

Successful Tobacco Dependence Treatment in Schizophrenia

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Individuals with schizophrenia smoke at rates three times higher than the general population in the United States, with smoking prevalence rates of at least 60% (1, 2). International studies have also typically found increased rates of smoking among persons with schizophrenia (3). A pattern of heavy smoking (more than 20 cigarettes per day) and severe nicotine dependence (4, 5) is characteristic. Smokers with schizophrenia have increased nicotine and cotinine levels that are attributed to increased nicotine intake per cigarette (6–8).

Higher blood nicotine levels are associated with greater severity of tobacco dependence and more difficulty quitting. High nicotine levels may be needed for activation of low-affinity alpha-7 nicotinic receptors, which are reduced in both number and function in schizophrenia (9, 10). Evidence for this self-medication hypothesis comes from abnormal electrophysiological measures and saccadic eye movements that are reversed or improved when nicotine is administered by smoking cigarettes or with high-dose nicotine gum or nasal spray (11–13). Despite nicotine being beneficial, tobacco is not a pharmaceutical and is associated with more than 4,000 toxins and more than 60 carcinogens. Nicotine can be delivered more safely in commercially available nicotine products, including gum, nasal spray, inhalers, and patches.

Schizophrenia is associated with a 20% reduced life expectancy and increased rates of smoking-related respiratory and cardiovascular diseases compared to members of the general population (14, 15). A 10-year study of elevated risk of coronary heart disease in schizophrenia showed that the risk remained extremely high even after control was added for factors such as weight and body mass index and was attributable mainly to smoking (16). Besides health, tobacco use results in other consequences, with smokers suffering financially and socially. Smokers with schizophrenia spend almost one-third of their monthly disability income on cigarettes (17). Smoking influences community integration because smokers have less income to spend on clothing and housing. As the smoking rate decreases among the general population, there is also the stigma in being a smoker in addition to the

stigma of having mental illness. This can reduce success in obtaining employment, housing, or interpersonal relationships. Studies have found that heavy smoking among individuals with schizophrenia is associated with higher levels of positive symptoms and higher antipsychotic medication doses (18, 19).

Despite the magnitude of tobacco use problems, quit rates for seriously mentally ill smokers are significantly lower than in the general population (5, 20). Individuals with schizophrenia are able to quit smoking, although the success is about half that of other groups (21–23). Contributing factors likely include lower motivation to quit tobacco use, fewer lifetime quit attempts, and increased severity of nicotine dependence. Another important consideration is that access to treatment for this group is reduced. Few mental health professionals identify and treat tobacco use in their patients (24, 25). Tobacco dependence interventions provided in primary care and public health settings are often brief and may lack the intensity or specialization needed for this population to stop smoking. These services often rely on a highly motivated and organized client who is ready to quit.

In 2001, the University of Medicine and Dentistry of New Jersey—Robert Wood Johnson Medical School and Tobacco Dependence Program both collaborated to develop specialized services for smokers with schizophrenia and other mental illnesses. These differed from traditional

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services in several ways: services were open ended and not limited to a set number of contacts, all patients were encouraged to use a combination approach of pharmacotherapy and counseling, and there was no requirement to set a quit date to be in treatment. An addictions psychiatrist and mental health social worker that was also a certified tobacco treatment specialist provided most services. Both individual and group counseling ser-

vices were available. More than 300 smokers with schizophrenia and other serious mental illnesses have received these specialty services and achieve long-term abstinence rates as high as those without a history of mental health problems (26). We describe here the treatment of one such patient.

