

A retrospective cohort study of the prevalence of anxiety and agitation in schizophrenic smokers and the unmet needs of smoking cessation programs

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Abstract

Achieving abstinence in schizophrenic smokers using a combination of medications and cognitive behavioral therapy is feasible; however, abstinence rates are significantly lower compared to the general population and studies are scanty. Additionally, maintaining sustained abstinence and preventing relapse is a major limiting factor and represents key tasks in managing tobacco dependence in schizophrenic patients. Several theories have been postulated to explain the higher tendency of tobacco use among schizophrenic individuals. Schizophrenic patients may use nicotine as a “self-medication” strategy to improve negative symptoms of schizophrenia. However, studies suggest that although nicotine may act as an anxiolytic acutely, chronic use of nicotine may lead to increased anxiety with the possibility of increased catecholamines, which is confirmed with the prevalence of tachycardia and hypertension in smokers in general. On this basis, the main objective of our present study was to assess anxiety in schizophrenic smoking and nonsmoking patients by comparing the number of anxiety and agitation episodes and evaluating the amount of antianxiety/antiagitation medication used by each group. A separate objective was to document the unmet needs of smoking cessation programs in treating schizophrenic patients. Consequently, in the present retrospective cohort study, it was observed that schizophrenic smokers tend to have higher anxiety episodes and utilize as-needed medications at a higher frequency compared to nonsmokers for the relief of anxiety and agitation symptoms. Further research is warranted to examine these results on a larger scale.

Abbreviation: U.S. = United States.

Keywords: agitation, anxiety, cigarette smoking, cognitive behavioral therapy, nicotine replacement, schizophrenia, smoking cessation, smoking relapse, tobacco addiction

1. Introduction

Schizophrenic patients are quite often smokers in relation to the general public. According to the Centers for Disease Control and Prevention, the smoking prevalence among those with schizophrenia is 88% compared to 18.3% in the general population

(Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report, 2013). Smokers with serious mental illness such as schizophrenia consume almost half of the cigarettes in the United States (U.S.) and die approximately 25 to 28 years earlier due to tobacco-related diseases such as cardiovascular disease.^[1,2]

Considering the prevalence of health risks, poverty, and lower education, patients with schizophrenia and schizoaffective disorders suffer from health disparities and represent an understudied population.^[3] Smokers with schizophrenia smoke more often, more heavily, inhale more nicotine from each cigarette, and are more likely to be nicotine dependent compared to smokers without psychiatric illness.^[1] Clearly, smokers with schizophrenia have severe nicotine addiction, and pharmacological and psychological support with smoking cessation needs to be addressed. Recent studies suggest that individuals with schizophrenia want to quit smoking and that the most effective treatment in this population is a combination of behavioral therapy with either varenicline or bupropion with or without nicotine replacement therapy.^[1] The pharmacotherapy approaches in these studies have been shown to be safe and effective in schizophrenic individuals.^[1] A large-scale placebo-controlled trial showed similar rates of psychiatric side effects in 4000 smokers with psychiatric illness (390 with schizophrenia) and 4000 smokers without psychiatric illness treated with either varenicline, bupropion, nicotine patch, or placebo.^[1] Despite the evidence, smoking cessation outcomes remain poor among those

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with schizophrenia and studies of this nature on the schizophrenic population are scanty.^[4] Recent policy has focused on documenting and reducing disparities in availability and quality of mental health care. The 1999 U.S. Surgeon General's report on disparity in mental health emphasized the high levels of unmet needs for diverse subpopulations that include the mental health population.^[5] Furthermore, the 2014 U.S. Surgeon General's Report emphasized that evidence-based tobacco control interventions are underutilized and under implemented. The US Surgeon General's Report has now made it a priority to expand tobacco control and prevention research efforts.^[6] New policies, treatment paradigms, and methodologies are needed to improve access to and quality of drug abuse treatment programs, and mental health treatment across diverse populations.

