

How to treat nicotine dependence in smokers with schizophrenia

Improve patients' health, help them kick addiction with this practical approach

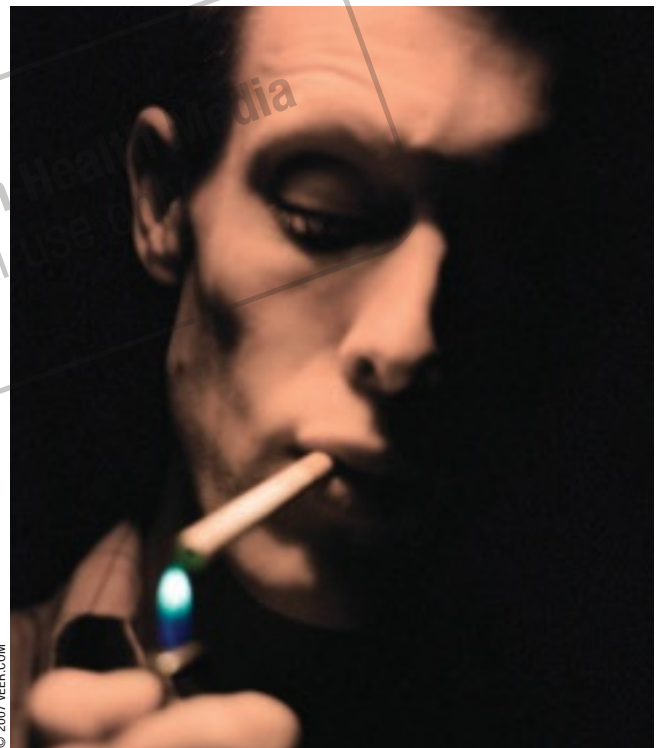
Mr. V, age 49, has stable but symptomatic schizophrenia and a 33-year cigarette smoking history. He is very concerned because his primary care physician told him he has 2 serious smoking-related health problems: diabetes and hypertension. He tried a smoking cessation program for the general public, but it was a poor fit because of his schizophrenia symptoms.

Despite adhering to his medications (ziprasidone, 20 mg hs; perphenazine, 8 mg hs; lorazepam, 1 mg hs; zonisamide, 200 mg/d, and bupropion mesylate, 2 mg hs), Mr. V has residual auditory hallucinations, paranoid ideation, and impaired concentration and attention. He smokes approximately 1.5 packs per day, particularly when very ill, to alleviate chronic boredom, and to diminish distress from the hallucinations. All of his friends smoke, and they do not support his attempts to quit.

Successfully treating nicotine dependence can seem a formidable challenge in patients with schizophrenia:

- 72% to 90% smoke cigarettes, compared with 21% of the general population¹ (*Box, page 66*).²⁻¹²
- They tend to smoke heavily, spending about one-third of their incomes on cigarettes.¹³
- Their negative symptoms (such as apathy), positive symptoms (such as disorganized thinking), and cognitive impairment can reduce motivation to quit and adhere to a smoking cessation strategy.
- Sociologic and physiologic aspects of schizophrenia reinforce their smoking habit (*Table 1, page 69*).^{9,12,14-17}

Even so, smokers with schizophrenia can be highly



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Nicotine dependence

Clinical Point

Using transdermal nicotine replacement plus a short-acting form (gum, lozenge, inhaler, or nasal spray) may improve sustained abstinence

Box Obstacles to smoking cessation for schizophrenia patients

Smokers with schizophrenia are more nicotine-dependent, more likely to become medically ill, and less likely to receive help in quitting, compared with the general population. They:

- begin smoking at a higher rate before diagnosis or treatment for schizophrenia, compared with persons who do not go on to develop the disorder²
- smoke each cigarette more intensely, extracting more nicotine per cigarette³⁻⁵
- have higher rates of smoking-related illness and medical morbidity⁶
- are much less likely to receive physician advice to quit smoking.⁷

Many persons with severe mental illness are misinformed about the risks and benefits of smoking vs nicotine dependence treatment.⁸ They often fear and overestimate the medical risks of nicotine replacement therapies.⁹ Many believe smoking relieves depression and anxiety,¹⁰ whereas nicotine actually is anxiogenic. Nicotine may improve some aspects of cognitive dysfunction in schizophrenia, which could be a disincentive for patients to quit smoking.^{11,12}

motivated and persistent in attempting to quit.¹⁸ Promising results have been reported in trials when psychopharmacologic treatments are combined with cognitive and behavioral interventions.

This article reviews these empiric studies and suggests practical ways for clinicians to create smoking cessation and relapse prevention plans for individuals with schizophrenia.

