Schizophrenia and Nicotine Use: Report of a Pilot Smoking Cessation Program and Review of Neurobiological and Clinical Issues

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Abstract

Nicotine use is a major public health problem that increases medical morbidity and mortality. Nicotine's action and the pathobiology of schizophrenic disorders have common neurobiological substrates. Tobacco smoking alters medication blood levels and effectiveness, modifies psychiatric symptoms, and is a clue for other substance abuse. This article presents an evaluation of a smoking cessation program for 24 smokers with schizophrenia. Fifty percent completed the program, 40 percent decreased use by 50 percent, and 13 percent remained abstinent (carbon monoxide verified) for 6 months. Nicotine replacement, motivational enhancement therapy, and relapse prevention behavioral therapy were important components of treatment. Pharmacotherapy strategies of a higher-dose nicotine patch, combining nicotine gum and a patch, and augmentation medication to nicotine replacement should be evaluated in future studies in this population.

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Nicotine dependence is the most common substance use disorder among individuals with schizophrenia. This type of dual diagnosis raises important issues for mental health staff because cigarette smoking alters medication blood levels, modifies psychiatric symptoms, and is a clue for the presence of other substance abuse. Although often untreated in mental health settings, nicotine dependence is a daily management issue on inpatient units. Unfortunately, there have been no published smoking cessation trials in the literature. After a general review of nicotine use and schizophrenia, this article presents outcomes from a pilot smoking cessation program in a community mental health center. Biological and clinical evidence is presented that suggests that nicotine's action and the pathobiology of schizophrenic disorders have common neurobiological substrates.

Nicotine Use and Schizophrenia

Epidemiology of Nicotine Use and Schizophrenia. Nicotine use is extremely common among individuals with schizophrenia. Compared with the 25 to 30 percent of the general population in the United States who are regular tobacco smokers, psychiatric patients are two to three times more likely to develop and maintain a nicotine addiction (Hughes et al. 1986; Goff et al. 1992; Lohr and Flynn 1992; Glassman 1993; MacKenzie et al. 1994; Ziedonis et al. 1994; Dalack et al. 1996). Rates of smoking range from approximately 40 to 50 percent in patients with depression and anxiety disorders to 70 to 90 percent in patients with chronic schizophrenia.

Many factors contribute to the increased smoking rate among individuals with schizophrenia, including the potential positive effect of nicotine on neurotransmitter systems involved in schizophrenia, nicotine's mitigation of the side effects of psychotropic agents, increased nicotine withdrawal symptoms in patients with schizophrenia, social factors such as lower income and educational attainment, and smoking's action as a "behavioral filler" (Goff et al. 1992; Lohr and Flynn 1992; Pomerleau 1992; Ziedonis et al. 1994). Clearly, an understanding of factors that contribute to the pervasive consumption of tobacco products among individuals with schizophrenia is essential from both public health and psychiatric perspectives.

Neurobiology of Nicotine and Psychosis. Nicotine may interact with many of the same central pathways thought to be aberrant in schizophrenia. Dopamine, serotonin, and glutamate are thought to play important roles in the pathophysiology of schizophrenia. Dopaminergic hyperactivity has been associated with psychotic symptoms. Mesotelencephalic dopamine pathways include the

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(1) nigrostriatal dopamine system involved in movement disorders; (2) mesolimbic structures, such as the nucleus accumbens and ventral tegmental area—regions implicated in the regulation of emotional expression, including positive symptoms of psychosis (delusions, hallucinations, and thought disorder) and in drug reinforcement and reward; and (3) the mesocortical system, which includes ventral tegmental projections to the prefrontal cortex, a region thought to be hypofunctional in chronic schizophrenia. In addition, recent studies have implicated other neurotransmitters, such as serotonin (Satel et al. 1995) and glutamate (Karler et al. 1995), in the neurobiology of psychosis and drug abuse. Glutamate, the major excitatory transmitter in the brain, can enhance the release of dopamine. Further investigations of these systems may enhance our understanding of the mechanisms of action of atypical antipsychotic drugs (i.e., clozapine or risperidone) and substances of abuse.