Case Description

“Mr. P” was a 41-year-old married man with schizophrenia who was diagnosed at age 19 when he was hospitalized for psychosis. Mr. P had had severe psychosis in the past, including symptoms of auditory hallucinations,

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ideas of reference (with beliefs that both the television and radio sent him messages), paranoia (being harassed and ridiculed by others), and delusional beliefs that he could read minds and was a prophet. His positive symptoms were well controlled with clozapine, 550 mg/day, although he struggled with persistent cognitive problems, including trouble with memory, attention, and organization. He had a blunted affect and slowed but coherent thoughts. He also took clomipramine, 50 mg/day, which helped his obsessive-compulsive symptoms, including frequent checking behaviors, excessive worrying, and obsessive thoughts of self-doubt and guilt. A Brief Psychiatric Rating Scale inventory of his symptoms in 2001 revealed a score of 33, with moderate scores on suspiciousness, hallucinations, unusual thought content, and blunted affect. His wife also had schizophrenia, although her symptoms were milder and remitted almost entirely with treatment. Both Mr. P and his wife were unemployed and received disability for their mental illnesses. His wife accompanied him to treatment visits, and they wanted to quit smoking together.

Mr. P started smoking cigarettes at age 14. He had made at least 20 previous serious attempts to quit, although none had lasted more than 3 days. When he first came in for treatment, he was smoking 30 cigarettes per day with an exhaled carbon monoxide level of 21 ppm. He reported smoking his first cigarette of the day within 5 minutes of awakening and also awoke at night to smoke. His serum blood nicotine and cotinine levels were 28 and 337 ng/ml, respectively. He was highly motivated to quit smoking, although he endorsed only moderate confidence that he could succeed. In 2001, he participated in a nicotine patch trial and was randomly assigned to the high-dose condition (42 mg/day of nicotine for the first 3 weeks then tapering down to 14 mg/day over the next 5 weeks). He set a date to quit and was continuously abstinent from smoking for 7 weeks before relapsing to 20 cigarettes (carbon monoxide level=25 ppm) as his nicotine-replacement dose was reduced.

Mr. P remained in treatment at the Tobacco Dependence Program, where he was seen approximately once per month for tobacco treatment by an addictions psychiatrist. He continued to see his usual psychiatrist and attended a psychosocial day program 4 days per week. He remained motivated to quit smoking and made a series of quit attempts. He was encouraged to use a variety of nicotine products to aid him in quitting. Because he was a heavy smoker, it was recommended that he use nicotine medications in combination to achieve a higher dose (the patch plus gum and the patch plus inhaler). During this time, Mr. P was not able to quit for longer than 3 or 4 days, and in counseling sessions, he reported that he experienced a great deal of nicotine craving and was easily triggered to smoking again when he saw others smoking.

The next year, Mr. P started treatment with nicotine nasal spray. It was hoped that this medication would provide him with a high daily dose of nicotine while also providing faster craving relief. Mr. P immediately preferred the nicotine nasal spray to other forms of nicotine that he had tried in the past. He used the nicotine nasal spray at 40 doses per day (one dose equals one spray in each nostril), which is the recommended dose limit. Mr. P used even more than this and at times would self-administer 2–4 sprays per nostril at each dose, thus con-

suming the 10-ml bottle in 1.5 days (almost 60 doses per day). Because of the unknown potential risk to his nasal mucosa from this high dose, he was advised to begin the inhaler and nicotine patch to supplement the nicotine nasal spray. He reported no nicotine toxicity or symptoms of nausea, vomiting, or dizziness with this high dose. He made several attempts to quit, lasting 2–6 weeks, with significant reductions in his carbon monoxide over the next year. In all, he made eight attempts to quit over an 18-month period of treatment.

As of 2006, he has achieved sustained tobacco abstinence for over 3 years. For most of this time, he continued to use nicotine nasal spray at 40 doses per day (consuming five 10-ml bottles every 2 weeks), along with 8–12 nicotine inhaler cartridges per day. He visited the tobacco program every 3–6 months for medication refills and brief follow-up visits. His expired carbon monoxide readings at these visits were consistently less than 3 ppm, providing biochemical verification of his self-reported smoking abstinence. He was encouraged to have a routine evaluation by an ear-nose-and-throat physician for evaluation of his nasal mucosa because of his long-term use of nicotine nasal spray, and this evaluation was normal. His wife quit smoking successfully with him in July 2003, and she used nicotine nasal spray (at about 20 doses per day) for 1 year before discontinuing.

