PHYSICIANS DISCUSS SMOKING AND SMOKING CESSATION IN PATIENTS WITH PSYCHIATRIC DISORDERS

Smoking is known to pose serious health risks and is particularly common in patients with mental illness, but clinicians sometimes fail to address smoking among these patients. However, patients with mental illness are able and should be encouraged to quit smoking. While maintaining awareness of the special issues regarding smoking motivation and smoking cessation among these patients, clinicians should promote cessation whenever possible and help patients who have quit to sustain cessation.

On February 16, 2007, Alan J. Gelenberg, M.D., from the Department of Psychiatry at the University of Arizona, assembled a group of experts in order to discuss smoking in patients with mental illness. Their discussion appears here.

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Smoking Cessation in Patients With Psychiatric Disorders

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Dr. Gelenberg: Smoking is an important concern for psychiatrists and their patients. Data show that about 1 person in 5 in the general population smokes or uses tobacco products[1] and that smoking is the leading cause of preventable death in the United States.[2] Patients with mental illness have a higher rate of smoking than the base population[3] and smoke twice as many cigarettes as smokers without mental illness.[4] The good news is that more approaches, both pharmacologic and psychosocial, are available now to help people, including psychiatric patients, stop smoking.

IMPORTANCE OF ENCOURAGING CESSATION

Dr. Gelenberg: How effective are we at making the various behavioral and pharmacologic cessation interventions available to people with mental illness?

Dr. Parks: We certainly could do much better. Clinicians do not often address smoking during patient interviews,[5] but a simple encouragement from a doctor to stop smoking usually results in at least temporary cessation or temporary reduction in the number of cigarettes smoked per day.[6] Many clinicians are not familiar with the appropriate use of nicotine replacement products, and so do not routinely offer them to patients.[7] However, it helps the relationship with the patient when we address smoking because it shows that we care about their general health as well as their psychiatric health.

Dr. de Leon: Use of tobacco is generally not addressed in substance-dependence treatment programs. In my study[8] of alcohol, drug, and smoking cessation, about 45% of the people with severe mental illness were able to stop using alcohol or drugs, but only 10% stopped smoking. If smoking is mindfully addressed, cessation rates may increase. When speaking with other psychiatrists, I emphasize the need for talking to patients about their smoking and including that information in the patient's chart.

Dr. Gelenberg: Just as we ask about alcohol and drugs of abuse, inquiries about tobacco use should be a routine part of every patient's initial history taken by any physician, including psychiatrists.

Dr. de Leon: A couple of questions[9] from the Fagerstrom Test for Nicotine Dependence[10,11] (Table 1) can give the clinician an idea of how addicted the patient is. At the least, the clinician needs to ask how much the patient is smoking and how soon after waking up he or she starts smoking. If somebody starts smoking within the first 5 minutes after waking up, that is a sign that he or she is very addicted. Waiting more than an hour is a sign that he or she is less addicted.

Dr. Evins: If smoking is included as a vital sign in patient charts, doctors will discuss smoking with patients more often and advise quitting.[12]

Table 1. Fagerstrom Test for Nicotine Dependence[a]

1. How soon after you wake up do you smoke your first cigarette?
   - Within 5 minutes = 3 points
   - 6–30 minutes = 2 points
   - 31–60 minutes = 1 point
   - Over 60 minutes = 0 points
2. Do you find it difficult to refrain from smoking in places where it is forbidden?
   - Yes = 1 point
   - No = 0 points
3. Which cigarette would you most hate to give up?
   - First cigarette of the day = 1 point
   - Any other cigarette during the day = 0 points
4. How many cigarettes do you smoke per day?
   - 10 or fewer = 0 points
   - 11–20 = 1 point
   - 21–30 = 2 points
   - 31 or more = 3 points
5. Do you smoke more in the first hours after waking than during the rest of the day?
   - Yes = 1 point
   - No = 0 points
6. Do you smoke when you are so ill that you are in bed?
   - Yes = 1 point
   - No = 0 points

Results:
- Low Nicotine Dependence = 0–3 points
- Medium Nicotine Dependence = 4–5 points
- High Nicotine Dependence = 6–10 points

[a]Reprinted with permission from K.O. Fagerstrom, Ph.D.

However, many doctors seem to have a therapeutic nihilism about the ability of patients with major mental illness to quit smoking. Patients with major mental illness, even schizophrenia, can be both highly motivated and persistent in attempts to quit smoking.[13] They understand that successful cessation can help reduce their elevated risk for smoking-related morbidity and mortality. However, their level of addiction is high.