Nicotine seems to play an important role in modulating both dopamine and glutamate transmission. Specifically, it modulates the release of dopamine in mesotelencephalic dopaminergic pathways (Clarke and Pert 1985; Carr et al. 1989). Activation of nicotinic acetylcholine receptors on dopaminergic neurons stimulates central dopamine release and turnover (Clarke and Pert 1985; Balfour 1994), although nicotine receptors undergo desensitization during chronic agonist stimulation (Balfour 1994). Nicotine can stimulate glutamatergic neurons in the prefrontal cortex that enhance basal ganglia glutamate and dopamine activity (Vidal 1994) and may do so presynaptically by increasing intracellular calcium (Ca^{2+}) (McGehee et al. 1995). In addition to nicotine's induction of dopamine transmission, other agents in cigarette smoke may synergistically enhance this effect through the inhibition of monoamine oxidase type B (Fowler et al. 1996). In summary, the mesolimbic dopaminergic pathways are especially important in mediating reward in nicotine dependence (Nisell et al. 1995; Dani and Heinemann 1996).

Impact of Smoking on Positive and Negative Symptoms of Schizophrenia. Given its effect on modulating dopamine and glutamate, nicotine may have an impact on the negative and positive symptoms of schizophrenia. In fact, schizophrenia patients may use nicotine to self-medicate negative symptoms.

A deficiency of dopamine has been postulated in the prefrontal cortical regions of individuals with chronic schizophrenia. This deficiency may underlie the so-called deficit or negative symptoms of schizophrenia, characterized by anergia, amotivation, affective blunting, and dysfunctional social relationships. The positive symptoms of schizophrenia—delusions, hallucinations, and conceptual disorganization—presumably relate to hyperfunctional mesolimbic dopamine systems. Several studies (Goff et al. 1992; Ziedonis et al. 1994) have evaluated the association between smoking and positive and negative symptoms. In smokers with schizophrenia, Ziedonis et al. (1994) found decreased negative symptom scores and increased positive symptom scores (see table 1), and Goff et al. (1992) found increased positive and negative symptoms.

Nicotine may have an effect similar to clozapine and the newer atypical antipsychotic agents (i.e., risperidone, olanzapine) that reduce negative symptoms by augmenting cortical dopamine release (Kane et al. 1988; Moghaddam and Bunney 1990; Chouinard et al. 1993). Two research groups found that smoking consumption was reduced in individuals with schizophrenia when they were given clozapine compared with when they were treated with typical neuroleptics (George et al. 1995; McEvoy et al. 1995).

Effects on Auditory Physiology. Schizophrenia is associated with poor attention to and processing of sensory stimulation. This deficit may be the result of reduced sensory gating (habituation) of hippocampal response to repetitive auditory stimulation, which makes filtering out background noise more difficult. Nicotine transiently improves sensory gating in schizophrenia as assessed by normalization of the P50 wave during auditory evoked potentials, implying that smoking may alleviate difficulties with processing of sensory information in schizophrenia (Adler et al. 1993).

Interactions Between Smoking and Other Forms of Substance Abuse. As in the general population, smokers with schizophrenia are two to three times more likely to have other substance use disorders than never-smokers (Ziedonis et al. 1994). Neurobiologically, nicotine enhances dopaminergic tone in mesolimbic structures, such as the nucleus accumbens and ventral tegmental area (Imperato et al. 1986; Merea et al. 1987); these structures have been shown to be critical in drug reinforcement,

Table 1. Association of smoking and SAPS/SANS scores in smokers with chronic schizophrenia

	Nonsmokers (n = 87)	Light smokers (n = 100)	Heavy smokers (n = 82)
SAPS total score	4.3	5.5	9.1[1]
SANS total score	28.3	24.5	21.5[1]

Note.—SAPS = Scale for the Assessment of Positive Symptoms (Andreasen 1984*b*); SANS = Scale for the Assessment of Negative Symptoms (Andreasen 1984*a*); data from Ziedonis et al. (1994).

