics. The combination appears safe, although as antipsychotic drug concentrations may rise, close monitoring of drug doses and possibly drug concentrations is needed. The evidence of SSRI augmentation in patients treated with second-generation antipsychotics is limited. However, SSRI augmentation in patients treated with clozapine, a serotonin antagonist, appear to improve negative symptoms (Silver, 2004). Although SSRIs have not been tested for nicotine dependence in patients with schizophrenia, the combination SSRI plus antipsychotics may be safe and efficacious for the treatment of persistent negative symptoms and nicotine dependence.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase (MAO) enzymes are involved in the metabolism of dopamine (MAO-B), as well as noradrenaline and serotonin (MAO-A). Tobacco smoke has been shown to inhibit MAO-A and -B in the central nervous system (Fowler et al., 1996). Preliminary clinical studies have shown that the MAO-B inhibitor selegiline appears safe and efficacious for the treatment of nicotine dependence (Biberman, Neumann, Katzir, & Gerber, 2003; George et al., 2003). MAO enzymes are also involved in the pathophysiology of schizophrenia. MAO inhibitors have been reported beneficial for negative symptoms of schizophrenia. They may also counteract the parkinsonian syndrome associated to the administration of typical neuroleptics. Indeed, two reports have demonstrated therapeutic effects of MAO inhibitors on negative symptomatology in schizophrenia (Bucci, 1987; Perenyi, Goswami, Frecska, Arato, & Bela, 1992). Future studies may evaluate the efficacy of MAO inhibitors for the treatment of nicotine dependence in individuals with schizophrenia who have predominantly negative symptoms or have significant extrapyramidal symptoms.

OPIOID RECEPTOR AGONIST/ANTAGONIST

Naltrexone, an opioid receptor antagonist, has been investigated for the treatment of nicotine dependence because nicotine appears to increase the release of endogenous opioids which contribute to its reinforcing effects. Currently, the results of clinical trials have been inconclusive (David, Lancaster, Stead, & Evins, 2006). A recent randomized clinical trial of three doses of naltrexone versus placebo in a sample of 400 smokers showed that patients who received the highest dose of naltrexone had significantly higher quit rates (O'Malley et al., 2006). It appears that naltrexone is more efficacious for the treatment of females with nicotine dependence than for males (Covey, Glassman, & Stetner, 1999). One study showed that naltrexone improved both positive and negative symptom of schizophrenia, mainly among patients with negative symptoms (Marchesi, Santone, Cotani, Giordano, & Chelli, 1995). No studies have been reported using opiate antagonists for the treatment of nicotine dependence and schizophrenia but one could hypothesize that naltrexone may be helpful to quit or reduce smoking among individuals with schizophrenia, mainly males with negative symptoms.

The effect of the opiate agonist and antagonist buprenorphine on smoking has been explored. It has been reported that buprenorphine increases cigarette smoking (Mello, Lukas, & Mendelson, 1985; Mutschler, Stephen, Teoh, Mendelson, & Mello, 2002). On the other hand, in a small study buprenorphine has been reported to have an antipsychotic effect (Schmauss, Yassouridis, & Emrich, 1987). To our knowledge there are no studies evaluating the effect of buprenorphine on smoking among individuals with schizophrenia. This study may be difficult to implement given that buprenorphine should be administered to individuals who also have opiate dependence and the comorbidity of this drug of abuse with schizophrenia is a rare occurrence.

NICOTINIC ANTAGONIST

Mecamylamine is a nonselective nAChR antagonist that may help to reduce nicotine reward and cigarette consumption. Because of the antagonist effect, mecamylamine has been associated with initial increase of cigarette consumption in an effort by smokers to overcome the nicotine blockade. It has been suggested that the efficacy of mecamylamine is associated with the administration of a nicotine agonist (Lancaster & Stead, 2000). Given the potential beneficial effects of nicotine to alleviate the symptoms of schizophrenia, it would be expected that mecamylamine worsen their psychotic symptoms. However, comparing smokers with schizophrenia versus controls, mecamylamine did not alter neuropsychological performance. The authors suggest that nAChR dysfunction in schizophrenia and neuropsychological sensitivity to nAChR antagonism may be dissimilar depending on the smoking status of the

patient (Sacco et al., 2006). Further studies are needed to evaluate the effect of mecamylamine on smoking and schizophrenia and its efficacy for patients with these comorbid conditions.