It has been well documented that attempts to help patients with schizophrenia quit smoking have been met with only limited success. Smoking cessation strategies that include cognitive behavioral therapy, pharmacotherapy including nicotine replacement methods are effective.^[7] A study by Crichton Royal hospital suggested that 21% of people who had schizophrenia were ultimately able to quit smoking after they started.^[8] A third of patients with schizophrenia reported that they wanted to quit for health reasons.^[8] Although smoking cessation in this population is a goal, there is limited research showing successful strategies for accomplishing this specific goal. Because of the divergent needs of this population in relation to general population, more research is needed on the biological and psychosocial factors that may explain higher rates of smoking in schizophrenic patients. Specifically, although schizophrenic smokers are able to quit and do quit successfully; the long-term abstinence rates (maintenance of remission) are generally poor or put in another way relapse is rapid in this population.^[1,9,10] In a population of patients with schizophrenia, only 8% of males were ex-smokers, compared with 31% of males in a local general population.^[8] Smoking cessation studies also report rapid relapse rates of 50% and 31% within 2 weeks of discontinuation of tobacco dependence treatment in schizophrenic smokers.^[9-11] This may suggest that the schizophrenic population may require novel treatment strategies, longer treatment duration, and more intensive tobacco dependence treatment.

There are many possible biological and psycho-social explanations as to why many patients with schizophrenia tend to smoke. Nicotine is used by schizophrenic patients as a "self-medication" strategy to improve difficulties with stress, attention, cognition, and information processing.^[12] Nicotine's primary effect on the cholinergic system can positively modulate dopamine activity. Dopamine plays a major role in reward mechanisms in the brain and in the initiation and maintenance of addictive disorders. Additionally, nicotinic receptors are found in brain regions believed to influence reinforcement and reward, including the ventral tegmental area and nucleus accumbens.^[13] Low dopamine levels in the prefrontal cortex result in the so-called negative symptoms of schizophrenia, which mimic depression.^[14] Furthermore, nicotine as a stimulant can increase alertness and the release of endorphins, making smoking feel pleasurable and blocking the awareness of troubling thoughts and feelings.^[15] Patients with schizophrenia may also smoke heavily often to reduce antipsychotic medications, which block dopamine receptors.^[14] It is important to mention that smoking is also known to decrease blood levels of antipsychotic medications such as haloperidol, fluphenazine, thiothixene,^[16] clozapine, and olanzapine. Hence, schizophrenic individuals may find the mood

enhancing and behavioral effects particularly helpful in reducing their level of psychopathology or medication side effects.

Smoking can have profound effects on anxiety, which is already present in schizophrenia. Despite patients' subjective reports that smoking reduces anxiety, chronic nicotine use in animal studies is related to increased anxiety.^[17] Data from animal and human studies suggests that under certain conditions, nicotine can act as an anxiolytic and antidepressant, but after chronic use, anxiety is increased.^[18] Studies have also found that heavy smoking among individuals with schizophrenia is associated with higher levels of positive symptoms and temporarily decreased negative symptoms.^[19,20] Contrary to the nicotine self-medication hypothesis, heavy smoking may be associated with a higher risk of panic disorder, generalized anxiety disorder, and agoraphobia, even after controlling for confounding variables, such as age, educational status, and parental smoking.^[21] Hence, the impact of acute versus chronic consumption of tobacco in schizophrenia has gained more importance suggesting opposite effects on cognitive functioning and negative symptoms.^[22]

Little data exists to support the notion that smoking may increase anxiety in schizophrenic patients. A study completed in Taiwan reported that compared to schizophrenic nonsmokers, Taiwanese schizophrenic smokers had more anxiety, depression, impulsivity, and suicidal risk. In this study, the authors used a subjective (qualitative) scale to assess anxiety.^[23] The major objective of the present study is to assess and compare the amount of antianxiety/antiagitation medications used in smoking versus nonsmoking schizophrenics. Innovative treatment methods that address relapse prevention and/or stress/anxiety management may improve abstinence in schizophrenic smokers. Since anxiety is a condition mediated mainly by excitatory neurotransmitters in the brain, and nicotine is a central nervous system excitatory drug; we hypothesized that in schizophrenic smokers, smoking will have exacerbated symptoms of anxiety disorders and smokers will require more as needed drugs to treat anxiety compared to nonsmokers. Another objective of this study was to document the unmet needs of smoking cessation programs in treating the schizophrenic population.

2. Methods

2.1. Study design

This retrospective cohort (chart review) study was conducted during a 3-month time period from September 2010 to November 2010. This study was approved by the Institutional Review Board.

