# Smoking and Schizophrenia: Prevalence, Mechanisms and Implications for Treatment

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## Introduction

Smoking represents a major public health problem and one that has been seriously neglected in schizophrenia. High rates of medical morbidity and early mortality have long been associated with schizophrenia. However, only recently have smoking cessation interventions been studied in this population.

Here we review the published data on the prevalence of smoking and heavy smoking in schizophrenia, the contribution of smoking to increased mortality risk in this population, potential neurobiologic factors that may underlie the increased prevalence of smoking in schizophrenia and, finally, treatment intervention studies. Although progress has been made in the development of smoking cessation interventions in this population, currently available treatments are less effective in promoting initial and sustained abstinence in schizophrenia than in the general population, a finding which may best be explained by neurobiological abnormalities found in patients with schizophrenia.

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## Smoking in the General Population

Each year over 440,000 people in the United States die from smoking-related illness, and $157 billion in health-related economic losses are directly attributable to smoking (1-3). Although cigarette smoking has been the single largest source of preventable morbidity and mortality in the U.S. for the last twenty-nine years, the global mortality toll of smoking of over five million lives annually is on the rise (2, 3). Smokers die on average ten years earlier than lifelong non-smokers, but smoking cessation has clear benefits in terms of reducing early mortality. For example, although cigarette smoking from early adult life triples age-specific mortality rates at middle age (43% vs. 15%), cessation at age fifty halves the hazard, and cessation by age forty nearly abrogates the elevated risk (4). An estimated 45% of all cigarettes sold in the U.S. are sold to people with a mental illness, and those with a major mental illness are more likely than those without psychiatric illness to be heavy smokers (5). Despite the availability of effective nicotine dependence treatments and clear evidence that quitting smoking decreases deaths from cancers, cardiovascular disease and respiratory illnesses (6), the proportion of people smoking fewer than 15 cigarettes/day is decreasing, while the proportion of people smoking more than 25 cigarettes/day is increasing (7).

## Smoking in Schizophrenia: Prevalence and Health Implications

Between 72% and 90% of schizophrenia patients smoke cigarettes, compared with 24% of the general population. Schizophrenia patients also smoke far more cigarettes on average per day (1, 8-11), often spending approximately one-third of their weekly income on cigarettes (12, 13), and, accordingly, attain higher serum levels of cotinine, the primary metabolite of nicotine, in most (14, 15), but not all (16) studies.

Mortality from smoking-related diseases such as pulmonary and cardiovascular disease is two to six times higher among those with schizophrenia as compared to age-matched nonpsychiatric controls (17-22). Women with schizophrenia have increased risk of premature death from cancer (23), and it is now thought that earlier studies which showed lower rates of cancer-related death in schizophrenia patients compared to the general population (24, 25) may have been an artifact of decreased lifespan due to early death from nonneoplastic diseases.

## Smoking and Schizophrenia: Evidence for Shared Neurobiological Pathways

It has been speculated that the high rates of nicotine dependence in individuals with schizophrenia represents an adaptive behavior to minimize side effects of conventional antipsychotic medications. In behavioral studies, smokers with and without schizophrenia do smoke more cigarettes during ad lib smoking periods following a single dose of haloperidol than after placebo (26, 27). Smoking, but not nicotine, reduces blood levels of many antipsychotic medications by increasing the metabolism of antipsychotic medications through induction of hepatic microsomal enzymes, particularly cytochrome P450 1A2, which is involved in the metabolism of antipsychotic medications such as clozapine and olanzapine (28). Consistent with this, smokers with schizophrenia receive significantly higher doses of conventional antipsychotics than nonsmokers, but do not show higher rates of, or more severe, tardive dyskinesia or parkinsonism (29-33). Haloperidol is associated with dose-dependent impairment in cognitive functioning in humans, an effect that is partially reversed by nicotine patch application, perhaps through increased dopamine release (34). In animals, nicotine administration reverses impairments in attentional performance caused by haloperidol, risperidone and clozapine (35).