[1] $p < 0.05$.

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reward, and discriminative stimulus effects of several substances of abuse, including cocaine, amphetamines, alcohol, and heroin (Corrigall et al. 1992; Dani and Heinemann 1996).

Smokers may have higher basal levels of dopamine in these mesolimbic regions than nonsmokers, and consequently nicotine exposure produces considerable reinforcement (Paulson 1992). These findings may explain the strong tobacco-seeking behaviors and the strong cravings between cigarette usages in many individuals with schizophrenia. These effects are likely to be amplified by the short half-life of nicotine (1 to 2 hours), which results in continuous usage in heavy smokers that is reminiscent of episodic binge use of cocaine and other short-acting psychostimulants. Nicotine is thought to be a gateway drug to the use of other substances of abuse such as cocaine, heroin, and alcohol (Breslau 1995), especially for adolescents (Kessler 1995), presumably since it interacts with similar mesolimbic dopaminergic pathways.

Of particular interest are observations that the atypical antipsychotic agent, clozapine, which has very low extrapyramidal side effect liability (Kane et al. 1988), may reduce consumption of cocaine, alcohol, and heroin (Albanese et al. 1994), attenuate conditioned place preference in rats (Kosten and Nestler 1994), and reduce drug craving (Buckley et al. 1994; Hameedi et al. 1995) for cocaine. Furthermore, clozapine, but not typical neuroleptic agents such as haloperidol, blocks the discriminative stimulus effects of nicotine in animal models (Brioni et al. 1994). As mentioned earlier, smoking consumption may be reduced in individuals with chronic schizophrenia who are given clozapine, rather than typical neuroleptics (George et al. 1995; McEvoy et al. 1995). The mechanism for this clinical effect could be clozapine's ability to substitute for nicotine by augmenting dopamine release (Imperato et al. 1986; Merea et al. 1987) or by blocking nicotine's effects at specific receptor sites, such as the dopamine D_4 receptor (Van Tol et al. 1991).

Genetic Basis for Nicotine Dependence. Evidence for a familial basis for drug reinforcement and reward comes from molecular genetic studies demonstrating that certain alleles of the dopamine D_2 (Noble et al. 1994) and D_4 (George et al. 1993) receptors are more prevalent in substance abusers and, in particular, alcoholics and heavy smokers. Hence, the same receptor systems implicated in schizophrenia disorders may also play a role in the pathobiology of nicotine and other substance dependence. Furthermore, a recent epidemiological study (Heath and Martin 1993) found that familial factors are involved in the development of smoking persistence (independent of smoking initiation).

Impact of Smoking on the Treatment of Schizophrenia

Nicotine Withdrawal Symptoms. The symptoms of nicotine withdrawal can confuse or exacerbate the symptoms of schizophrenia. Nicotine withdrawal usually occurs within the first 12 to 24 hours of smoking cessation, and its symptoms include depressed mood, insomnia, irritability, anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite (*DSM–IV;* American Psychiatric Association 1994). Nicotine withdrawal can be confused with alcohol/drug withdrawal, affective disorders, sleep disorders, mania, neuroleptic-induced akathisia, and exacerbation of the negative or positive symptoms of schizophrenia (Hughes 1993). On a smoke-free inpatient unit, these withdrawal symptoms may alter the patient's psychiatric presentation and response to treatment. The use of nicotine replacement can substantially reduce but not completely eliminate these symptoms.