2.2. Participants

Participants included: individuals diagnosed with schizophrenia or schizoaffective disorder (DSM IV criteria) who were between the ages of 18 and 60 years, and who were admitted as inpatients in a long-term psychiatric facility in California for at least 3 consecutive months. The exclusion criteria were concomitant mental illness, any coexisting medical disorders such as asthma, diabetes, chronic obstructive pulmonary disorder, hypertension, or cardiovascular disorders. All schizophrenic patients in this center were admitted involuntarily as they might be a risk to themselves or others. Patients admitted in a long-term psychiatric facility usually transfer from an acute psychiatric facility for the

continuous phase of medication stabilization and programming to improve activities of daily living and typically in a 3-month period. Patients had the option to go outside to smoke escorted by the nursing staff. Each patient who smoked had up to 9 smoking breaks per day with a maximum of 1 cigarette per smoking break. Each smoking break was 15 minutes.

2.3. Outcomes

The primary outcome was the average number of as-needed medication doses received by schizophrenic smokers and nonsmokers during a 3-month psychiatric inpatient stay. The secondary outcome measures included: the mean number of anxiety and agitation episodes during the study period in both groups. The nurse's notes (Medication Administration Record; MAR) were reviewed for the frequency of as-needed medication given and patient's behavioral logs, interprofessional notes, physician's progress notes, and nursing notes were reviewed for the number of episodes of anxiety and agitation.

2.4. Statistical analysis

The unpaired Student *t* test or Mann–Whitney *U* test, whichever appropriate, was used to compare the total number of as-needed medications and episodes of anxiety and agitation. All statistical tests were 2-tailed, and all hypotheses were tested at the 5% α level of significance.

3. Results

A total of 38 schizophrenic participants were included in the study; of these 28 (73.6%) were smokers and 10 (26.3%) were nonsmokers. As shown in Table 1, the sample was predominantly male and the average age (mean \pm SD) of smokers and nonsmokers were 42 ± 12 and 45 ± 9.8 , respectively. All the patients in the study received at least 2 antipsychotics, one of which included a dibenzodiazepine (clozapine, olanzapine, and quetiapine) and either a classic antipsychotic (first generation like haloperidol or chlorpromazine) or aripiprazole. Notably, chlorpromazine's dose ranged from 50 to 500mg orally per day, which is typically prescribed. Generally, the dosage did fluctuate based on changes of psychotic condition, patient's smoking level, and enzyme induction (olanzapine and clozapine). Thus, the antipsychotic dosages were determined by patient's psychiatrist based on patient's psychotic condition and usually based on Nursing reports and Psychiatric interviews. Selection of antipsychotics was decided based on the symptom presentation and clinical preference of the treating psychiatrist and was (independent of) not related to the present study. Olive Vista is a long-term psychiatric facility and patients usually get admitted after stabilization of psychosis from acute psychiatric facility. However, when severity of the patients' schizophrenic psychosis increases, patients do get admitted back to an acute psychiatric

Table 1
Baseline characteristics (N=38).

Gender/age	Smoker	Nonsmoker
Male	22 (78.5%)	7 (70%)
Female	6 (21.4%)	3 (30%)
Mean(\pm SD) age in years	42 ± 12	45 ± 9.8

SD=standard deviation.

Table 2

The number of anxiety/agitation episodes and medication usage in schizophrenic smokers versus nonsmokers.

	Smoker	Nonsmoker	P value
Frequencies	28.0	10.0	
Frequency, anxiety episodes	889	196	
Mean \pm SD, anxiety episodes	31.8 ± 28.5	19.6 ± 28.1	.310
Frequency, agitation episodes	364	162	
Mean \pm SD, agitation episodes	13.0 ± 13.1	16.2 ± 18.6	.920
Frequency, as-needed medication given (no. of doses)	118	6	
Mean \pm SD, as-needed medication given (no. of doses)	4.21 ± 5.4	0.60 ± 1.35	.011

SD=standard deviation.

facility. There were no differences in the antipsychotic regimen between the groups. All the patients in the study had a history of substance abuse and had been diagnosed with schizophrenia or schizoaffective disorder. At the time of the study, the patients did not have any anxiety disorder diagnosis. Most of the time, schizoaffective or schizophrenia was classified as either paranoid or undifferentiated type.

3.1. Primary outcome

During the 3-month study period, the nursing staff administered significantly more doses of as-needed antianxiety/antiagitation medications on average (mean \pm SD) to schizophrenic smokers (4.21 ± 5.4) compared to nonsmokers (0.60 ± 1.35) ($P=0.011$), see Table 2. There were only 2 nonsmokers (20%, 2/10) compared to 19 smokers (67.9%, 19/28) who were given as-needed medications during the anxiety/agitation episodes. For the 21 schizophrenic patients who received as-needed medication during anxiety/agitation episodes, the majority (85.7%) received on average 2 medications per episode, 9.5% received only 1 medication per episode, and only 1 patient (4.8%) was given 3 medications per episode (data not shown). Fifty percent of the time haloperidol was given during anxiety/agitation episodes. Lorazepam (39.5%), diphenhydramine (7.9%), benztropine (5.3%), olanzapine (2.6%), and chlorpromazine (2.6%) were other medications used during the episodes (data not shown).