Although reduction of adverse effects of antipsychotic medication may partly explain elevated rates of smoking and heavy smoking in schizophrenia patients, reports of increased smoking rates in healthy adolescents who later develop schizophrenia (40), and among a cohort with first-episode psychosis with little or no exposure to antipsychotic medications, suggest that amelioration of adverse medication effects does not entirely account for this phenomenon (36).

## Nicotinic Cholinergic Receptor Abnormalities in Schizophrenia

Multiple lines of evidence have converged to implicate the nicotinic cholinergic system in the pathophysiology of schizophrenia. Independent of smoking behavior, postmortem studies find decreased high (alpha4beta2) and low affinity (alpha7) nicotinic acetylcholine receptor (nAChR) number in the hippocampus and other brain regions of schizophrenia patients compared to controls (37-39). Polymorphisms in the promoter regions of the alpha7 nAChR gene that result in reduced nAChR transcription have been identified (40) that may partly explain the finding of reduced nAChR expression in schizophrenia. A functional nAChR abnormality consistent with abnormally rapid receptor desensitization related to sensory gating hypofunction has been described (41). Abnormal auditory P50 evoked potentials and smooth pursuit eye movements that have been described in individuals with schizophrenia and their first-degree relatives are associated with the gene that codes for the alpha7 nAChR (42-45) and are transiently normalized by nicotine patch or smoking (46), suggesting that nicotine at least transiently improves the ability to filter irrelevant sensory information. In summary, schizophrenia is associated with abnormally low expression of nAChRs that may be unavailable for stimulation much of the time due to rapid desensitization, and sensory deficits characteristic of a neurobiological vulnerability to schizophrenia are to some extent reversed by nicotine administration.

Heavy smoking in schizophrenia is consistent with a need for high nicotine concentrations to compensate for the decrease in receptor efficacy and/or number. Nicotinic receptors interact with dopamine, glutamate, norepinephrine, serotonin, GABA and other systems, suggesting that nicotine may have broad spectrum effects on a number of brain regions. For example, hippocampal hyperactivity has been identified in schizophrenics during smooth pursuit eye movements (47), and nicotine administration is thought to improve sensory gating via its effects on diminished hippocampal activation (48). Nicotine administration improves perception and attention to moving stimuli in schizophrenia, effects that are correlated with reduced hippocampal activation and consistent with diminished nicotinic neurotransmission as mediating inhibitory neuronal dysfunction in schizophrenia (47).

Nicotinic receptors modulate anterior cingulate cortex

(ACC) activity, a brain region known to mediate attention, and nicotine administration elicits improvements in attentional performance concomitant with increased ACC activity (49, 50). Subjective craving is mediated by thalamocortical circuitry and ACC, and these areas are differentially activated by nicotine in those with schizophrenia compared with controls (49).

Negative symptoms of schizophrenia are linked to NMDA receptor hypofunction (51). Chronic nicotine administration increases NMDA receptor density in the hippocampus (52) and further increases glutamatergic activity through stimulation of presynaptic nAChRs on limbic glutamatergic neurons (53-56). Activation of nAChRs stimulates central dopamine release and turnover (57, 58), providing another possible mechanism by which nicotine may improve cognitive deficits, negative affect and reward responsivity.

In nonsmokers with schizophrenia, nicotine replacement therapy (NRT) gum improves performance on attentional tasks (59). Consistent with nAChR hypofunction in schizophrenia, a single-dose 14 mg NRT patch elicits greater improvement in impulsive responding on attentional tasks in nonsmokers with schizophrenia than controls (60).

In smokers with schizophrenia, the NRT patch improves reaction time on attentional and spatial rotation tasks (34). The NRT nasal spray improves spatial organization, some measures of verbal memory and two-choice reaction time (61). Nicotine 1 mg by nasal spray normalized memory in a delayed spatial recognition task, an effect mediated by reduced false alarms (enhanced inhibition) (62). The high-dose nicotine patch normalized working memory performance in schizophrenia and worsened performance in normal controls, as well as increased ACC, right thalamus and hippocampus activity during attentional tasks in schizophrenia patients significantly more than in controls (49).