SPECIAL CESSATION ISSUES FOR SMOKERS WITH SERIOUS MENTAL ILLNESS

Dr. Gelenberg: What are some of the special issues and considerations involved in helping patients with psychiatric disorders in various settings to stop smoking? Should we give different guidance to doctors who care for our most seriously mentally ill patients in the public health system than we would give to primary care doctors who practice in an outpatient setting or even to psychiatrists treating middle-class, basically intact, ambulatory patients?

Dr. Parks: Many patients with mental illness have more difficulty quitting smoking compared with smokers without mental illness.[3] However, they can stop smoking. People with mental illness such as schizophrenia may smoke differently than other people, inhaling more deeply so that they consume higher doses of nicotine.[14,15] They also spend a lot of their disposable income on cigarettes. Many of them try to quit repeatedly, and each of those cessation trials is helpful for them. They reduce some; they quit for a while. The only different guidance I would give is that cessation is going to be a longer process for patients with serious mental illness. The clinician conducting the cessation intervention will need to repeat the prompts to psychiatric patients more frequently than to smokers in the general population, but that is because of the general problems with new learning that you see with severe chronic mental illness. Other than that, the approaches we use are similar. We have to keep it simpler and repeat more often, but, most of all, we just have to do it.

REASONS FOR ELEVATED SMOKING AMONG PATIENTS WITH SCHIZOPHRENIA AND OTHER MENTAL ILLNESS

Dr. Gelenberg: The observation that people with schizophrenia and other major mental illnesses smoke at a higher rate than the general population is certainly an old one, but, over the years, several hypotheses about the reason for this have been advanced. Some have thought that smoking helps patients counteract side effects of medication. Others have thought that smoking is an attempt at self-medication to correct some of the core symptoms of schizophrenia.

Dr. Evins: Over the years, we have learned an extraordinary amount. We have known for decades that smoking—not nicotine but smoking—increases metabolism of antipsychotic medicines, so smokers with schizophrenia have a lower ratio of serum concentration to dose of antipsychotics and other medications that are metabolized by the cytochrome P450 system.[16–23] In the past decade, evidence has accumulated that implicates dysregulation of the neuronal nicotinic acid acetylcholine receptor system in the pathophysiology of schizophrenia.[24–30] Postmortem studies and positron emission tomography (PET) imaging studies show reduced expression of nicotinic receptors in the hippocampus and reduced smoking-related upregulation of the high affinity or $\alpha_4\beta_2$ receptors in the cortex, hippocampus, and caudate.[28,29,31–33] Nicotine improves deficits in auditory sensory gating in those with schizophrenia[34] and their healthy, nonsmoking first-degree relatives.[35]

Nicotine improves attention or inhibitory function in schizophrenic patients to a greater extent than in the general population.[36–39] Until recently, these studies have been conducted with smokers who had been withdrawn from smoking for a brief period, usually overnight, so you often could not be sure if this improvement was merely due to a reversal of some of the detrimental effects of nicotine withdrawal or not. However, a recent study[40] of nonsmokers show that nicotine improves attention in people with schizophrenia as well as controls, but there is a differential

or almost disease-specific improvement in inhibitory processing in patients with schizophrenia. Nicotine helps these patients have more control over their responses and inhibit impulsive responses.

Dr. de Leon: I do not really like the self-medication hypothesis,[41] because most (3 of 4) people with schizophrenia start to smoke before the illness is diagnosed.[42,43]

Dr. Gelenberg: In the last few decades, it has become increasingly clear that the vulnerability to alcohol dependence has a genetic component independent of psychiatric disorders. Besides the influence of simply growing up in a household where your parents smoked, to what extent might there be a genetic component to smoking, perhaps akin to the deficit in nicotinic receptors or nicotinic receptor firing in patients with schizophrenia that we discussed?