TOPIRAMATE

Topiramate is an anti-epileptic medication that facilitates mesocortical GABAergic function and inhibits the action of glutamate. It also appears to increase dopamine and serotonin release. Given these actions, topiramate can be a good candidate medication for the treatment of nicotine dependence. In one study conducted in alcoholics, topiramate appeared to promote smoking cessation (Johnson, Ait-Daoud, Akhtar, & Javors, 2005). However, a human laboratory study showed that topiramate may increase the subjective pleasurable effects of nicotine (Sofuoglu, Poling, Mouratidis, & Kosten, 2006). Because of the modulator effects of topiramate on the GABA receptors, it has been proposed as adjuvant therapy for schizophrenia. It has been reported that topiramate may help to control aggression and psychosis (Gobbi, Gaudreau, & Leblanc, 2006) and reverse catatonia (McDaniel, Spiegel, & Sahota, 2006). Topiramate has also been associated with weight loss (Astrup & Toubro, 2004). This effect may be beneficial for schizophrenic patients who gain weight as a side-effect of the antipsychotic medication (Lin, Liu, & Hsiao, 2005) or as a result of trying to quit smoking. Further research is needed to evaluate the efficacy of topiramate for the treatment of nicotine dependence and as adjuvant medication for some of symptoms of schizophrenia, while concomitantly preventing weight gain.

DOPAMINE D3 RECEPTORS

The dopamine D3 receptors appear to control the phasic activity of the dopamine neurons and may be involved in the pathophysiology of several neuropsychiatric disorders, including schizophrenia and drug addiction, particularly nicotine addiction. It has been suggested that the efficacy of some antipsychotic medications (including clozapine) for the treatment of schizophrenia may be associated with their effect on the D3 receptors. These receptors are also emerging as potential medications for the treatment of tobacco dependence. Studies have shown that the D3 receptor antagonists are able to decrease the motivation to reduce nicotine-seeking and relapse in rodents. They may also prevent the reinstatement of extinguished drug-seeking behavior and therefore be effective for smoking relapse prevention (Heidbreder et al., 2005; Le Foll, Goldberg, & Sokoloff, 2007; Sokoloff et al., 2006). Further studies of D3 receptor modulators should evaluate not only their efficacy as antipsychotic agents but also their ability to prevent smoking relapse in schizophrenics who successfully quit smoking.

OTHER MEDICATIONS

Cognitive impairment has a great impact on the outcome of schizophrenia and may as well worsen the outcome of nicotine dependence. Medications such as acetylcholinesterase inhibitors (physostigmine and rivastigmine), ampaikines, glycine/D-cycloserine, D-serine, and mGluR 2/3 agonists of the glutamatergic system, erythropoietin, memantine, sarcosine, galantamine, and modafinil appear to produce cognitive improvements and may be potential therapeutic agents for schizophrenia. They may have the potential to be efficacious for nicotine dependence. Galantamine, which also act on the nicotine receptors and may produce stronger cognitive effects in schizophrenia (Sharma, Reed, Aasen, & Kumari, 2006). Modafinil is currently being investigated for smoking cessation (ClinicalTrials.gov identifier NCT00258479), as well as mem antine (NCT00136747 and NCT00136786). Further research is warranted with these medications for the treatment of comorbid schizophrenia and nicotine dependence.

IMMUNOTHERAPIES

Immunotherapies for nicotine dependence are currently being investigated and may be a therapeutic option for patients with schizophrenia who smoke. Active immunization with a nicotine vaccine is under intense clinical research. The nicotine vaccines produce an antigen-antibody reaction in the blood stream and limit the amount of nicotine that reaches the brain and reduces the psychopharmacological effects of nicotine. The vaccines can prevent the nicotine-induced increase in dopamine release in the nucleus accumbens. There are three vaccines currently under clinical evaluations. Results from phase II clinical trials show that the vaccine appears safe, have good specificity, and efficacious for the treatment of nicotine dependence (Hatsukami et al., 2005). Results from phase III trials are yet not available and the safety and efficacy in specific populations have not been evaluated (Fagerstrom et al., 2006; Schnoll et al., 2006). It is possible to speculate that the reduction of nicotine in the brain of schizophrenics who smoke may precipitate or worsen some of the symptoms of schizophrenia that otherwise had been kept under control by nicotine. Further research of the effectiveness of the vaccine should consider the potential adverse reaction in individuals with schizophrenia who smoke.