Nicotine thus facilitates performance of patients on tasks involving high cognitive load, activates brain areas facilitating attention and increases inhibition of impulsive responses. Some have postulated that such effects are limited by tachyphylaxis and are not clinically significant (59). However, while low-affinity nAChR subtypes desensitize rapidly (41), the positive effects of nicotine treatment on attention and memory, nevertheless, appear to persist and may become more robust over time (63). The nicotine patch, administered for four weeks, improves attention and memory in diverse clinical groups including patients with: dementia of the Alzheimer's type (64), attention deficit disorder (65, 66), and age-associated memory impairment (67), as well as in animal models of schizophrenia (68). However, if nAChRs desensitize more rapidly in schizophrenia, chronic agonist therapy may be expected to have limited efficacy.

Both smoking and nicotine administration increase nicotinic transmission through providing exogenous agonist and also by increasing nAChR number (52, 69). The atypical antipsychotic, clozapine, while not a direct nicotinic agonist, indirectly increases release of acetylcholine in the hippocampus, a property not shared by older dopamine D2 receptor antagonists (70). Clozapine increases inhibition of the P50 auditory response in schizophrenia (71), and in animal models this effect is mediated by stimulation of alpha7 nAChRs (72). Interestingly, clinical response to clozapine is greater in schizophrenics who smoke, perhaps due to increased nAChR number in smokers. Further, clozapine treatment is associated with decreased smoking (73, 74), consistent with nicotinic cholinergic agonism as a mechanism of its therapeutic effect (75). In an animal model of schizophrenia, acute administration of nicotine and clozapine significantly improve attention and working memory; the effects are of equal magnitude and not additive, again implying a common mechanism (76). An exploratory analysis in one study suggested that schizophrenia patients treated with atypical antipsychotics are more likely to quit smoking with NRT and cognitive behavioral therapy (CBT), although it is not known if atypical antipsychotic treatment in general, or clozapine treatment specifically, reduces relapse to smoking in schizophrenia patients (77).

## Nicotine Dependence Treatment in Schizophrenia

Individuals with schizophrenia can be both highly motivated and persistent in their attempts to quit smoking, despite long histories of smoking and high levels of nicotine dependence (78-81). In a sample of 105 schizophrenia patients who were smokers, 81% reported having made at least one serious attempt to quit (Evins, unpublished). Similarly, 70% of a sample of smokers with schizophrenia with a mean age of fifty-seven and a mean smoking history of twenty years, reported a history of at least one serious attempt to quit smoking (82).

Conventional treatment regimens of eight-to-twelve week therapy with bupropion or single-preparation nicotine replacement therapy (NRT) added to cognitive behavioral therapy (CBT) are well tolerated by individuals diagnosed with schizophrenia, but are only modestly effective. Abstinence rates have been 4 to19% at three-to-six month follow-up with bupropion or NRT and CBT, and 0 to 6% with placebo and CBT (77, 83-90). Relapse rates are high after discontinuation of bupropion or NRT and CBT. For example, in a twelve-week trial of bupropion 300 mg/day for smoking cessation in fifty-three schizophrenia patients, the abstinence rates at the end of treatment were 16% in the bupropion + CBT group and 0% in the placebo + CBT group. The relapse rate was 50% within two weeks of discontinuation of bupropion and 75% at the three-month follow-up (89).

Tailored nicotine dependence therapy with higher dose NRT and longer duration pharmacotherapy may improve abstinence rates and reduce relapse rates in schizophrenia patients. Combined treatment with bupropion plus NRT has shown promise in both general and psychiatric populations. Bupropion SR + NRT was superior to placebo and to NRT alone, but not to bupropion alone for smoking cessation in a nonpsychiatric population (91). In an open, nonrandomized smoking cessation study in 115 smokers with comorbid psychiatric and substance use disorders, patients randomized to receive bupropion SR + NRT + CBT had significantly greater smoking reduction than those on bupropion SR + CBT, NRT + CBT, or CBT alone (92). Patients tolerated the combined treatment, and there were significantly fewer dropouts in the combined bupropion + NRT group.