Dr. Evins: Up to 70% of the variance of smoking behavior is thought to be attributable to genetic factors, and several genes have been associated with smoking cessation success, smoking relapse, nicotine dependence, craving, and the amount of nicotine one consumes.[44–49] Genetic variation is now being examined as a way to identify individuals who are at risk for nicotine dependence or relapse and, perhaps more clinically relevant, those who may respond better to one treatment or another.[50–52]

Dr. de Leon: People respond differently to medications; I am sure that this is also true for agents of abuse. Your genetic background makes you more susceptible to respond positively to one drug rather than another. I think there is an overlap between the genetics of nicotine dependence and alcohol abuse, and that is why they tend to co-occur. There may be a similar overlap between nicotine dependence and schizophrenia, but associations between nicotine dependence and alcohol and drug abuse are stronger than associations between smoking and schizophrenia.[53]

I have been doing a study of 4000 patients asking which substances of abuse are their favorite, and, without a doubt, nicotine is the one that they prefer. It is also the substance that is hardest for them to quit.

Dr. Rigotti: Because many children try a cigarette but only some of them become nicotine-dependent, genetic differences may predict who will develop nicotine dependence. Right now, we do not know enough about these genetics for it to influence our treatment, although we are trying to identify characteristics of patients who might respond better to one treatment than another.

Dr. Gelenberg: People who develop alcohol dependence often have a more profound recollection of their first drink than people who do not become alcohol-dependent. Is someone with a genetic predisposition for nicotine dependence likely to say, "It was a peak experience when I had my first cigarette at age 15"?

Dr. Evins: To my knowledge, those data have not been published. Those who have the more negative experience are the fast metabolizers, so they essentially have nicotine withdrawal very quickly after being exposed to nicotine. I think the strongest data right now show that those with very fast metabolism of nicotine are much more likely to become addicted.[54]

SMOKING CESSATION TREATMENTS FOR PATIENTS WITH MENTAL ILLNESS

Dr. Parks: The hypotheses about the reasons for increased smoking among the mentally ill may help us to understand the illnesses or develop new therapies for treating mental illness, but they do not help us address the smoking that our patients are doing now. The point is that these patients are dying 25 years younger than the general population,[55] and they are dying of smoking-related illnesses—heart disease and lung disease. We spend more time trying to understand why they smoke than trying to understand what we can do to reduce their smoking and prevent premature mortality.

Dr. Evins: That is a very good point.

Dr. Gelenberg: I understand that we have several different types of cessation treatments, psychosocial behavioral and pharmacologic. In recent years, the U.S. Food and Drug Administration (FDA) approved nicotine replacement. We have an antidepressant, bupropion, which is approved under a different brand name for smoking cessation. Recently, a new product with a different mechanism of action, varenicline, has become available. If a patient comes to me this afternoon and says, "I want to quit," how do I decide which treatment approach to use?

Dr. Rigotti: The U.S. Public Health Service guidelines[56] for treating tobacco use and dependence were published in 2000, and I think they are still relevant. The guidelines were for general medical patients, not specifically for psychiatric patients, but the guidelines were the result of an extensive meta-analysis of existing literature at that time, and they concluded that there were effective treatments.

The evidence of efficacy was examined for 2 types of treatments—psychosocial support and medication.[56] In terms of psychosocial support, the most effective types of treatment were psychoeducational, habit-changing, cognitive-behavioral strategies that help smokers identify their cues to smoke and then begin to break the link between the cue and the smoking. People begin to learn alternative ways of coping with urges and cravings to smoke. Social support was also recommended, both within the context of the treatment and outside the context of the treatment, which sometimes means going to a formal program that provides support or finding a buddy who is a nonsmoker.

In terms of medication, the recommendation was that all forms of nicotine replacement were essentially the same.[56] Consequently, a form of nicotine replacement or

the sustained-release form of bupropion were considered first-line drugs, based on the fact that they were all FDA-approved for the indication of smoking cessation and that they each approximately doubled quit rates compared with placebo. The second-line drugs were nortriptyline and clonidine. More recently, varenicline, which works with a different action, was approved. The guidelines did not make a recommendation about the specific type of cessation aid to use with patients but said that it was up to patient preference and physician judgment, perhaps weighing the various side effects.

In my own experience, it makes the most sense to first ask the patient if he or she has ever tried to quit before, what cessation aids he or she has used, and how well the aid worked. Often people can build on their previous quitting experience, and I think that patients should have a role in deciding what they think will work. Do they want a pill? Do they want a patch, gum, lozenge, or some other treatment? Sometimes, financial issues are involved, and it is simply a matter of what is best covered by their insurance, which is a public insurance in many cases.

Dr. Parks: Different people will be motivated by different reasons to stop smoking. Some are motivated by the health reasons; others are motivated just by the amount of money it costs them. We need to be careful in our patient interviews to search the full range of reasons to stop smoking, whether it is health, money, social relationships, or just not wanting to smell like stale cigarettes.