PHARMACOGENETICS

The study of the genetic factors associated with the safety and efficacy of medications (pharmacogenetics) for nicotine dependence or schizophrenia is at a nascent stage. Advances in the study of the genetics of both disorders are providing important clues to study the genetic factors that influence their outcome. Given the potential shared genetic vulnerability to both disorders, the prescription of medications tailored to the genetic characteristics of individuals may be developed in a not too distant future. The pharmacogenetics of nicotine dependence has witnessed significant progress in recent years. The response to NRT and bupropion among individuals with genetic variations of the CYP2B6, CYP2A6, DRD2, COMT, and serotonin transporter promoter polymorphisms have been investigated, with promising results (Lerman, 2006). On the other hand, pharmacogenetic studies have indicated that both the therapeutic response and side effects of antipsychotic medications may be related to polymorphisms in the dopamine and serotonin receptor genes (Andreassen & Steen, 2006; Gupta, Jain, Brahmachari, & Kukreti, 2006; Reynolds, Templeman, & Godlewska, 2006). Research is needed to evaluate the genetic commonalities of nicotine dependence and schizophrenia and the safest and most efficacious pharmacotherapies for this comorbidity based on the individual's genetic characteristics.

CLINICAL STRATEGIES TO HELP SCHIZOPHRENICS QUIT SMOKING

The treatment of nicotine dependence in patients with schizophrenia poses a significant challenge to the clinician (who is not always ready to initiate a treatment) because of misconception about the results of the treatment or assumptions that smoking is an attribute of the disease (Montoya, Herbeck, Svikis, & Pincus, 2005). In many instances, the treatment starts with the education of mental health professionals about the health consequences of nicotine addiction among schizophrenic patients and their role in preventing and treating smoking in this population. The routine assessment of the patient with schizophrenia should include his/her smoking history and readiness to quit smoking.

Tobacco dependence interventions for individuals with schizophrenia should combine optimal pharmacological and non-pharmacological treatments for both disorders. The treatment is feasible, cost-effective, and has important long term health benefits. The treatment of schizophrenia should include the appropriate antipsychotic medication in combination with psychoeducation, social and financial skills training, techniques to address neurocognitive

deficits (e.g., attention, memory, processing capacity), and management of medication side-effects.

The treatment of tobacco dependence in this population should include pharmacological and behavioral interventions. NRTs and bupropion should be the first-line treatment until results of testing other smoking cessation medications in patients with this comorbidity are available. The doses of NRT required to improve their nicotine craving and withdrawal may higher (doses of 42 mg/day). The nasal spray of NRT appears to be a promising approach for these patients. Bupropion can be used alone or in combination with NRT and should start at least 1 week before the scheduled quit date at doses of 150 to 300 mg/day. If the treatment with NRT and bupropion fail, other medications such as varenicline, clonidine or nortriptyline may be tried. Non-pharmacological smoking cessation interventions may include motivational enhancement therapy, cognitive behavioral therapy, contingency management techniques, as well as education about the use of nicotine replacement therapies and/or the administration of other pharmacotherapies. It is important for health care professionals to keep in mind that when patients with schizophrenia reduce or quit smoking it is possible to observe changes or fluctuations in their psychotic symptoms and the dose of antipsychotics may need to be adjusted (Addington et al., 1998; George et al., 2000; McCloughen, 2003; Williams & Ziedonis, 2004; Ziedonis & Brady, 1997; Ziedonis, 2004).

A great deal of research is still needed to elucidate the shared vulnerabilities between nicotine dependence and schizophrenia and their best pharmacotherapies. Currently, important progress is being made to understand the genetic mechanisms that underlie the combination of both disorders. In the meantime, research studies are yielding important results about the safety and efficacy of interventions (pharmacological and non-pharmacological) for individuals with this comorbidity. The evaluation of the safety and efficacy of medications already available or the development of new medications for the treatment of these disorders is a public health priority. Hopefully, in a not too distant future there will be safe and effective pharmacotherapies for the treatment of nicotine dependence among patients with schizophrenia.