3.2. Secondary outcome

During the 3-month study period, the nursing staff or counselors recorded a total of 889 anxiety episodes for the 28 smokers compared to only 196 anxiety episodes in the 10 nonsmokers, see Table 2. The average (mean \pm SD) number of anxiety episodes for each smoker and nonsmoker was 31.8 ± 28.5 versus 19.6 ± 28.1 ($P=0.31$). The nursing staff or counselors recorded a total number of 364 and 162 agitation episodes for smoker and nonsmoker groups, respectively, during the 3-month study period. The average (mean \pm SD) number of agitation episodes per smoker versus nonsmoker was 13.0 ± 13.1 and 16.2 ± 18.6 ($P=0.92$), respectively.

4. Discussion

This is the first preliminary study to suggest that in schizophrenic individuals, smoking was associated with increased anxiety episodes and as-needed medication usage. Although the average

number of anxiety episodes was higher among smokers, the number of agitation episodes was slightly higher for nonsmokers; however, this difference was not significant. The nonsignificant increased agitation seen in the nonsmoker schizophrenics conflicts with the common belief that smoking can help calm schizophrenic patients.^[15] While smoking increases cholinergic and noradrenergic functioning, tobacco withdrawal decreases these. Smoking or abstinence from smoking may obscure the relationship of neurotransmitter systems to psychiatric disorders. Recently, the nicotine self-medication hypothesis has gained some interest in trying to explain the role of nicotine and smoking in alleviating negative symptoms and cognitive deficits in schizophrenic patients.^[12] Also, the impact of acute versus chronic consumption of nicotine in schizophrenia has gained more importance suggesting opposite effects on cognitive functioning and negative symptoms.^[22]

A possible explanation for our results is that both smoking and nicotine can increase the level of circulating cortisol via the hypothalamic–pituitary–adrenal axis and catecholamines, which can cause anxiety and transiently lead to an increase in blood pressure and heart rate. It is generally deemed that a large proportion of nicotine’s cardiovascular effects are mediated via the autonomic nervous system in accordance with its well-established capacity to stimulate, and then paralyze all autonomic ganglia.^[24] The target organs also include the peripheral and central nervous systems, affecting agitation, headache, sweating, dizziness, auditory and visual disturbances, confusion, weakness, and lack of coordination.^[24,25] All these factors predispose a psychotic patient toward anxiety, agitation, and aggression, frequently observed in psychiatric facilities with schizophrenic patients that smoke, and in our clinical experience disturbances in sleep patterns as well.

Traditionally, antipsychotics have also been used for anxiety, agitation, and aggression. However, this study involved as-needed medications that were associated with treatment of anxiety episodes related to smoking. Authors are quite aware that some episodes of agitation may be different from the others; however, anxiety, agitation, and aggression are considered spectral, based on the degree of the role of monoamines in the limbic striatum. It could have been the clinical impression of the psychiatrist to use anticholinergic medications for agitation based on its basal nuclei origin rather than cortical origin.

It is noteworthy to state that smoking may reduce blood levels of antipsychotic agents through pharmacokinetic mechanisms. Polycyclic hydrocarbons in cigarette smoke stimulate the hepatic microsomal system, inducing liver enzymes to increase the metabolism of psychotropic medications.^[26] Induction of the cytochrome P450 1A2 isoform may explain the increased metabolism of antipsychotics. The cytochrome P450 isoenzymes are involved in the oxidative metabolism of several different types of drugs including most of antidepressants and antipsychotics. Several studies have reported that smokers require higher levels of antipsychotics than nonsmokers.^[27] Smoking can lower the blood levels of some antipsychotics by as much as 50%, requiring a corresponding increase in dosage to achieve therapeutic blood levels.