Schizophrenia

Dr. Evins: For some time, it was recommended that patients with schizophrenia not take bupropion because of its mild dopaminergic properties, but those recommendations were made before any studies on this issue were published. There are now several studies[57–61] of bupropion for smoking cessation in patients with schizophrenia, and bupropion seems to be well-tolerated. It does not cause increase in psychosis and may, if anything, improve depressive or negative symptoms.

We have no new cessation strategies for people with psychiatric illness. We have what is out there for the general population but perhaps in higher doses—combining a short-acting nicotine replacement therapy with a longer acting patch or combining nicotine replacement therapy and bupropion—than you might consider using in the general population.

Dr. Gelenberg: So, if a smoking patient has a chronic psychotic disorder like schizophrenia, approach it more or less the same way, with a few modifications, as you would with anyone in the general population?

Dr. Evins: Make the psychoeducational support more concrete, and perhaps give more than one form of pharmacotherapy. Otherwise, the cessation strategies are mostly the same in the general population and in patients with mental illness.

Dr. de Leon: I would also like to point out that, because smoking increases the metabolism of clozapine, olanzapine, and typical antipsychotics, doses of those medications need to be increased in smokers, and subsequent smoking cessation can raise the blood levels of these drugs,[16] so the psychiatrist has to lower the dose and closely follow these patients to avoid side effects.

Dr. Evins: Short-term cessation treatment (i.e., 8 to 12 weeks) may not be adequate for patients with schizophrenia, in particular. If they have nicotinic receptor hypofunction at baseline, their receptors do not upregulate normally when they smoke. Then, when they stop smoking, you should not expect their receptor function to normalize during abstinence. Long-term treatment with a nicotinic agonist may be required to reduce the high rates of relapse that occur when patients with schizophrenia discontinue nicotine dependence treatment.[60,62]

Dr. Gelenberg: Rather than advising short-term nicotine treatment using patches or gum, would you suggest long-term treatment for people with serious mental illness?

Dr. Evins: Yes. We need to test this hypothesis, but our understanding of nicotinic receptor hypofunction in this illness tells us that these patients may initially need higher doses or more treatment to quit smoking, and we may need to continue treatment chronically.

Dr. Gelenberg: I think the reason that understanding nicotine in the context of a disorder of fundamental sensory gating like in schizophrenia is relevant in today's clinical world is because it gives us some hints about how cessation might be different in these patients. The basic concept of smoking cessation is to get someone over the hump of withdrawal and then leave them on their own. But in patients with schizophrenia, if there is a fundamental deficit in cognitive processing that nicotine helps to reverse, then chronic nicotine replacement, perhaps in a vehicle better than what we currently have available, might assist people with schizophrenia to quit smoking long-term.

Dr. Rigotti: Working with smokers who have major mental illness is like working with patients without mental disorders who are very addicted to nicotine. Sometimes they need more than one medication, sometimes more than two, and sometimes for a prolonged period of time. The idea that nicotine dependence is something that can be cured within a fairly short time frame is true for some patients but not for all patients. I would submit that patients with chronic mental illnesses are in the category of those who might need chronic treatment. Many of them do try to quit and can be helped with medication, but they relapse at high rates, which would suggest that a longer period of treatment, perhaps lifelong treatment, might be required.

Dr. de Leon: An article[63] focusing on one patient with schizophrenia, who had tried to quit smoking 20 times in

his lifetime prior to coming in for specialized treatment, reported that to get this patient to quit smoking, it took a total of 16 doctor visits over 18 months, while he made 8 more quit attempts. Both counseling and nicotine replacement therapy were used. Ten follow-up visits over the next 3 years indicated continued abstinence. That is a major effort which may not be possible in facilities with limited resources.

A study[64] of cessation and continued abstinence at 12 months in patients with psychotic disorders using behavioral therapy and pharmacologic treatment found that treatment worked for a minority of patients. Among those who completed all treatment sessions, point-prevalence abstinence rates were 30.0% at 3 months and 18.6% at both 6 and 12 months. Continuous abstinence rates at 12 months were 0.7% in the comparison group, and 3.4% in the treatment group, with a maximum of 7.1% in those who attended all sessions. A need exists for finding new cessation treatments that will benefit people for whom the current treatments have poor outcomes.