Combined treatment with nicotine patch and nicotine gum or nasal spray has shown superiority over single-form NRT (93-95). The combination of NRT patch and nasal spray was twice as effective as the combination of patch and placebo at twelve weeks (94). In a recent study, fifty-one individuals with schizophrenia were randomly assigned to receive bupropion SR or placebo added to high-dose combination NRT patch and gum, and 60% of those receiving combination pharmacotherapy had significant reduction or abstinence compared to 31% of those assigned to placebo and NRT (96). Those on combination pharmacotherapy had significantly lower expired air carbon monoxide (CO) levels than those on placebo + 2 forms of NRT and demonstrated higher rates of continuous abstinence prior to the NRT taper. However, as in previous studies, the relapse rate was quite high during and after discontinuation of nicotine dependence treatment: 31% of those who had quit relapsed during NRT taper and 77% had relapsed by twelve months, suggesting a role for maintenance nicotine dependence treatment to reduce relapse rates.

## Relapse Prevention

In the general population, relapse rates are 41 to 58% at one year if pharmacologic treatment is discontinued after seven to twelve weeks (91, 97-99). In schizophrenia, relapse rates have been reported of 70 to 83% six-to-twelve months after discontinuation of eight-to-twelve week treatment (86, 89, 96). Thus, relapse rates are approximately 25% higher among individuals with schizophrenia who successfully quit smoking than among successful quitters in the general population. Longer duration pharmacotherapy may be necessary to reduce relapse in schizophrenia patients who are able to achieve abstinence.

Longer duration pharmacotherapy has been associated with higher rates of sustained smoking abstinence in the general population. Continuation treatment with bupropion for one year in those who achieved abstinence on bupropion was well tolerated and associated with a lower relapse rate at twelve months (45%) compared with placebo (58%) (99-101), perhaps through reduction in craving (100). Similarly, one year of treatment with nortriptyline + CBT resulted in significantly lower relapse rates (20%) compared with the same intervention over the more standard twelve-week duration (58%) (101). Trials of longer duration pharmacotherapy are underway in patients with schizophrenia.

## Varenicline

Varenicline, a newly approved pharmacotherapy for nicotine dependence, is a partial agonist at alpha4beta2 nAChRs (102, 103) and a full agonist at alpha7 nAChRs (104) that has been shown to be effective for smoking cessation and to have superior efficacy to placebo (105, 106) and bupropion (107, 108). It has significantly greater abstinence rates at one year when compared with placebo (105, 106, 109) and, in one study, when compared with bupropion (108). Varenicline has demonstrated safety when dosed at 1 mg twice per day for up to one year (110) and has been demonstrated to reduce craving, withdrawal and the reinforcing effects of smoking (105, 106, 108).

Varenicline, when dosed at either 0.5 or 1.0 mg twice daily, appears to be more effective than placebo for smoking cessation (105, 106). Treatment with varenicline 1 mg twice daily has produced four-week continuous quit rates at end of treatment ranging from 44 to 49%, compared with 12 to17% in placebo-treated subjects (105-108).

Although there have been no studies comparing the efficacy of varenicline to that of NRT, varenicline has demonstrated superior efficacy to bupropion SR in two studies. Jorenby and colleagues (2006) compared twelve weeks of varenicline 1 mg bid, bupropion SR 150 mg bid and placebo in 1,027 smokers. Continuous quit rates at weeks nine to twelve were 44% in the varenicline group, 30% in the bupropion SR group, and 18% in the placebo group. Comparable results were found in a study of 1,025 smokers randomized to varenicline 1 mg titrated to twice daily, bupropion SR 150 mg titrated to twice daily or placebo. End of treatment four-week continuous quit rates were 44% for varenicline, 30% for bupropion and 17% for placebo (107).