Since 2003, Mr. P has achieved significant improvements in his mental status and functioning. In 2005, his clozapine dose was reduced to 300 mg/day. He has reduced symptoms and improved cognitive functioning. He left the day program he formerly attended to enroll in a college-level program to become a psychosocial rehabilitation counselor. He maintained a B grade point average in this program. He has also become active as a group leader in the local mental health self-help center. He is very satisfied with his life success.

Mr. P self-tapered off nicotine nasal spray and nicotine inhaler successfully over a period of 1 month in 2006 when his Medicare part D would not pay for any more prescriptions. He reports no nicotine craving or feeling that he would relapse to smoking. He and his wife feel confident that they will not smoke again in the future.

Discussion

Smokers with schizophrenia appear to be able to stop smoking, but cessation studies have reported overall quit rates that are only half that seen with the general population of smokers. A criticism of tobacco cessation studies has been that the criteria for defining abstinence are often rigidly defined and do not allow for multiple quit attempts or brief lapses back to smoking. An important question regarding this case is “Was Mr. P successful merely because he made so many attempts to quit?” Tobacco dependence can be viewed as a chronic condition, requiring a long-term treatment approach. Even in the general population, few smokers are successful with their first attempt at quitting, and most require numerous attempts before they are successful.

Mr. P made eight attempts to quit while in specialized treatment, in addition to the 20 he reported in his lifetime. These repeated attempts resulted in a reduction in his

overall exposure to tobacco toxins, as well as leading to his successful attempt to quit.

It has been proposed that reduced smoking may be a viable treatment option for some smokers, especially those who are unable or unwilling to quit completely (27). One concern is that reduced smoking still exposes the smoker to carbon monoxide and other harmful tobacco toxins in smoke and that no safe level for exposure has been established. Although reduction in smoking was not an explicit treatment goal for Mr. P, it is common in clinical practice to tolerate reductions as evidence of behavior change and movement toward abstinence, and this may help to retain smokers in treatment who do not initially achieve abstinence. A 2-year follow-up study found that smokers with schizophrenia who reduced smoking were more likely to subsequently quit smoking (28), making it also a reasonable intermediary goal for lower-motivated smokers. The use of tobacco treatment medications in persons who continue to smoke appears to be well tolerated and may also have a role for smokers who are not yet ready to quit and does not undermine future quit attempts. Mr. P used nicotine medications for 18 months before successfully quitting without any difficulty or adverse effect.

Both pharmacotherapy and counseling interventions are considered first-line treatments in the U.S. Public Health Service's *Treating Tobacco Use and Dependence: Clinical Practice Guideline* and should be offered to all smokers wanting to quit (29). Pharmacotherapy may be particularly important in smokers with high nicotine dependence, which is very common in smokers with schizophrenia. There are several treatments approved by the Food and Drug Administration for tobacco-dependence treatment. Five are different types of nicotine-replacement therapies—nicotine polacrilex (gum), the nicotine transdermal patch, nicotine inhaler, nicotine nasal spray, and the nicotine lozenge—that have similar efficacies and low overall risk for abuse liability. Both the nicotine patch and bupropion have been found to be well tolerated and to improve outcomes in schizophrenia (21, 23, 30) in small studies.

Nicotine treatment may have particular advantages for smokers with schizophrenia because it improves abnormal electrophysiological measures, saccadic eye movements, and measures of working memory (11, 12, 31–33). The restorative effect of nicotine is short lived and may be gone within 10 minutes after smoking (11, 34), which is likely due to inactivation or desensitization of the alpha-7 nicotinic receptor. Promising alpha-7 receptor agonists, which are less sensitive to the effects of desensitization, are in development (35); however, it is not known if and how these compounds will affect smoking in schizophrenia. These compounds are also not currently available for clinical use. Thus, there continues to be an immediate need for the development of more effective pharmacotherapies for this high-risk group, and high-dose nicotine treatment is one such approach given the obvious hazards of tobacco smoke.