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TABLE 1

Published studies evaluating the effects of Nicotine Replacement Therapies (NRT) in individuals with nicotine-dependence and schizophrenia. The studies are ordered by year of publication. When more than one study was published in a single year, they were ordered alphabetically for that year

Author/Year published	n	Design	Pharmacotherapy NRT	Behavioral Therapy	Duration of Intervention	Smoking Effect	Changes in Schizophrenia Symptoms	Extrapyramidal Symptoms
Hartman, Leong, Glynn, Wilkins, & Jarvik, 1991	13*	Double-blind Inpatient	Patch 8 mg vs placebo	Not reported	2days	Significant reduction of mean number of cigarettes smoked per day	No Change	Not Reported
Levan, Wilson, Rose, & McRoy, 1996	15	Double-blind Random assignment In/outpatient	Patch/placebo	Not reported	4 weeks	Not reported	Improve memory and complex reaction time	Nicotine reversed some side-effects of haloperidol
Ziedonis & George, 1999	24	Open-label Outpatient	Patch, gum	Group CBT Individual MET	10 weeks F-u: 6 months	13% quit at F-u	Not Reported	Not Reported
Adlington, El Guebaly, Campbell, Hodgins, & Adlington, 1998	50	Open-label Outpatient	Patch	Group Therapy	Tx:7 weeks F-u: 3, 6 month	Stopped smoking: 42%, 16%, 12%, respectively	No Change	No Change
Dalack, Becks, Hill, Poncelet, & Meador-Woodruff, 1999	19	Crossover In/outpatient	Patch/placebo	Not Reported	3 days	N/A	No Change	No Change
Dalack & Meador-Woodruff, 1999	10	Crossover Inpatient	Patch/placebo	Not Reported	32 hours	Reduce CO leves. Up to 20% in heavy smokers	No Change	Dyskinesias increased with patch
Dalack, Ritter, & Meador-Woodruff, 2000	13	Crossover Outpatient	Patch/placebo	Group Therapy	1 month	Reduce CO levels, not sustained	No Change	No Change
DePue et al., 2002	29**	Double-blind Crossover Inpatient	Patch/placebo	Not Reported	2 days	N/A	Partial improvement	Not Reported
Chen, Chen, Lee, Ku, & Lu, 2004	68	Placebo-Control Outpatient	Patch/Placebo	Not Reported	8 weeks F-u: 3 months	Abstinent: Patch 26.9%, 23.1% Placebo: 0%	Not Reported	Not Reported
Williams, Ziedonis, & Foulds, 2004	12	Retrospective Case series	Nasal spray	Individual psychosocial and group therapy	14 to 811 days	Abstinence 90 days 42%	Not Reported	Not Reported
Harris et al., 2004	20	Open-label inpatient	Gum	Not Reported	1 day	N/A	Increased attention	Not Reported
Smith et al., 2006	27	Double-blind, placebo-controlled, Inpatient	Nasal spray	Not Reported	2-4 weeks	N/A	Modest improvement in attention and special working memory	Not Reported

CBT: Cognitive Behavioral Therapy

F-u: Follow-up

N/A: Non Applicable

* 10 subjects had schizophrenia or schizoaffective disorder

** 15 with schizophrenia

TABLE 2

Published studies evaluating the effects of bupropion in individuals with nicotine-dependence and schizophrenia. The studies are ordered by year of publication. When more than one study was published in a single year, they were ordered alphabetically for that year

Author/Year published	n	Design	Bupropion Treatment	Behavioral Therapy	Duration of Intervention	Smoking Effect	Changes in Schizophrenia Symptoms	Extrapyramidal Symptoms
Evins & Tisdale, 1999	1	Case report	150 mg/day	Not Reported	7 months	Quit	Clozapine dose reduced No change	Not reported
Weiner, Ball, Summerfelt, Gold, & Buchanan, 2001	9	Open-label	150-300 mg/day	Group therapy	14 weeks	Decreased CO levels Quit rate: 0%	Agitation (n=1) No cognitive change	Not reported
Evins et al., 2001	19	Double-blind placebo-controlled	150 mg/day	CBT	3 months tx 3-month f-u	Reduction in smoking (self-report verified by expired-air carbon monoxide)	BUP: improve negative Ss PLA: worsen psychopathology	Not reported
George et al., 2002	32	Randomized, double-blind, placebo-controlled	300 mg/day	Group therapy	10 weeks	7 day abstinence at week 10: BUP:50%, Placebo: 12.3%)	Reduction of negative symptoms	No change
Evins et al., 2004	18	Naturalistic	N/A	N/A	2 year follow-up	22% abstinence	Not reported	Not reported
Evins et al., 2005a	53	Randomized, double-blind, placebo-controlled	300 mg/day	Weekly group CBT	12 weeks	7 day abstinence at week 4: BUP: 36%, Placebo: 7% At week 12: BUP: 16%, Placebo: 0%	Improve depressive and negative symptoms	No change
Evins et al., 2005b	53	Randomized, double-blind, placebo-controlled	150 mg/day	Weekly group CBT	4 weeks	Overall, 22% abstinence	Bupropion improved reaction time and perseverative errors	Not reported
Fatemi, Talar, Hattak, & Murphy, 2005	10	Randomized, cross-over, double-blind, placebo-controlled	Not reported	Not reported	8 weeks	Non-significant trend towards reduction of smoking	No change	Not reported

