Abstract

Why is it important to treat nicotine addiction in schizophrenia? The prevalence of smoking in schizophrenia, as in other mental disorders, is higher than in the general population. Smoking is also associated with higher rates of medical morbidity, including cardiovascular and lung diseases, and with higher mortality in schizophrenic patients. Schizophrenia is characterized by a constellation of clinical and cognitive deficits, and these patients may remediate such deficits by cigarette smoking. Genetic and environmental factors may also play a role in the high comorbid rates of smoking in schizophrenia. Preclinical and human laboratory studies have elucidated factors which may determine this comorbidity in schizophrenia, and recent treatments for both nicotine dependence (eg, nicotine replacement, bupropion) and schizophrenia (atypical antipsychotic drugs) may be useful for smoking reduction and cessation in this population. We review the biology of nicotine addiction in schizophrenia, and findings from the laboratory and clinic which suggest that: (1) there may be biological factors which explain the high rates of comorbid nicotine addiction in schizophrenic patients; and (2) based on an understanding of this neurobiology, effective treatment for nicotine addiction in these patients is possible. A clinical approach, including pharmacologic and behavioral treatments, is discussed.

Introduction

Epidemiologic and clinical studies have consistently revealed remarkable results indicating that the prevalence of cigarette smoking is markedly elevated in patients suffering from mental illness. In schizophrenic populations alone, rates of cigarette smoking approach 90%, in comparison to 25% in the general United States population. Clinicians are well aware that tobacco smoking poses dangerous health risks such as cardiovascular disease and lung cancer. In spite of the long-term health hazards associated with cigarette smoking, nicotine dependence has been difficult to treat in the schizophrenic population.

It has been speculated that individuals with schizophrenic disorders may be utilizing nicotine administered through tobacco smoking to remediate clinical and cognitive deficits. Indeed, a growing number of studies have found evidence that there may be biological and
psycnosocial factors which may explain these high rates of smoking comorbidity in schizophrenic patients, and that based on such knowledge, effective pharmacologic and behavioral treatments can be developed for the treatment of nicotine addiction in schizophrenia. This article reviews the epidemiology, neurobiology, clinical impact, and approach to treatment for nicotine and tobacco addiction in patients with schizophrenic disorders.

Epidemiology of Smoking in Patients With Schizophrenia

The prevalence of smoking in clinical samples of patients with schizophrenia in Western countries ranges from 58% to 88%, and these rates may vary as a function of setting (inpatient versus outpatient treatment) and illness severity. Interestingly, a study of Chinese schizophrenic patients in Singapore reported that the rate of smoking in schizophrenics was 31.8%, as compared to a rate of 15% in the general population. Researchers speculate that the lower rates observed may have been a function of societal prohibitions on smoking in Singapore. Hughes and colleagues' published a clinical survey of smoking prevalence in 277 psychiatric outpatients from Minnesota compared to local and national population-based control groups, which documented higher (1.6-fold overall) rates of smoking in a variety of psychiatric disorders. This study is one of the few that have controlled for important confounding variables such as age, sex, treatment with psychotropic medication, alcohol and caffeine use, and socioeconomic status.

A population-based study recently published by Lasser and colleagues examined smoking prevalence in various psychiatric patient groups using the National Comorbidity Study (NCS) database. This method probably gives a more accurate estimate of smoking prevalence in individuals with psychiatric disorders than data from surveys of clinical samples. In general, current (past 30 days) smoking rates were comparable to those obtained in studies of clinical samples including major depression (43.7%), bipolar disorder (60.6%), panic disorder (42.6%), and posttraumatic stress disorder (44.6%). The notable exception was in the schizophrenic disorders (defined loosely in this study as the “nonaffective psychoses”), which were found to be at lower rates (45.3%) compared to a composite rate derived from published studies from clinical samples (72.5%). The Figure depicts these higher rates of smoking in schizophrenics as compared to the general population (24.7%). In addition, lower quit rates in persons with mental illness compared to those without mental illness have been observed in clinical populations, and were confirmed in this population-based study.