There is limited information on the severity of nicotine withdrawal symptoms in individuals with schizophrenia. In a carefully assessed sample of 12 male veteran smokers with schizophrenia (Dalack et al. 1996), there were no differences in heart rate measures (one index of withdrawal) between subjects receiving a nicotine patch or no nicotine replacement during the first 3 days of nicotine withdrawal. In our smoking cessation program, 20 of the 24 patients reported a previous quit attempt lasting longer than 24 hours. Of these 20 patients, 71 percent reported experiencing substantial withdrawal symptoms during that attempt to quit that resulted in their return to smoking. The patients recalled substantial symptoms of craving (71%), anxiety (52%), concentration problems (67%), irritability (38%), increased appetite (62%), and restlessness (14%).

Blood Levels of Antipsychotic Medications. Cigarette smoking also affects clinical care by lowering the blood levels of antipsychotic medications. The hydrocarbon agents in smoking (not the nicotine) are known to induce liver enzymes that increase the metabolism of neuroleptic and other psychotropic drugs, including antidepressants and antianxiety medications. This effect may occur through the induction of the cytochrome P450 1A2 isoform (Nemeroff et al. 1996). Several studies have documented that smoking lowers the blood levels of typical neuroleptic agents, such as haloperidol and fluphenazine, by up to 50 percent (Perry et al. 1993). And clinical epidemiology studies have reported that smokers are prescribed higher dosages of neuroleptics than nonsmokers (Hughes et al. 1986; Glassman 1993). Recent studies have

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documented that clozapine-treated schizophrenia patients who are smokers have lower clozapine and norclozapine plasma levels than nonsmokers (Hasegawa et al. 1993). Accordingly, smoking may reduce side effects related to antipsychotic drug administration.

Medication blood levels may be substantially altered during changes in smoking patterns. Patients who smoke fewer cigarettes or become abstinent may experience nicotine withdrawal symptoms and changes in symptoms secondary to medication blood level fluctuations, including changes in neuroleptic-induced movement disorder symptoms. Smoking also induces caffeine metabolism.

Association With Neuroleptic-Induced Movement Disorders. Neuroleptic-induced parkinsonism is reduced in patients who smoke cigarettes, and the use of prophylactic anticholinergic medication is significantly lower in neuroleptic-exposed patients with schizophrenia who smoke (Menza et al. 1991; Balfour 1994). Since nicotine enhances central dopaminergic activity, the reduced neuroleptic-induced Parkinsonism is consistent with the understanding that this condition is related to central dopaminergic hypofunction in nigrostriatal dopamine systems that is produced by traditional antidopaminergic neuroleptic agents. This extrapyramidal movement disorder improves with facilitation of dopaminergic function, such as with administration of dopamine precursors, anticholinergics, dopamine receptor agonists, monoamine oxidase B inhibitors and, potentially, replacement of dopaminergic cells by fetal neural transplantation (Spencer et al. 1992). In fact, patients with Parkinson's disease (PD) have lower rates of smoking than the general population, presumably because of lower mesolimbic dopamine function (Paulson 1992). Smokers have lower rates of idiopathic PD and a later onset of PD symptoms than nonsmokers (Baron 1986; Decina et al. 1990; Menza et al. 1991).

A confounding variable in smoking's effect on neuroleptic-induced Parkinsonian symptoms is that smoking induces liver enzymes, with an attendant reduction in serum neuroleptic levels (Glassman 1993). Our preliminary findings in a group of chronic medicated patients with schizophrenia indicated that 21 percent of smokers had a severe degree of Parkinsonism compared with 32 percent of nonsmokers (Ziedonis et al. 1994).

Tardive dyskinesia (TD), another neuroleptic-related movement disorder, is characterized by involuntary movements of the orolingual, facial, truncal, and extremity regions. Its incidence increases with the duration of neuroleptic exposure and is an important medicolegal factor in the long-term prescription of these agents. This increased incidence is thought to be related to dopamine receptor supersensitivity. From a theoretical standpoint, one would expect that smoking would exacerbate preexisting TD or promote its emergence, but studies to date have proven equivocal in this regard (Binder et al. 1987; Yassa et al. 1987). Our initial findings are consistent with complex effects of smoking on TD based on assessment of the Abnormal Involuntary Movement Scale (National Institute of Mental Health 1974) scores in smoking and nonsmoking medicated patients with schizophrenia (nonsmokers 1.2, light smokers 1.4, heavy smokers 1.1; Ziedonis et al. 1994).