The nicotine nasal spray has features, such as a rapid onset of action, intermittent dosing, more immediate

craving relief, and physiological effects, that more closely resemble smoking. Venous nicotine levels with the nicotine nasal spray peak after 4–15 minutes of use (36), and doses can be repeated in quick succession—up to five in a 1-hour period—and the self-administration can have the advantage of giving patients a greater sense of control over their withdrawal symptoms and craving. This is in contrast to the nicotine skin patch, which has slow absorption, rising gradually to a relatively flat nicotine level in 6 hours, and provides no immediate control over nicotine craving. In the general population, use of the nicotine nasal spray lags behind other forms of nicotine replacement. Irritation to the nasal mucosa is common, with many smokers discontinuing the product early because of this unpleasant side effect (36, 37).

It is believed that one of the unique effects of nicotine nasal spray is as a primary reinforcer. Satisfaction with nicotine, which is one of its positive reinforcing effects, may be linked to a rapid rate of absorption and thus enhanced with nicotine nasal spray compared with the slow onset of the nicotine patch. In a comparative trial of nicotine medications, the subjects who preferred nicotine nasal spray tended to be heavier smokers (29). Smokers with schizophrenia may gain particular benefit from the rapid nicotine delivery provided by the nicotine nasal spray, and we previously reported on a case series with subjects who did well with nicotine nasal spray (38). Increased use of the nicotine nasal spray was correlated with better outcomes, and low discontinuation rates were observed in these smokers with schizophrenia. Nicotine nasal spray has also been studied for its short-term effects on symptoms and cognitive function in schizophrenia (33). Use of nicotine nasal spray use was associated with increased scores on tests of verbal memory; the highest doses were associated with stronger effects on performance. Mr. P seemed to benefit from high-dose nicotine treatment that included nicotine nasal spray.

Mr. P may also have been aided in his attempt to quit smoking by his pharmacological regimen for psychosis because outcomes are improved with atypical antipsychotics (39). Clozapine treatment, in particular, is associated with reduced smoking versus conventional antipsychotics (40, 41). Clozapine is the only atypical antipsychotic that consistently improves P50 gating, likely through its activity as a serotonin 5-HT₃ receptor antagonist, which would increase the release of acetylcholine (42, 43). Clozapine increases acetylcholine release, particularly in the hippocampus, activating nicotinic receptors, which could thereby reduce the desire to smoke, although Mr. P had been taking clozapine for more than 10 years without apparent change in his smoking behavior.

An important clinical consideration is the effect that tobacco smoking has on medications metabolized by the P450 1A2 isoenzyme. This effect is not caused by nicotine, but rather it is secondary to the tars in tobacco smoke that induce this enzyme, thus increasing the metabolism of several commonly used antipsychotic medications, including olanzapine and clozapine (44). There are case re-

ports of clozapine toxicity and seizures during early tobacco abstinence; patients should be monitored closely for possible drug toxicity, and dose reductions should be considered (45). Mr. P's clozapine dose was reduced appropriately after smoking cessation occurred.

Although pharmacotherapy works even in the absence of psychosocial treatments, outcomes are enhanced when these modalities are combined. Unfortunately, only a minority (about 5%) of smokers who make an attempt to quit receive counseling. Effective psychosocial treatments for tobacco dependence include cognitive behavior therapy, relapse prevention, social skills training—all psychotherapies that are practiced routinely by behavioral health practitioners. Intensive counseling interventions are more effective than briefer ones; however, “intensive” is a relative term because many studies compare treatment intensities by the number of minutes of treatment provided in the primary care setting. The effectiveness of psychosocial treatments for tobacco dependence depends on factors such as the duration of the intervention and the number of contacts with the patient. Behavioral health practitioners take a long-term approach in treating other co-occurring mental health and addiction disorders, a model that may also be useful for treating tobacco.

Although Mr. P received intensive treatment, when one considers that the patient received a total of 26 visits (16 before eventual quitting and 10 follow-up visits over the next 3 years), this is not excessive compared to other mental health care or substance abuse treatments. Studies are underway to examine the effectiveness of intensive counseling for smoking cessation in schizophrenia by using a modified approach of motivational interviewing, relapse prevention, and social skills training that compares 24 to nine sessions of individual counseling in a mental health center (an unpublished presentation by D.M. Ziedonis and colleagues, Washington, D.C., July 2006). Tobacco treatment counseling is effective when delivered in either individual or group sessions. Because most individuals with schizophrenia receive treatment in mental health settings, integrating tobacco dependence treatment into the standard of care makes the most sense, despite current barriers that exist. Changes require a long-term treatment perspective and staff training and policy changes, and the addressing of restrictive reimbursement and formulary issues is required.