Neurobiology of Comorbid Nicotine Addiction in Schizophrenia

There has been an increasing understanding of both the neurobiology of schizophrenia and nicotine addiction in the past 20 years. The purposes of this discussion, nicotine is assumed to be the active ingredient in tobacco and cigarette smoking that exerts psychopharmacologic effects, though other components of tobacco smoke may be active in this respect. There are three possible reasons for the high comorbid rates of nicotine addiction in schizophrenia: (1) self-medication of clinical and cognitive deficits associated with schizophrenia by tobacco use; (2) abnormalities in brain reward pathways in schizophrenia which make these patients vulnerable to tobacco (and other drug) use; and (3) common genetic and environmental factors that are independently associated with both smoking and schizophrenia. We briefly describe the pharmacologic effects of nicotine, and how these effects may link nicotine addiction with schizophrenia.

Nicotine alters the function of neurotransmitter systems implicated in the pathogenesis of major psychiatric disorders, including dopamine (DA), norepinephrine, serotonin, glutamate, γ-aminobutyric acid, and endogenous opioid peptides. Nicotine’s receptor in the brain is the nicotinic acetylcholine receptor (nAChR). Nicotine’s stimulation of presynaptic nAChRs on these neurons increases transmitter release and metabolism. Unlike most agonists, chronic nicotine administration leads to desensitization and inactivation of nAChRs, with subsequent upregulation of nAChR sites. This may explain why most smokers report that the most satisfying cigarette of the day is the first one in the morning.

Mesolimbic DA (reward pathway) neurons are of particular importance since these neurons project from the ventral tegmental area (VTA) in the midbrain to anterior limbic forebrain structures such as the nucleus accumbens and cingulate cortex, and may mediate the rewarding effects of nicotine since they have presynaptic nAChRs. These are the same subcortical DA pathways that are implicated in the expression of

Figure
Prevalence of Smoking in Schizophrenic Patients as Compared to the General United States Population*

<table>
<thead>
<tr>
<th>Smoking Prevalence (%)</th>
<th>US General Population</th>
<th>Schizophrenics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>40</td>
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<tr>
<td>20</td>
<td>60</td>
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<td>40</td>
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the positive symptoms of schizophrenia. Similarly, there are α7 nAChRs present presynaptically on midbrain DA neurons which project from the VTA to the prefrontal cortex (PFC) that evoke DA release and metabolism when α7 nAChRs are activated by nicotine (during smoking). The PFC is known to be dysregulated in schizophrenia—a finding possibly related to hypofunction of cortical DA and other transmitter systems. It is this hypofunction of PFC DA which is thought to mediate the cognitive deficits and negative symptoms associated with schizophrenia, and which may be ameliorated by cigarette smoking. Nicotine also stimulates glutamate release and could thereby alter abnormalities in central glutamatergic systems (eg, hypofunction) associated with schizophrenia.

**Effects of Smoking in Patients With Schizophrenia**

**Antipsychotic Blood Levels**

There is strong evidence that tobacco smoking induces cytochrome P450 (CYP) 1A2 enzyme system in the liver—a major route for the metabolism of antipsychotic drugs such as haloperidol, chlorpromazine, olanzapine, and clozapine. Thus, given the same daily dose of antipsychotic drug, antipsychotic blood levels have been found to be lower in smokers versus nonsmokers with schizophrenia. Accordingly, smoking cessation would be expected to lead to increases in plasma concentrations of antipsychotic drugs metabolized by the CYP 1A2 system. Such an increase in circulating levels would be expected to increase the likelihood of extrapyramidal symptoms and other antipsychotic side effects (sedation, anticholinergic side effects), but evidence for an increase in antipsychotic side effects has not been demonstrated in controlled smoking cessation studies. Nonetheless, adjustment of antipsychotic drug in schizophrenic patients who quit smoking may need to be considered, as well as close monitoring of plasma antipsychotic levels and extrapyramidal symptoms.

**Movement Disorders**

Cigarette smoking may reduce neuroleptic-induced parkinsonism and worsen symptoms of tardive dyskinesia, but these studies have been of cross-sectional designs. Smokers with schizophrenia are typically prescribed approximately twice the daily dose of neuroleptics compared to nonsmokers. The increased dosages are most likely due to the fact that smoking induces the metabolism of antipsychotic drugs and reduces therapeutic efficacy. Goff and colleagues found that while there was less neuroleptic-induced parkinsonism among schizophrenic smokers compared to nonsmokers, they had higher levels of akathisia. These effects may relate to nicotine’s enhancement of norepinephrine DA systems.