Dr. Evins: Abstinence rates of 20% to 30% indicate that patients with schizophrenia can quit. The patients who are able to stay off cigarettes probably have less attentional impairment at baseline. I agree that we need more effective treatments. Varenicline now is being studied in schizophrenia.

Depression

Dr. Gelenberg: There seems to be a correlation between depression and smoking[65–68]—that smokers have a higher rate of depression and that when people who have a propensity to depression stop smoking, they often get depressed again.[69]

Dr. Rigotti: There is a higher prevalence of smoking with patients with current or past mood disorders, [65–68] but we know less about what cessation strategies work for this group of patients. In many trials of smoking cessation treatments, patients with mood disorders were excluded. We are learning more in this area, and, as with schizophrenic patients, trials are needed to identify optimal therapies for these patients.

In the absence of definitive data, I think clinicians can assume that smokers with depression will perhaps need to be treated with more medication, meaning a combination of medications, and for longer periods of time than smokers without depression and should be followed more closely after quitting in case of a recurrence of depressive symptoms or depression.

Dr. Gelenberg: Psychiatrists treating ambulatory patients are particularly likely to be in a situation in which a patient who has been successfully treated for depression and has been stable for the past year will decide she wants to quit smoking. She may come into my office and say, "By the way, Dr. Gelenberg, I'm going to stop smoking." I might say, "Let's meet a little sooner than usual, and let's keep a very close eye on your depression over the next month."

Dr. Evins: Right, and while you might have been planning to taper or stop her antidepressant treatment, if she is planning to quit smoking, you would want to continue the antidepressant for at least 6 months or longer.

Dr. Parks: The first thing you want to do is congratulate and support her on her decision and ask what you can do to help her be successful in not smoking. Only after you positively reinforce the decision should you begin to manage the potential problems.

Dr. Evins: I wholeheartedly agree. I would add that, for people with depression, there is a lot of data now for cessation treatment with nortriptyline and bupropion.[70,71] It seems that they work, are well-tolerated, and appear to be safe in patients with depression, but they work with a mechanism that seems to be separate from their effect on depressive symptoms.

Dr. Gelenberg: Is there evidence supporting the use of serotonin selective reuptake inhibitors (SSRIs) in assisting smoking cessation?

Dr. Rigotti: The existing literature does not support that they have any efficacy for smoking cessation.[70]

Dr. Gelenberg: If my patient is taking an SSRI for depression and wants to stop smoking, then should I tell her that, among the cessation agents, 2 are also antidepressants—bupropion and nortriptyline—and that I can add one of them to her SSRI?

Dr. Rigotti: Right, or she can try nicotine replacement.

Smoke-Free Facilities

Dr. Rigotti: Clinicians need to ask patients about the smoking status of their homes and the cues that they get that encourage or discourage smoking.

Dr. Gelenberg: I believe few psychiatric units in public or private settings currently permit smoking, and many of the residential and partially residential facilities where mentally ill patients live discourage or forbid it. Obviously, patients can smoke outside.

Dr. Evins: People often fret that smoke-free hospitals are a real problem for patients who may be having a psychotic or depressive decompensation because they will also go into nicotine withdrawal. This problem should be alleviated with nicotine replacement therapy.

Dr. Gelenberg: The idea of smoke-free facilities scared us when we first contemplated it 20 years ago.

Dr. Evins: The worries of the staff far exceeded any consequences.[72–76]

CONCLUSION

Dr. Gelenberg: Tobacco use is more prevalent among patients with mental illness than among the general population. The powerful adverse impact of smoking on longevity and a variety of health indices is well known.

Psychiatric patients are at a much greater risk for adverse events due to increased smoking, a substantial portion of which may be attributable to genetic factors. If someone has schizophrenia, with the accompanying nicotine receptor deficit and trouble gating excessive extraneous stimuli and paying attention, there may be a strong temptation to smoke or use other forms of nicotine that will improve attention deficits.

Clinicians should document smoking status of their patients and discuss cessation strategies with them. The range of psychosocial and pharmacologic treatments available to assist people in quitting can be employed with some modifications for psychiatric patients. Patients with mental illness have a reasonable short-term prospect of quitting smoking. The long-term prospect is daunting, but that does not mean we should not keep trying. Among people with certain chronic disorders like schizophrenia, long-term nicotine replacement may improve long-term abstinence rates, although this hypothesis needs study. An unmet need in this area is longitudinal, empirical testing of various interventions that would improve the low long-term quit rate.