Methods

Treatment of Nicotine Dependence. Unfortunately, very little is known about nicotine dependence treatment outcomes in individuals with schizophrenia, although several clinical approaches have been suggested (Dalack and Glassman 1992). The American Psychiatric Association has recently published guidelines on the treatment of nicotine dependence in psychiatric settings (Docherty et al. 1996). Unfortunately, smoking cessation outcome studies for individuals with schizophrenia have not been reported.

Connecticut Mental Health Center (CMHC) Smoking Cessation Program Evaluation. In a pilot study, 24 smokers with schizophrenia were treated for 10 weeks in a smoking cessation program within a community mental health center. The patients continued to receive their usual treatment from their primary clinicians and psychiatrist, and the clinicians and psychiatrists within the smoking cessation program maintained regular contact with the primary treatment team. Patients were recruited into the program through advertisements posted in the CMHC. The treatment, including the nicotine replacement medication, was offered at no cost. Baseline and ongoing carbon monoxide testing was conducted.

In the CMHC outpatient programs about 750 patients are diagnosed with schizophrenia or schizoaffective disorder, and about 70 percent of these individuals smoke. Hall et al. (1995) found low motivation to quit smoking among their sample of 300 chronic psychiatric patients. About 85 percent were in the precontemplation or contemplation stage of the Prochaska and DiClemente (1983) readiness for change model: These clients were not interested in stopping smoking in the next 6 months. Interestingly, about three-fourths of the patients in this study presented in the contemplation stage (admit smoking is a problem, but probably will not want to quit in the next 6 months).

Sample. During a 1-year period, 24 individuals with schizophrenia (63%) and schizoaffective disorder (37%)

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entered treatment. In this sample, 75 percent were female, 17 percent married, 75 percent white, and 42 percent employed. The mean level of education was completion of 11th grade, and the mean age was 42 years old. On average, the psychotic disorder began at 24 years of age, and the age of smoking onset was 15. They smoked an average of 27 cigarettes per day and presented with a baseline carbon monoxide level of 27 and a baseline Fagerstrom scale score of 7. All 24 patients met *DSM–IV* criteria for nicotine dependence. About 85 percent had a past quit attempt lasting longer than 24 hours and three additional quit attempts; of these 29 percent used the nicotine patch and 8 percent used nicotine gum. About 40 percent lived with a smoker.

Treatment Program. The treatment varied, but included some combination of nicotine replacement, behavioral group therapy, and individual motivational enhancement therapy. During the 2 weeks before starting the program, patients received a comprehensive psychiatric and medical evaluation, including assessments of their nicotine and other substance use. Patients had baseline and weekly carbon monoxide monitoring to compare with their self-reported nicotine use.

The weekly group therapy was supportive, behavioral, and psychoeducational. The behavioral therapy component focused on relapse prevention strategies, including identifying personal triggers to use substances and developing coping strategies to manage those triggers. Common triggers included environmental cues, specific times of the day, friends, and mood states.

The weekly individual therapy used motivational enhancement therapy (MET) strategies of engagement. MET is described in *Motivational Interviewing* (Miller and Rollnick 1991) and the National Institute on Alcohol Abuse and Alcoholism Project MATCH *Motivational Enhancement Therapy Manual* (Miller et al. 1992). It focuses on strengthening the client's motivation and commitment to change. The therapist maintains an empathic approach through eliciting client's own self-motivational statements, affirming that change is difficult, and helping the client consider the advantages and disadvantages of continued smoking versus smoking cessation. The therapist actively uses followup letters and phone calls. He or she helps the patient develop a change plan that is acceptable, accessible, appropriate, and effective (Ziedonis and Fisher 1996). Eighteen patients (75%) received both individual and group therapy. The other six patients received only group or individual therapy.