Despite concerns that smokers with schizophrenia will suffer a worsening of their illness, preliminary studies indicate no worsening of psychotic symptoms during early abstinence or cessation (23, 30, 46). Nicotine's effect on neuropsychological function in schizophrenia is still not well understood. Studies have shown worsening in selective aspects of cognitive functioning (i.e., visuospatial working memory) in smokers with schizophrenia during early abstinence (31), which is improved by a return to smoking (32), but other investigators have failed to find an effect of nicotine on various cognitive measures (47). A pattern of worsening cognition during nicotine absti-

nence is not different from that seen in dependent smokers generally, who experience transient worsening of attention and concentration. Long-term effects have not been studied and may be countered by other benefits of quitting smoking. Mr. P had no clinical evidence of worse cognitive function, and his case history indicates improved academic performance. Poor performance on prefrontal cortex-dependent tests of executive functioning have also been found to be associated with smoking cessation failure in schizophrenia (48).

Clinical practice guidelines published a decade ago acknowledged the need for psychiatrists to address tobacco dependence in all patients they treat (49). One reason for the lack of progress in this area may be the lack of tobacco training opportunities for psychiatrists. Mental health professionals are in need of a large educational effort on treating tobacco dependence. Implementing existing recommendations for treatment (i.e., U.S. Public Health Service guidelines) is a reasonable first strategy as research continues to develop more specialized treatments for this group of smokers. Treatment for smokers with schizophrenia will likely be optimal when delivered by providers with mental health and tobacco experience and will support an expanding role for behavioral health care professionals treating tobacco. As behavioral health treatment moves from symptom-reduction approaches toward wellness and recovery models that address helping the whole person, there is a greater emphasis on improving physical health and healthy lifestyles. Tobacco dependence is an important addiction that should be addressed as part of recovery-based mental health treatment.

In summary, this case demonstrates that intensive and sustained pharmacotherapy and psychosocial treatment can help smokers with schizophrenia to quit using tobacco and to go on to lead healthier lives without a worsening of mental health. Recovery from tobacco dependence is an important part of recovery from mental illness.