Drug names: bupropion (Zyban), clonidine (Catapres, Duraclon, and others), clozapine (Clozaril, Fazaclo, and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), varenicline (Chantix).

Disclosure of off-label usage: The chair has determined that, to the best of his knowledge, clonidine and nortriptyline are not approved by the U.S. Food and Drug Administration for smoking cessation.

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REFERENCES

1. Center for Disease Control and Prevention (CDC). Cigarette smoking among adults: United States, 2004. MMWR Morb Mortal Wkly Rep 2005;54:1121–1124
2. Mokdad AH, Marks JS, Stroup DF, et al. Actual causes of death in the United States, 2000. JAMA 2004;291:1238–1319
3. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness: a population-based prevalence study. JAMA 2000;284:2606–2610
4. Haustein KO, Haffner S, Woodcock BG. A review of the pharmacological and psychopharmacological aspects of smoking and smoking cessation in psychiatric patients. Int J Clin Pharmacol 2002;40:404–418
5. Vokes NI, Bailey JM, Rhodes KV. "Should I give you my smoking lecture now or later?": characterizing emergency physician smoking cessation and cessation counseling. Ann Emerg Med 2006;48:406–414
6. Law M, Tang JL. An analysis of the effectiveness of interventions intended to help people stop smoking. Arch Intern Med 1995;155:1933–1941
7. Wilson DM, Lindsay EA, Best JA, et al. A smoking cessation intervention program for family physicians. CMAJ 1987;137:613–619
8. de Leon J, Susce MT, Diaz FJ, et al. Variables associated with alcohol, drug, and daily smoking cessation in patients with severe mental illnesses. J Clin Psychiatry 2005;66:1447–1455
9. Diaz FJ, Jane M, Salto E, et al. A brief measure of high nicotine dependence for busy clinicians and large epidemiological surveys. Aust N Z J Psychiatry 2005;39:161–168
10. Heatherton TF, Kozlowski LT, Frecker RC, et al. The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. Br J Addict 1991;86:1119–1127
11. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. J Behav Med 1989;12: 159–182
12. Robinson MD, Laurent SL, Little JM Jr. Including smoking status as a new vital sign: it works! J Fam Pract 1995;40:556–561
13. Evins AE, Cather C, Rigotti NA, et al. 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
14. 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
15. Tidey JW, Rohsenow DJ, Kaplan GB, et al. Cigarette smoking topography in smokers with schizophrenia and matched non-psychiatric controls. Drug Alcohol Depend 2005;80:259–265
16. de Leon J, Armstrong SC, Cozza KL. The dosing of atypical antipsychotics. Psychosomatics 2005;46:262–273
17. de Leon J. Atypical antipsychotic dosing: the effect of smoking and caffeine. Psychiatr Serv 2004;55:491–493
18. Rostami-Hodjegan A, Amin AM, Spencer EP, et al. Influence of dose, cigarette smoking, age, sex, and metabolic activity on plasma clozapine concentrations: a predictive model and nomograms to aid clozapine dose adjustment and to assess compliance in individual patients. J Clin Psychopharmacol 2004;24:70–78
19. van der Weide J, Steijns LS, van Weelden MJ. The effect of smoking and cytochrome P450 CYP1A2 genetic polymorphism on clozapine clearance and dose requirement. Pharmacogenetics 2003;13:169–172
20. Salokangas RK, Saarijarvi S, Taiminen T, et al. Effect of smoking on neuroleptics in schizophrenia. Schizophr Res 1997;23:55–60
21. Seppala NH, Leinonen EV, Lehtonen ML, et al. Clozapine serum concentrations are lower in smoking than in non-smoking schizophrenic patients. Pharmacol Toxicol 1999;85:244–246
22. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. CNS Drugs 2001; 15:469–494
23. Theisen FM, Haberhausen M, Schultz E, et al. Serum levels of olanzapine and its N-desmethyl and 2-hydroxymethyl metabolites in child and adolescent psychiatric disorders: effects of dose, diagnosis, age, sex, smoking, and comedication. Ther Drug Monit 2006;28:750–759
24. Mastropaolo J, Rosse RB, Deutsch SI. Anabasine, a selective nicotinic acetylcholine receptor agonist, antagonizes MK-801–elicited mouse popping behavior, an animal model of schizophrenia. Behav Brain Res 2004;153:419–422
25. Paterson D, Nordberg A. Neuronal nicotinic receptors in the human brain. Prog Neurobiol 2000;61:75–111
26. Hogg RC, Raggenbass M, Bertrand D. Nicotinic acetylcholine receptors: from structure to brain function. Rev Physiol Biochem Pharmacol 2003; 147:1–46
27. Court JA, Martin-Ruiz C, Graham A, et al. Nicotinic receptors in human brain: topography and pathology. J Chem Neuroanat 2000;20:281–298
28. Ripoll N, Bronnec M, Bourin M. Nicotinic receptors and schizophrenia. Curr Med Res Opin 2004;20:1057–1074
29. Leonard S, Adams C, Breese CR, et al. Nicotinic receptor function in schizophrenia. Schizophr Bull 1996;22:431–445
30. Leonard S, Gault J, Hopkins J, et al. Association of promoter variants in the alpha7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. Arch Gen Psychiatry 2002;59:1085–1096
31. Freedman R, Hall M, Adler LE, et al. Evidence in postmortem brain tissue