**Neurocognitive Symptoms of Schizophrenia**

Researchers have shown that a psychophysiological measure of auditory information processing (P50 responses, which involve “gating” of sensory inputs in response to two stimuli) is deficient in schizophrenic patients and their first-degree relatives compared to controls, and that nicotine and cigarette smoking transiently reverse these deficits. Animal studies suggest that P50 responses are related to low-affinity (α7) nAChR dysfunction in the hippocampus, and genetic studies have suggested that variations in regulatory regions of the α7 nAChR subunit gene on chromosome 15 may be a genetic marker for schizophrenia, and could explain high comorbid rates of nicotine use in schizophrenia. Interestingly, atypical antipsychotics, such as clozapine and olanzapine, may normalize P50 deficits in schizophrenic patients. This may be of importance for treatment of nicotine addiction in schizophrenia since clozapine has been shown to reduce smoking in schizophrenic patients, and atypical, compared to typical antipsychotic medications, have been shown to enhance smoking cessation rates when combined with nicotine patch in schizophrenic smokers.

Regarding neuropsychological effects of smoking in schizophrenia, Levin and colleagues have demonstrated that nicotine patch can dose-dependently reverse haloperidol-induced deficits in working memory, attention, and the authors of this article have recently demonstrated that prolonged smoking abstinence is associated with worsening of deficits in spatial working memory in schizophrenic, but not control smokers.

**Effects of Antipsychotic Drugs on Smoking in Schizophrenia**

Our research group has found that switching schizophrenic smokers from typical antipsychotic agents to clozapine leads to reductions in self-reported cigarette smoking, especially in heavier smokers. Similar findings were reported by McEvoy and colleagues, who found that the degree of reduction may be dependent on clozapine plasma levels. A related study found that the typical antipsychotic drug haloperidol leads to increased smoking in schizophrenics compared to a baseline medication-free condition. Most recently, two cross-sectional studies by Procysyn and colleagues have found that schizophrenic patients treated with clozapine smoke less than those on depot neuroleptic agents, and that patients treated with...
the combination of clozapine plus risperidone smoke fewer cigarettes and have reduced carbon monoxide levels compared to patients treated with risperidone alone. Thus, a role for clozapine in reducing smoking behavior is suggested.

Use of the nicotine transdermal patch (NTP) is known to facilitate smoking reduction and cessation in schizophrenic smokers albeit at lower rates (36% to 42% at trial endpoint) than in healthy control smokers (50% to 70%). Nonetheless, nicotine patch use (at 21 mg/day) appears to effectively reduce cigarette smoking and nicotine withdrawal symptoms in schizophrenic smokers.

Our recent studies indicate that in combination with the NTP, atypical antipsychotics, particularly risperidone and olanzapine, may enhance smoking cessation rates compared to typical antipsychotic drugs, in schizophrenic smokers who had high motivation to quit smoking. Furthermore, recent data from a preliminary placebo-controlled trial comparing bupropion versus placebo in schizophrenic smokers suggests that atypical antipsychotic treatment significantly enhances smoking cessation responses to bupropion.

We speculate that atypical antipsychotic drugs compared to typical neuroleptic agents may be helpful for smoking cessation in schizophrenics for the following reasons: (1) atypical agents produce fewer extrapyramidal side effects and improve negative symptoms, both of which may be improved by cigarette smoking; (2) treatment with atypical agents is associated with improvement in deficits in certain aspects of neuropsychological function (eg, spatial working memory, executive function) which also appear to be alleviated by smoking; (3) sensory gating deficits (eg, P50 responses, prepulse inhibition) that are transiently normalized by nicotine administration or cigarette smoking are also ameliorated by some of the atypical antipsychotic drugs possibly by increasing acetylcholine release and α7 nAChR-mediated neurotransmission in the hippocampus; and (4) atypical agents are associated with augmentation of DA release in the prefrontal cortex in rodent studies, and may normalize presumed deficits in cortical DA function in schizophrenia, which may also be remediated by nicotine/cigarette smoking.