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CME Disclosure

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References

- Hughes JR, Hatsukami DK, Mitchell JE, Dahlgren LA: Prevalence of smoking among psychiatric outpatients. *Am J Psychiatry* 1986; 143:993–997
- de Leon J, Abraham G, Nair C, Verghese C, McGrory A, McCann E: Nicotine addiction in chronic schizophrenic inpatients. *Biol Psychiatry* 1995; 37:593–683
- de Leon J, Diaz FJ: A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005; 76:135–157
- Williams JM, Ziedonis DM, Foulds J: Case series of nicotine nasal spray in the combination treatment of tobacco dependence among patients with schizophrenia. *Psychiatr Serv* 2004; 55:1064–1066
- Etter M, Mohr S, Garin C, Etter JF: Stages of change in smokers with schizophrenia or schizoaffective disorder in the general population. *Schizophr Bull* 2004; 30:459–468
- Williams JM, Ziedonis DM, Abanyie F, Steinberg ML, Foulds J, Benowitz NL: Increased nicotine and cotinine levels in smokers with schizophrenia and schizoaffective disorder is not a metabolic effect. *Schizophr Res* 2005; 79:323–335
- Olincy A, Young DA, Freedman R: Increased levels of the nicotine metabolite cotinine in schizophrenic smokers compared to other smokers. *Biol Psychiatry* 1997; 42:1–5
- Strand JE, Nyback H: Tobacco use in schizophrenia: a study of cotinine concentrations in the saliva of patients and controls. *Eur Psychiatry* 2005; 20:50–54
- Freedman R, Adams CE, Leonard S: The α 7-nicotinic acetylcholine receptor and the pathology of hippocampal interneurons in schizophrenia. *J Chem Neuroanat* 2000; 20:299–306
- Breese CR, Lee MJ, Adams CE, Sullivan B, Logel J, Gillen KM, Marks MJ, Collins AC, Leonard S: Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. *Neuropsychopharmacology* 2000; 23:351–364
- Adler LE, Hoffer LD, Wiser A, Freedman R: Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *Am J Psychiatry* 1993; 150:1856–1861
- Olincy A, Ross RG, Young DA, Roath M, Freedman R: Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. *Neuropsychopharmacology* 1998; 18:175–185
- Depatie L, O'Driscoll GA, Holahan AL, Atkinson V, Thavundayil JX, Kin NN, Lal S: Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. *Neuropsychopharmacology* 2002; 27:1056–1070
- Brown S, Inskip H, Barraclough B: Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 2000; 177:212–217
- Joukamaa M, Heliovaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V: Mental disorders and cause-specific mortality. *Br J Psychiatry* 2001; 179:498–502
- Goff DC, Cather C, Evins AE, Henderson DC, Freudenreich O, Copeland PM, Bierer M, Duckworth K, Sacks FM: Medical morbidity and mortality in schizophrenia: guidelines for psychiatrists. *J Clin Psychiatry* 2005; 66:183–194
- Steinberg ML, Williams JM, Ziedonis DM: Financial implications of cigarette smoking among individuals with schizophrenia. *Tob Control* 2004; 13:206
- Dalack GW, Healy DJ, Meador-Woodruff JH: Nicotine dependence in schizophrenia: clinical phenomena and laboratory findings. *Am J Psychiatry* 1998; 155:1490–1501
- Ziedonis DM, Kosten TR, Glazer WM, Frances RJ: Nicotine dependence and schizophrenia. *Hosp Community Psychiatry* 1994; 45:204–206
- Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH: Smoking and mental illness: a population-based prevalence study. *JAMA* 2000; 284:2606–2610
- 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; 23:247–254
- Addington J, el-Guebaly N: Group treatment for substance abuse in schizophrenia. *Can J Psychiatry* 1998; 43:843–845
- George TP, Vessicchio JC, Termine A, Bregartner TA, Feingold A, Rounsaville BJ, Kosten TR: A placebo controlled trial of bupropion for smoking cessation in schizophrenia. *Biol Psychiatry* 2002; 52:53–61
- Peterson AL, Hryshko-Mullen AS, Cortez Y: Assessment and diagnosis of nicotine dependence in mental health settings. *Am J Addict* 2003; 12:192–197
- Montoya ID, Herbeck DM, Svikis DS, Pincus HA: Identification and treatment of patients with nicotine problems in routine clinical psychiatry practice. *Am J Addict* 2005; 14:441–454
- Foulds JGK, Steinberg MB, Richardson D, Williams JM, Burke M, Rhoads GG: Factors associated with quitting smoking at a tobacco dependence treatment clinic. *Am J Health Behav* 2006; 30:400–412
- McChargue DE, Gulliver SB, Hitsman B: Would smokers with schizophrenia benefit from a more flexible approach to smoking treatment? *Addiction* 2002; 97:785–793
- Evins AE, Cather C, Rigotti NA, Freudenreich O, Henderson DC, Olm-Shipman CM, Goff DC: Two-year follow-up of a smoking cessation trial in patients with schizophrenia: increased rates of smoking cessation and reduction. *J Clin Psychiatry* 2004; 65:307–311
- Fiore MC, Bailey WC, Cohen SJ: Treating Tobacco Use and Dependence: Clinical Practice Guideline. Rockville, Md, US Department of Health and Human Services, Public Health Service, June 2000
- Evins AE, Mays VK, Rigotti NA, Tisdale T, Cather C, Goff DC: A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. *Nicotine Tob Res* 2001; 3:397–403
- George TP, Vessicchio JC, Termine A, Sahady DM, Head CA, Pepper WT, Kosten TR, Wexler BE: Effects of smoking abstinence on visuospatial working memory function in schizophrenia. *Neuropsychopharmacology* 2002; 26:75–85
- Sacco KA, Termine A, Seyal A, Dudas MM, Vessicchio JC, Krishnan-Sarin S, Jatlow PI, Wexler BE, George TP: Effects of cigarette smoking on spatial working memory and attentional deficits in schizophrenia: involvement of nicotinic receptor mechanisms. *Arch Gen Psychiatry* 2005; 62:649–659
- Smith RC, Singh A, Infante M, Khandat A, Kloos A: Effects of cigarette smoking and nicotine nasal spray on psychiatric symptoms and cognition in schizophrenia. *Neuropsychopharmacology* 2002; 27:479–497
- Kumari VSW, Sharma T: Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Hum Psychopharmacol* 2001; 16:321–326
- Olincy A, Harris JG, Johnson LL, Pender V, Kongs S, Allensworth D, Ellis J, Zerbe GO, Leonard S, Stevens KE, Stevens JO, Martin L, Adler LE, Soti F, Kem WR, Freedman R: Proof-of-concept trial of an α 7 nicotinic agonist in schizophrenia. *Arch Gen Psychiatry* 2006; 63:630–638
- Sutherland G, Stapleton JA, Russell MA, Jarvis MJ, Hajek P, Belcher M, Feyerabend C: Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992; 340:324–329
- Hjalmarson A, Franzon M, Westin A, Wiklund O: Effect of nicotine nasal spray on smoking cessation. *Arch Intern Med* 1994; 154:2567–2572
- Williams JM, Ziedonis DM, Foulds J: A case series of nicotine nasal spray in the treatment of tobacco dependence among patients with schizophrenia. *Psychiatr Serv* 2004; 55:1064–1066