Other studies have investigated the connection between specific antipsychotics and the rate of smoking among patients with schizophrenia.^[28] For example, when patients were switched to therapeutic effective dosages of clozapine, their smoking decreased, while those whose dosages were below therapeutic ranges showed no change in smoking behavior. This finding is

interesting because several of the atypical antipsychotics – clozapine, risperidone, and olanzapine – may increase cortical dopamine release in a manner similar to that of nicotine.^[29] This finding strengthens the position that the newer antipsychotics may reduce hypofrontality and thus reduce nicotine dependence among patients with schizophrenia.^[29] Nicotine’s stimulation of dopamine in cortical area could help explain the high use of tobacco by patients with schizophrenia as a form of self-medication to reduce negative symptoms. As a result, individuals with schizophrenia who smoke may require higher daily dosage of neuroleptics. A relationship between increased tardive dyskinesia and smoking has been reported, which may be due to the higher doses of neuroleptics required by these patients.^[30]

Studies reveal higher levels of akathisia (motor restlessness) in schizophrenic smokers compared to nonsmokers despite a lower incidence of neuroleptic-induced parkinsonism among the smokers.^[14] Increased agitation and akathisia in our study may also be partially explained by the central (sympathetic) effects of nicotine. This can precipitate the need for antipsychotic therapy in general; specifically, the development of anxiety symptoms requiring treatment, as we have observed in our study.

Some of the limitations of the study include: the small sample size and an inpatient setting, which may not be generalizable to all schizophrenic patients. However, this study was designed as a preliminary study and further research using larger populations of schizophrenic individuals is needed to confirm our results. Generally nonsmoking schizophrenics are in low number and they were limited in numbers in our facility. Additionally, the minimum 3-month duration of stay at the facility may have led to progressive mood stabilization, which may have required lower use of as-needed medications. Furthermore, the determination of anxiety and agitation and decision to medicate may have differed among nursing staff because all behavioral assessments carry some subjectivity. Moreover, during the period of medication stabilization, the as-needed medication may have been increased due to the scheduled medication not exerting its full effect potentially as a result of increased metabolism induced by cigarette smoke. Lastly, we did not classify and study the type of agitation, which will be the subject of a future study.

Various efforts to get patients with schizophrenia to stop smoking have been met so far with only limited success. This type of assessment is essentially biased. Our own survey revealed that 25% of our study participants reported to be interested in smoking cessation program within the psychiatric facility. Nevertheless, schizophrenia patients come in various levels of cognition and functioning. Higher functioning schizophrenic patients in our experience are more cognizant of the problems of smoking and would consider smoking cessation program, and these patients are more prone to develop anxiety with chronic nicotine use in schizophrenia. We believe the studies done on the relationship between smoking or tobacco addiction on schizophrenia and subsequent development of increased anxiety are crucial for successful treatment outcomes in schizophrenic patients. It is important not to compromise with the concept that smoking is a crucial component of schizophrenic patient’s activity, or that schizophrenic patients are not interested in smoking cessation and do not have the ability to stop smoking. Research suggests that smoking cessation is safe and effective for patients with schizophrenia with various combination treatments, including the use of motivational techniques as well as combinations of pharmacotherapy and behavioral therapy.^[1,9–11] It is vital to develop the pharmacotherapy and behavioral therapy models

through research and expand research support and techniques for circulating these advances to the schizophrenic population. There is a great need for a well-organized effort that includes the patient, healthcare providers, and healthcare systems to address and utilize evidence-based tobacco addiction treatment in smokers with schizophrenia. This endeavor will need to include education as well as efforts to bridge the gap between the tobacco control and behavioral health communities to highlight the huge impact of this problem and begin to address implications for policy development, prevention, and treatment. Tobacco addiction in individuals with schizophrenia can no longer be ignored. Long-term longitudinal studies are required for a better understanding of the interactions of smoking and anxiety among schizophrenic tobacco users.