Given the severity of nicotine dependence among these patients, we offered nicotine replacement to all patients. Most patients (83%) attempted to quit with the aid of nicotine replacement. Fourteen (58%) received a nicotine patch, and one received gum alone (4%). In addition, four patients (17%) requested adjunctive nicotine gum with the patch, and one requested an initial higher dose of nicotine replacement (35 mg patch combination).

Results

Fifty percent of the patients (n = 12) completed the 10-week program, and the average number of weeks in treatment was 7.3 weeks. During the course of treatment, about 30 percent did not change their smoking pattern, and about 40 percent decreased by half the baseline number of cigarettes smoked daily. Three of the 24 patients (13%) remained completely abstinent (carbon monoxide verified) for at least 6 months after the 10-week smoking cessation program; all of these patients had received nicotine replacement. Another four patients (17%) had several episodes of weekly abstinence and visited the program with plans to make another serious quit attempt in the next 6 months.

Given their heavy nicotine dependence, the patients' need for nicotine replacement was expected. Initial nicotine replacement dosing was 21 mg per day; however, higher dosing was used in several patients through either adjunctive nicotine gum or a higher initial dose of nicotine. The role of other medications, such as bupropion, buspirone, and atypical antipsychotics, needs to be evaluated in this population.

Given the low motivational level on entrance into the program, the relatively low quit rate of 13 percent is not surprising. These low-motivation patients initially need support, hope, and information. MET strategies seemed to be useful with the patients with low motivation. MET was used to engage patients in treatment and to supplement their group therapy experience. In weighing the advantages and disadvantages of quitting smoking, these patients reported that the benefits included reducing the risk of long-term health problems (cancer, pulmonary, and cardiac problems), financial savings, reduced home fire risk, and less stigma in public places.

In summary, smoking cessation treatment can work, but more study is required in this area. MET seemed to improve outcomes, and nicotine replacement was an essential ingredient of treatment. The role of motivation as a prognostic and outcome factor requires further study. Of importance, patients in this smoking cessation program who had periods of extended abstinence did not have an exacerbation of their psychiatric symptoms.

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Conclusions

Nicotine dependence is the most common dual diagnosis for individuals with schizophrenia, and cigarette smoking is an important clinical issue in the management of psychiatric patients. Nicotine use and withdrawal modify psychiatric symptoms and medication blood levels. Smoking cigarettes is a clear health issue for our patients, and nicotine has strong addictive and reinforcing properties (Benowitz and Henningfield 1994).

Nicotine has important central effects on neurotransmitter systems relevant to schizophrenia and substance abuse. Nicotine itself may ameliorate some psychiatric symptoms, and its effects may suggest mechanisms to improve psychiatric medications. Atypical antipsychotic medication, which may mimic some of nicotine's central nervous system effects, may improve the effectiveness of schizophrenia treatment and attenuate drug reinforcement and reward produced by known substances of abuse (Van Tol et al. 1991; Albanese et al. 1994; Brioni et al. 1994; Kosten and Nestler 1994). More prospective and longitudinal studies are required on the relationship between nicotine use and schizophrenia. Further basic and clinical research is needed to define both the mechanisms of action of nicotine and the common pathophysiological processes involved in schizophrenia.

Smoking cessation treatment can be effective for psychiatric patients. However, there has been limited study among smokers with schizophrenia. Our pilot study of 24 smokers with schizophrenia supports the general guidelines for treating heavily dependent smokers. Nicotine replacement is critical, although most health plans do not provide reimbursement for this intervention. Randomized clinical trials are needed to document this clinical experience, and health plans should be encouraged to support nicotine replacement.

The intensity of our psychosocial intervention exceeds the traditional smoking cessation program. Our experience was that group therapy was less effective than individual motivational enhancement therapy and that patients benefited from combined twice-weekly therapy. Future smoking cessation studies should be undertaken in individuals with schizophrenia and should consider the role of adjunctive medication in improving treatment outcomes.

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