for decreased numbers of hippocampal nicotinic receptors in schizophrenia. Biol Psychiatry 1995;38:22–33
32. Durany N, Zochling R, Boissl KW, et al. Human post-mortem striatal alpha4beta2 nicotinic acetylcholine receptor density in schizophrenia and Parkinson's syndrome. Neurosci Lett 2000;287:109–112
33. Breese CR, Lee MJ, Adams CE, et al. Abnormal regulation of high affinity nicotinic receptors in subjects with schizophrenia. Neuropsychopharmacology 2000;23:351–364
34. Adler LE, Hoffer LD, Wiser A, et al. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. Am J Psychiatry 1993;150:1856–1861
35. Adler LE, Hoffer LJ, Griffith J, et al. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. Biol Psychiatry 1992;32:607–616
36. Tanabe J, Tregellas JR, Martin L.F. Effects of nicotine on hippocampal and cingulate activity during smooth pursuit eye movement in schizophrenia. Biol Psychiatry 2006;59:754–761
37. Tregellas JR, Tanabe JL, Martin LF, et al. FMRI of response to nicotine during a smooth pursuit eye movement task in schizophrenia. Am J Psychiatry 2005;162:391–393
38. Avila MT, Sherr JD, Hong E, et al. Effects of nicotine on leading saccades during smooth pursuit eye movements in smokers and nonsmokers with schizophrenia. Neuropsychopharmacology 2003;28:2184–2191
39. Olincy A, Johnson LL, Ross RG. Differential effects of cigarette smoking on performance of a smooth pursuit and a saccadic eye movement task in schizophrenia. Psychiatry Res 2003;117:223–236
40. Barr RS, Culhane MA, Jubelt LE, et al. The effects of transdermal nicotine on cognition in nonsmokers with schizophrenia and nonpsychiatric controls. Neuropsychopharmacology 2007;[Epub ahead of print]
41. de Leon J, Diaz FJ, Aguilar MC, et al. Does smoking reduce akathisia? testing a narrow version of the self-medication hypothesis. Schizophr Res 2006;86:256–268
42. de Leon J. Smoking and vulnerability for schizophrenia. Schizophr Bull 1996;22:405–409
43. 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
44. Osler M, Holst C, Prescott E, et al. Influence of genes and family environment on adult smoking behavior assessed in an adoption study. Genet Epidemiol 2001;21:193–200
45. Kendler KS, Thornton LM, Pedersen NL. Tobacco consumption in Swedish twins reared apart and reared together. Arch Gen Psychiatry 2000;57:886–892
46. Straub RE, Sullivan PF, Ma Y, et al. Susceptibility genes for nicotine dependence: a genome scan and follow up in an independent sample suggest that regions on chromosomes 2, 4, 10, 16, 17, and 18 merit further study. Mol Psychiatry 1999;4:129–144
47. Lerman C, Caporaso NE, Audrain J, et al. Interacting effects of the serotonin transporter gene and neuroticism in smoking practices and nicotine dependence. Mol Psychiatry 2000;5:189–192
48. Lerman C, Berrettini W. Elucidating the role of genetic factors in smoking behavior and nicotine dependence. Am J Med Genet B Neuropsychiatr Genet 2003;118:48–54
49. Beuten J, Payne TJ, Ma JZ, et al. Significant association of catechol-O-methyltransferase (COMT) haplotypes with nicotine dependence in male and female smokers of 2 ethnic populations. Neuropsychopharmacology 2006;31:675–684
50. Berrettini WH, Wileyto EP, Epstein L, et al. Catechol-O-methyltransferase (COMT) gene variants predict response to bupropion therapy for tobacco dependence. Biol Psychiatry 2007;61:111–118
51. Lerman C, Jepson C, Wileyto EP, et al. Role of functional genetic variation in the dopamine D2 receptor (DRD2) in response to bupropion and nicotine replacement therapy for tobacco dependence: results of 2 randomized clinical trials. Neuropsychopharmacology 2006;31:231–242