39. George TP, Ziedonis DM, Feingold A, Pepper WT, Satterburg CA, Winkel J, Rounsaville BJ, Kosten TR: Nicotine transdermal patch and atypical antipsychotic medications for smoking cessation in schizophrenia. *Am J Psychiatry* 2000; 157:1835–1842
40. McEvoy J, Freudenreich O, McGee M, VanderZwaag C, Levin E, Rose J: Clozapine decreases smoking in patients with chronic schizophrenia. *Biol Psychiatry* 1995; 37:550–552
41. George TP, Sernyak MJ, Ziedonis DM, Woods SW: Effects of clozapine on smoking in chronic schizophrenic outpatients. *J Clin Psychiatry* 1995; 56:344–346
42. Adler LE, Olincy A, Cawthra EM, McRae KA, Harris JG, Nagamoto HT, Waldo MC, Hall MH, Bowles A, Woodward L, Ross RG, Freedman R: Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. *Am J Psychiatry* 2004; 161:1822–1828
43. Nagamoto HT, Adler LE, Hea RA, Griffith JM, McRae KA, Freedman R: Gating of auditory P50 in schizophrenics: unique effects of clozapine. *Biol Psychiatry* 1996; 40:181–188
44. Desai HD, Seabolt J, Jann MW: Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs* 2001; 15:469–494
45. Derenne JL, Baldessarini RJ: Clozapine toxicity associated with smoking cessation: case report. *Am J Ther* 2005; 12:469–471
46. Dalack GW, Becks L, Hill E, Pomerleau OF, Meador-Woodruff JH: Nicotine withdrawal and psychiatric symptoms in cigarette smokers with schizophrenia. *Neuropsychopharmacology* 1999; 21:195–202
47. Harris JG, Kongs S, Allensworth D, Martin L, Tregellas J, Sullivan B, Zerbe G, Freedman R: Effects of nicotine on cognitive deficits in schizophrenia. *Neuropsychopharmacology* 2004; 29:1378–1385
48. Dolan SL, Sacco KA, Termine A, Seyal AA, Dudas MM, Vessicchio JC, Wexler BE, George TP: Neuropsychological deficits are associated with smoking cessation treatment failure in patients with schizophrenia. *Schizophr Res* 2004; 70:263–275
49. American Psychiatric Association: APA Practice Guideline for the Treatment of Patients with Nicotine Dependence. Washington, DC, APA Press 1996; 153:1–30