A Clinical Approach to Smoking Cessation in Patients With Schizophrenia

The use of atypical agents and improvements in psychosocial and medical care probably affords an enhanced quality of life to individuals with schizophrenia. In addition, it is becoming increasingly apparent that cigarette smoking schizophrenic patients are more vulnerable to developing smoking-related morbidity and mortality, including an increased risk of cardiovascular disease and some forms of cancer compared to the general population of smokers.

Previous epidemiological studies have suggested that schizophrenic smokers were protected against the development of malignancies, and this was thought to relate to neuroleptic drug exposure. In addition, there is evidence that urinary levels of the peptide bombesin, a possible marker of precancerous cigarette smoking-induced lung damage, are lower in schizophrenic patients compared to controls. This reduction in urinary bombesin levels is independent of smoking status in schizophrenic patients, supporting the notion that schizophrenic patients may be less vulnerable to the development of cancer. However, several subsequent epidemiological studies have found no evidence for a decreased (or increased) risk of malignancy in schizophrenic patients or other patients with serious mental illness. Previous studies may have been confounded by a selection bias where rates of these medical illnesses in older schizophrenics were lower since most of this cohort had died from other causes related to their psychiatric illness (eg, suicide) by the time they reached the age at which cancer risk is substantially increased (50 years or higher). Thus, disease prevention through smoking cessation/reduction in this population is an important public health issue, as schizophrenic patients comprise about 1% of the population in the United States.

It appears that schizophrenic patients typically show low interest in quitting. However, based on ratings of motivational level on the Stages of Change scale (eg, preparation or action stages), there are approximately 20% to 40% whose desire to quit smoking is substantial. In many cases where smoking cessation is not possible, a reduction in smoking consumption (eg, a "harm reduction" approach) might accrue some health benefits for schizophrenic smokers, but no studies have been published to suggest that reducing smoking can reduce the risk of developing smoking-related illness in nonpsychiatric or schizophrenic smokers. Thus, an understanding of biological and psychosocial factors which render schizophrenic patients at high risk for developing nicotine addiction, as well as which contribute to their low intrinsic motivation to change smoking behaviors, are both critical to guiding efforts directed toward improving smoking cessation treatment in this population. A summary of patient and treatment factors which predict successful nicotine addiction treatment outcomes in patients with schizophrenia is presented in Table 1.

Table 1
Factors Predicting Positive Treatment Outcomes in Schizophrenic Smokers

- High motivation to quit smoking at the beginning of treatment
- Stable psychiatric symptoms
- Illicit drug and alcohol abstinence for at least 1 year
- Stable living conditions
- Moderate level of nicotine dependence
- Living in a residence where no smoking is permitted
- Strong encouragement by clinician to quit smoking
- Treatment with atypical antipsychotic drugs
- Minimal prefrontal cortex-dependent neuropsychological deficits

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quit smoking, and subsequently maintain abstinence. It is notable that patients typically know very little about the dangers of smoking on their health, so education about the health risks related to tobacco smoking is an important first step in working with patients to motivate them to quit smoking. Psychoeducation, in combination with classical motivational enhancement techniques (MET), can be combined to move patients through the stages of change toward abstinence. For example, many patients come to our program in the “contemplation” stage. Our clinicians work with these patients to identify the pros and cons of quitting smoking. Once patients achieve smoking abstinence, it becomes crucial to employ cognitive-behavioral coping skills techniques to reduce the likelihood of a relapse. \textsuperscript{20,55,59} Skills such as drug refusal and coping with cravings are especially important for schizophrenic patients, as they are often in environments with other smokers and peer pressure to smoke is strong. This treatment is done in a group setting, and we work from a social skills training model which encourages schizophrenic patients to practice skills which help facilitate social interaction and trust of fellow group attendees and therapists. We have found that this combination of education, MET, and skills training can be quite effective for helping schizophrenic patients quit smoking and, with classic relapse-prevention skills training, remain abstinent.