TABLE 3

Published studies evaluating the effects of antipsychotic medications in individuals with nicotine-dependence and schizophrenia. The studies are ordered by year of publication. When more than one study was published in a single year, they were ordered alphabetically for that year

Author/Year published	n	Design	Antipsychotic Medication	Behavioral Therapy	Duration of Intervention	Smoking Effect	Changes in Schizophrenia Symptoms	Extrapyramidal (EPS) Symptoms
Haring et al., 1989	148	Open label	Clozapine 12.5-700 mg/day	Not reported	> 8 days	Smokers had lower plasma levels of clozapine	Not reported	Not reported
Hasegawa, Gutierrez-Esteinou, Way, & Meltzer, 1993	59	Open label	Clozapine 100 to 900 mg/day	Not reported	6 weeks and 6-month follow-up	No difference in plasma levels of clozapine between smokers and no smokers	No difference between smokers and no smokers	Not reported
Dave, Gerada, Russell, & Gray, 1995	15	Open label	Haloperidol 5 mg p.o.	N/A	1 dose	Increase smoking	Restless, agitation, insomnia	Stiff jaw that required procyclidine
Mavroy, Freudenreich, Leim, & Rose, 1995	10	Open-label, inpatient	Haloperidol	Not reported	Variable	Increase smoking	Not reported	Not reported
Mavroy et al., 1995	12	Open random assignment	Clozapine plasma leves (50-150, 200-300, or 350-459 ng/ml)	Not reported	12 weeks	> 200 ng/ml reduce smoking 25%-35%	Not reported	Not reported
George, Semyak, Zisemonis, & Woods, 1995	29	Retrospective interview	Clozapine variable doses	Not reported	N/A	Significant reduction of number of packs of cigarettes smoked per day	Not reliable data	Not reported
Wazzel et al., 1998	30	Open-label, Prospective	Clozapine adjusted to body-weight	Not reported	27-38 days	Smokers had lower plasma levels of clozapine	Not reported	Not reported
Mavroy, Freudenreich, & Wilson, 1999	70	Open-label	Clozapine < 900 Mg/day versus conventional antipsychotics	Not reported	12 weeks	Less smoking with clozapine	Smokers greater therapeutic response to clozapine	Not reported
Sagala, Leinonen, Lehtonen, & Kivisto, 1999	44	Out/inpatient human laboratory study	Clozapine	150-800 mg/day	> 2 weeks	Smokers had clozapine lower level	Not reported	Not reported
George et al., 2000	45	Random assignment	Atypical versus typical (plus NRT)	Tow group therapies	10 weeks	Smoking cessation rate: atypical: 55.6%, typical: 22.2% No group therapy differences	Not reported	Typical received more benzotropine equivalents
(Combs & Advokat, 2000)	39	Open-label, inpatient, random selection	Typical (n=15) Clozapine (n=6) Other atypical (n=18)	Not reported	Not reported	Clozapine group had ower smoking rates than the other groups.	No group differences	Atypical and clozapine received less EPS medications

Author/Year published	n	Deisgn	Antipsychotic Medication	Behavioral Therapy	Duration of Intervention	Smoking Effect	Changes in Schizophrenia Symptoms	Extrapramidal (EPS) Symptoms
Apud, Egan, & Wyatt, 2000	101	Secondary analysis of data from smoker and non-smoker inpatients	Haloperidol disc ontinuation	Not reported	5 weeks	N/A	No group differences in schizophrenia deterioration	Smokers more paranoia
Procyslyn, Ihsan, & Thompson, 2001	20	Retrospective Cross-sectional outpatient	Clozapine (n=9) Depot neuroleptics (n=11)	Not reported	2 months	Clozapine group had lower expired CO levels	No group differences	No group differences
Procyslyn, Tse, Sin, & Flynn, 2002	14	Open-label and chart review	Risperidone (n=6) Risperidone plus clozapine (n=8)	Not reported		Risperidone plus clozapine group smoke less	No group differences	No group differences
Hutchison et al., 2004	59	Single blind. Random assignment	Olanzapine (n=31) Placebo(n=28)	Not reported	1 week	Olanzapine reduce cueelicted craving for tobacco	Cigarette decreased negative affect	Nicotine decrease sedation