Importantly, varenicline-treated subjects demonstrate lower relapse rates at one-year follow-up compared to placebo-treated subjects in randomized, controlled trials with smokers (105, 106, 108). Rates of continuous abstinence at one year range from 14.4 to 23% with varenicline 1 mg bid compared with 3.9 to 10.3% with placebo (see Table 1). Preliminary evidence for the efficacy of continuation treatment with varenicline for cessators comes from a study which randomized 1,210 smokers who achieved one week of con-

tinuous abstinence at the end of twelve-week open treatment with varenicline to twelve weeks of continuation varenicline or placebo. Continuous abstinence rates were higher for the varenicline-treated group at thirteen to fifty-two weeks (44%) compared to 37% of those who received placebo (109).

Nausea is the most common adverse effect of varenicline with 16 to 52% of varenicline-treated subjects reporting nausea compared to 8 to19% of those receiving placebo (105-108). Although there is one published case report of psychiatric symptom exacerbation in an individual with schizophrenia soon after starting on varenicline (111), a case series of thirteen individuals with schizophrenia prescribed varenicline for nicotine dependence reported no symptomatic worsening or psychiatric hospitalizations over a six-month period (112). Studies are needed to demonstrate the efficacy and safety of varenicline in patients with schizophrenia.

## Conclusions

Individuals with schizophrenia are significantly more likely to smoke and to smoke more heavily than are members of the general population. Cigarette smoking is a critical contributor to the elevated rates of smoking-related illness and early mortality in this population, underscoring the pressing need for smoking cessation treatments that are effective for and well tolerated by those with schizophrenia.

Reduced nAChR expression and function have been reported in schizophrenia, and smoking rates are elevated among those with the recent onset of illness who are antipsychotic naive. Nicotine improves sensory gating and attentional deficits in schizophrenia by activating brain areas associated with attention and by improving response inhibition and has been reported to improve negative symptoms. The nAChR hypofunction may underlie both reward deficiency and attentional impairment, suggesting that cigarette smoking may function to remediate both cognitive and negative symptoms of schizophrenia to some degree, although it is unclear whether the beneficial effects of acute nicotine administration on cognition and negative symptoms are sustained with longer term nicotine administration.

Although rates of smoking cessation are lower among smokers with schizophrenia than in the general population, increased intensity of standard treatments may improve cessation rates. Combination pharmacotherapy (bupropion + NRT), higher dose NRT or concomitant use of both short- and long-acting forms of NRT may substantially increase the cessation rate over bupropion or NRT alone in this population. Relapse rates are also higher among individuals with schizophrenia than in the general population. Longer term pharmacotherapy and psychosocial treatment reduces relapse to smoking in nonclinical samples. Relapse following discontinuation of pharmacotherapy for smoking cessation in schizophrenia patients is very high and may be due to the abrupt loss of nicotinic activity in patients with underlying nAChR hypofunction. As a result, longer term or even chronic treatment with nicotine or a nicotinic agonist or partial agonist may hold promise for enhancing maintenance of smoking abstinence in those with schizophrenia.

**Table 1 Continuous Quit Rates (Weeks 9-52) in Smokers Treated with Varenicline, Bupropion or Placebo**

| Study | N | Treatment Groups | % Abstinent |
|---|---|---|---|
| Oncken et al. (2006) | 647 | placebo<br>varenicline 0.5 mg BID*<br>varenicline 1.0 mg BID* | 3.9<br>18.5<br>22.4 |
| Jorenby et al. (2006) | 1027 | placebo<br>bupropion SR 150 mg BID<br>varenicline 1.0 mg BID | 10.3<br>14.6<br>23.0 |
| Nides et al. (2006)† | 1027 | placebo<br>bupropion SR 150 mg BID<br>varenicline 0.3 mg QD<br>varenicline 1.0 mg QD<br>varenicline 1.0 mg BID | 4.9<br>6.3<br>7.9<br>5.6<br>14.4 |
| Gonzales et al. (2006) | 1025 | placebo<br>bupropion SR 150 mg BID<br>varenicline 1.0 mg BID | 8.4<br>16.1<br>21.9 |

*Results based on pooled titrated and nontitrated groups
†Continuous quit rate calculated from weeks 4-52

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