Pharmacologic Interventions

Standard Food and Drug Administration-approved smoking cessation pharmacotherapies like NTP\textsuperscript{17,18} and sustained-release bupropion\textsuperscript{19,20} appear to be safe and efficacious in schizophrenic patients during the course of controlled studies. Smoking cessation rates at the end of drug treatment with nicotine patch (36% to 42\%)\textsuperscript{17,18} and bupropion (11% to 50\%)\textsuperscript{19,20} in schizophrenic patients are modest compared to those achieved in nonschizophrenic control smokers (50% to 75\%),\textsuperscript{41} but may be improved when patients are prescribed atypical antipsychotic agents.\textsuperscript{15,19} Differences in study design, patient selection (eg, level of motivation to quit smoking), medication dose (in the studies with bupropion, used at 150–300 mg/day) and criteria used to determine smoking abstinence may explain the variability in quit rates amongst these studies. In studies that have used NTP, patients are expected to stop all smoking when they begin NTP on the “quit date.”

When using the NTP, patients should be cautioned not to smoke while they are wearing the patch due to concerns about nicotine toxicity: symptoms include tremor, nausea, vomiting, dizziness, and, in very rare cases, seizures, arrhythmias, and death. In our research clinic, we have not encountered nicotine toxicity. Craving to smoke and continuing withdrawal symptoms typically indicates incomplete nicotine replacement, and if needed, another patch of 7–21 mg/day can be added to therapy with the 21 mg/day NTP.

For bupropion, controlled studies have started dosing at 150 mg PO daily with an increase to 150 mg BID by day 4 of treatment. The quit date is typically set once levels reach steady-state, usually 3–4 days after beginning the full dose of 300 mg/day. A history of seizures of any etiology is a contraindication to the use of bupropion as indicated by the product labeling, and we recommend not exceeding the dose of 300 mg/day, since most antipsychotic drugs reduce seizure threshold. At the same time, bupropion 150–300 mg/day does not appear to worsen positive symptoms of schizophrenia, and may reduce negative symptoms.\textsuperscript{20,21}

The typical duration of therapy studied in schizophrenic patients with these agents is 8–12 weeks; studies with longer durations of treatment in this population have not yet been conducted. A summary of pharmacologic and behavioral treatment that have been evaluated in controlled studies of nicotine addiction is listed in Table 2.

Conclusion

The high rates of comorbid smoking in schizophrenic patients may relate to abnormal biology of nicotinic receptor systems and central dopamine pathways associated with this disorder. Hence, these patients may self-medicate clinical and cognitive deficits associated with schizophrenia that are nicotine-responsive. These findings have profound implications for understanding the neurobiology of schizophrenic disorders and for development of better treatments for nicotine addiction in this population, given that these patients appear to be at increased risk for developing smoking-related medical illnesses. In addition, motivation to quit smoking is often low in schizophrenic patients and efforts need to be undertaken to increase the awareness of both patients and their clinicians of the dangers of habitual tobacco smoking. Psychoeducation, motivational enhancement, and relapse-prevention techniques are the mainstays of behavioral treatment for nicotine addiction in patients with schizophrenia.

Furthermore, there is increasing evidence from controlled studies that certain pharmacologic agents (eg, atypical antipsychotic drugs, nicotine replacement, and bupropion), in combination with behavioral support (eg, psychoeducation, MET, relapse-prevention, and social skills training), promote smoking reduction and cessation, and that these agents can be used safely for the treatment of cigarette smoking and nicotine dependence in clinically stable patients with schizophrenic disorders. While there is little evidence from controlled clinical studies that smoking cessation

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Table 2: Pharmacologic and Behavioral Treatments for Smoking Cessation in Schizophrenia

- Nicotine replacement therapies
- Atypical antipsychotic medications
- Antidepressants (eg, bupropion sustained release)
- Psychosocial interventions (eg, motivational enhancement techniques, relapse-prevention, combined with social skills training and psychoeducation)
- Combined treatments

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produces a deterioration of clinical function (e.g., positive and negative symptoms) in stabilized patients, clinicians should not attempt to persuade patients to quit smoking when they are clinically unstable since the likelihood of success is low.

References