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References

- [1] Cather C, Pachas GN, Cieslak KM, et al. Achieving smoking cessation in individuals with schizophrenia: special considerations. *CNS Drugs* 2017;31:471–81.
- [2] Griffiths M, Kidd SA, Pike S, et al. The Tobacco Addiction Recovery Program: initial outcome findings. *Arch Psychiatr Nurs* 2010;24:239–46.
- [3] De Hert M, Cohen D, Bobes J, et al. Physical illness in patients with severe mental disorders. II. Barriers to care, monitoring and treatment guidelines, plus recommendations at the system and individual level. *World Psychiatry* 2011;10:138–51.
- [4] Roll JM, Higgins ST, Steingard S, et al. Use of monetary reinforcement to reduce the cigarette smoking of persons with schizophrenia: a feasibility study. *Exp Clin Psychopharmacol* 1998;6:157–61.
- [5] Cook BL, Wayne GF, Kafali EN, et al. Trends in smoking among adults with mental illness and association between mental health treatment and smoking cessation. *JAMA* 2014;311:172–82.
- [6] Surgeon General's Report. The Health Consequences of Smoking – 50 Years of Progress. 2014. https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm
- [7] Fiore MC, Jaen CR. A clinical blueprint to accelerate the elimination of tobacco use. *JAMA* 2008;299:2083–5.
- [8] Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *Am J Psychiatry* 1999;156:1751–7.
- [9] Evins AE, Cather C, Culhane MA, et al. A 12-week double-blind, placebo-controlled study of bupropion sr added to high-dose dual nicotine replacement therapy for smoking cessation or reduction in schizophrenia. *J Clin Psychopharmacol* 2007;27:380–6.
- [10] Evins AE, Cather C, Deckersbach T, et al. A double-blind placebo-controlled trial of bupropion sustained-release for smoking cessation in schizophrenia. *J Clin Psychopharmacol* 2005;25:218–25.
- [11] Cather C, Dyer MA, Burrell HA, et al. An open trial of relapse prevention therapy for smokers with schizophrenia. *J Dual Diagn* 2013;9:87–93.
- [12] Glassman AH. Cigarette smoking: implications for psychiatric illness. *Am J Psychiatry* 1993;150:546–53.
- [13] Carr LA, Rowell PP, Pierce WM Jr. Effects of subchronic nicotine administration on central dopaminergic mechanisms in the rat. *Neurochem Res* 1989;14:511–5.
- [14] Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *Am J Psychiatry* 1992;149:1189–94.
- [15] Pomerleau OF, Pomerleau CS. Cortisol response to a psychological stressor and/or nicotine. *Pharmacol Biochem Behav* 1990;36:211–3.
- [16] Ereshefsky L, Saklad SR, Watanabe MD, et al. Thiothixene pharmacokinetic interactions: a study of hepatic enzyme inducers, clearance inhibitors, and demographic variables. *J Clin Psychopharmacol* 1991;11:296–301.
- [17] Irvine EE, Bagnalasta M, Marcon C, et al. Nicotine self-administration and withdrawal: modulation of anxiety in the social interaction test in rats. *Psychopharmacology (Berl)* 2001;153:315–20.
- [18] Picciotto MR, Brunzell DH, Caldarone BJ. Effect of nicotine and nicotinic receptors on anxiety and depression. *Neuroreport* 2002;13:1097–106.
- [19] Dalack GW, Healy DJ, Meador-Woodruff JH. Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am J Psychiatry* 1998;155:1490–501.
- [20] Ziedonis DM, Kosten TR, Glazer WM, et al. Nicotine dependence and schizophrenia. *Hosp Community Psychiatry* 1994;45:204–6.
- [21] Johnson JG, Cohen P, Pine DS, et al. Association between cigarette smoking and anxiety disorders during adolescence and early adulthood. *JAMA* 2000;284:2348–51.
- [22] Peto R, Lopez AD, Boreham J, et al. Mortality from smoking worldwide. *Br Med Bull* 1996;52:12–21.
- [23] Kao YC, Liu YP, Cheng TH, et al. Cigarette smoking in outpatients with chronic schizophrenia in Taiwan: relationships to socio-demographic and clinical characteristics. *Psychiatry Res* 2011;190:193–9.
- [24] Greenspan K, Edmands RE, Knoebel SB, et al. Some effects of nicotine on cardiac automaticity, conduction, and inotropy. *Arch Intern Med* 1969;123:707–12.
- [25] Najem B, Houssiere A, Pathak A, et al. Acute cardiovascular and sympathetic effects of nicotine replacement therapy. *Hypertension* 2006;47:1162–7.
- [26] Ziedonis DM, George TP. Schizophrenia and nicotine use: report of a pilot smoking cessation program and review of neurobiological and clinical issues. *Schizophr Bull* 1997;23:247–54.
- [27] Salokangas RK, Saarijarvi S, Taiminen T, et al. Effect of smoking on neuroleptics in schizophrenia. *Schizophr Res* 1997;23:55–60.
- [28] George TP, Sernyak MJ, Ziedonis DM, et al. Effects of clozapine on smoking in chronic schizophrenic outpatients. *J Clin Psychiatry* 1995;56:344–6.
- [29] Lyon ER. A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatr Serv* 1999;50:1346–50.
- [30] Addington J. Group treatment for smoking cessation among persons with schizophrenia. *Psychiatr Serv* 1998;49:925–8.