52. Johnstone EC, Yudkin PL, Hey K, et al. Genetic variation in dopaminergic pathways and short-term effectiveness of the nicotine patch. Pharmacogenetics 2004;14:83–90
53. Diaz FJ. Epidemiology of comorbid tobacco use and schizophrenia: thinking about risks and protective factors. J Dual Diagnosis. In press.
54. Tyndale RF, Sellers EM. Genetic variation in CYP2A6-mediated nicotine metabolism alters smoking behavior. Ther Drug Monit 2002; 24:163–171
55. Colton CW, Manderscheid RW. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. Prev Chonic Dis [Serial Online] 2006;3:1–14
56. US Public Health Service. A Clinical Practice Guideline for Treating Tobacco Use and Dependence: a US Public Health Service report. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. JAMA 2000;283:3244–3254
57. Evins AE, Mays VK, Rigotti NA, et al. A pilot trial of bupropion added to cognitive behavioral therapy for smoking cessation in schizophrenia. Nicotine Tob Res 2001;3:397–403
58. Weiner E, Ball MP, Summerfelt A, et al. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. Am J Psychiatry 2001;158:635–637
59. George TP, Vessicchio JC, Termine A, et al. A placebo controlled trial of bupropion for smoking cessation in schizophrenia. Biol Psychiatry 2002;52:53–61
60. 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: 218–225
61. Evins AE, Cather C, Culhane MA, et al. A 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. In press
62. Cui Y, Wen W, Moriarty CJ, et al. Risk factors and their effects on the dynamic process of smoking relapse among veteran smokers. Behav Res Ther 2006;44:967–981
63. Williams JM, Foulds J. Successful tobacco dependence treatment in schizophrenia. Am J Psychiatry 2007;164:222–227
64. Baker A, Richmond R, Haile M, et al. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. Am J Psychiatry 2006;163:1934–1942
65. Breslau N, Kilbey M, Andreski P. Nicotine dependence, major depression, and anxiety in young adults. Arch Gen Psychiatry 1991;48:1069–1074
66. Breslau N, Kilbey MM, Andreski P. Nicotine dependence and major depression: new evidence from a prospective investigation. Arch Gen Psychiatry 1993;50:31–35
67. Glassman AH, Helzer JE, Covey LS, et al. Smoking, smoking cessation, and major depression. JAMA 1990;264:1546–1549
68. Hughes JR, Hatsukami DK, Mitchell JE, et al. Prevalence of smoking among psychiatric outpatients. Am J Psychiatry 1986;143:993–997
69. Tsoh JY, Humfleet GL, Munoz RF, et al. Development of major depression after treatment for smoking cessation. Am J Psychiatry 2000; 157:368–374
70. Hughes JR, Stead L, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007:CD000031
71. Wilhelm K, Arnold K, Niven H, et al. Grey lungs and blue moods: smoking cessation in the context of lifetime depression history. Aust N Z J Psychiatry 2004;38:896–905
72. Taylor NE, Rosenthal RN, Chabus B, et al. The feasibility of smoking bans on psychiatric units. Gen Hosp Psychiatry 1993;15 :36–40
73. Beemer BR. Hospital psychiatric units: nonsmoking policies. J Psychosoc Nurs Ment Health Serv 1993;31:12–14
74. Haller E, McNiel DE, Binder RL. Impact of a smoking ban on a locked psychiatric unit. J Clin Psychiatry 1996;57:329–332
75. Velasco J, Eells TD, Anderson R, et al. A two-year follow-up on the effects of a smoking ban in an inpatient psychiatric service. Psychiatr Serv 1996;47:869–871
76. Greeman M, McClellan TA. Negative effects of a smoking ban on an inpatient psychiatry service. Hosp Community Psychiatry 1991;42: 408–412

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