Clinical trials of smoking cessation

Inadequate interventions. Conventional regimens—consisting of 8 to 12 weeks with sustained-release bupropion or nicotine replacement therapy (NRT) added to supportive or cognitive-behavioral therapy (CBT)¹⁹—are well-tolerated by patients with schizophrenia but only modestly effective. CBT alone (or with placebo) has not been effective for smoking cessation in schizophrenia. In clinical trials, abstinence rates have been:

- 4% to 19% after 3 to 6 months with bupropion or NRT and CBT
- ≤6% with placebo and CBT.²⁰⁻²³

Multifaceted interventions. High-dose NRT patch treatment (2 patches at a time) has not consistently shown additional benefits compared with single-patch treatment.^{24,25} However, combining short-acting NRT (gum, lozenge, inhaler, or nasal spray) with a long-acting NRT preparation (transdermal patch) is well-tolerated and has been shown to improve sustained abstinence rates²⁶ (Table 2, page 70).

In a double-blind, placebo-controlled trial,²⁷ 51 smokers with schizophrenia were randomly assigned to receive combination NRT (21-mg NRT patch plus ≤18 mg/d NRT polacrilex gum pm) added to bupropion SR, 150 mg bid, or placebo. Smoking cessation—defined as quitting on the assigned date and maintaining continuous abstinence for 4 weeks (measured by expired air carbon monoxide <9 ppm and self-report of abstinence at weekly visits)—was achieved by:

- 52% of those receiving bupropion and dual NRT
- 19% who received placebo and the 2 forms of NRT.

Preventing relapse. Relapse is common among all smokers but especially in those with schizophrenia. In clinical trials, 70% to 83% of smokers with schizophrenia who attained abstinence relapsed to smoking within 6 to 12 months of stopping nicotine dependence treatment.^{21,22,27,28}

In one clinical trial, >50% of patients achieved 4 weeks of continuous abstinence on a regimen of bupropion SR, 150 mg bid; nicotine patch (21 mg/d); and as-needed nicotine gum (≤18 mg/d). However:

- 31% relapsed to smoking while NRT was being tapered from ~40 to 20 mg/d
- 77% relapsed after nicotine dependence treatment was discontinued.²⁷

Longer use of pharmacotherapy may be needed to prevent relapse to smoking in the schizophrenia population. In a recent open case series, 17 of 42 smokers with

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schizophrenia were able to quit for at least 2 weeks with a combination of bupropion SR, 150 mg bid, and dual NRT. Among those who quit, 13 (76%) remained abstinent for 12 additional months when offered continued pharmacotherapy and tapering CBT (AE Evins, under review).

CASE CONTINUED

Treating nicotine dependence

Mr. V cut down to 10 cigarettes a day during a 4-week motivational enhancement/psychoeducation intervention for smokers with major mental illness.²⁹ He then enrolled in a 12-week study in which subjects received high-dose dual NRT and bupropion SR or placebo.

Mr. V was reluctant to use the NRT patch because he believed rumors that it could cause a heart attack, especially if he smoked while using a patch. He did try the patch, however, after his clinicians informed him it would increase his chances of quitting.

He received bupropion SR, 150 mg bid; NRT patch, 21 mg/d; and nicotine polacrilex gum, up to 18 mg/d as needed, and tolerated the regimen well. After 4 weeks, he quit smoking on the quit date. His blood pressure—monitored weekly for the first month then monthly thereafter—remained stable throughout the intervention.

Prescribing considerations

Metabolic changes. Smoking—but not NRT—induces hepatic clearance of many psychotropics, and smoking cessation can be associated with increased drug serum levels. Polycyclic aromatic hydrocarbons present in cigarette smoke—but not NRT—induce hepatic aryl hydrocarbon hydroxylases and cytochrome P (CYP)-450 isozymes, primarily CYP 1A1, 1A2, and 2E1, thereby increasing metabolic clearance of medications—such as clozapine—that are substrates for these enzymes.

Smoking cessation is associated with a 30% to 42% reduction in activity of CYP

Table 1

Why up to 90% of schizophrenia patients smoke cigarettes

Sociologic barriers to quitting

- Their social groups often include a high percentage of heavy smokers
- Some fear NRT is ‘unhealthy,’ causes cardiac arrest, or increases nicotine cravings⁹ (see *Table 2, page 70*, for an accurate NRT side effect profile)
- They are unlikely to achieve sustained abstinence from a single cessation attempt

Physiologic reinforcers and disease factors

- Nicotine may modulate schizophrenia’s cognitive dysfunction, including sensory gating (a measure of ability to filter out irrelevant environmental stimuli) and attention^{12,14}
- Nicotine may increase disease-associated reduction in nicotinic acetylcholine receptor activity^{15,16}
- Smoking (but not nicotine) reduces antipsychotic blood levels by increasing metabolism and may reduce side effects of antipsychotic medications¹⁷
- Schizophrenia’s cognitive impairment can make smoking cessation strategies difficult to follow

1A2, and the half-life of this reduction is 27 to 54 hours. Thus, therapeutic drug monitoring and dose reduction of 10% over the first 4 days of tobacco abstinence is recommended to avoid toxicity. If the patient remains abstinent from tobacco, further reducing the antipsychotic dose may be warranted, based on individual assessment.

Weight gain. Patients who quit smoking gain an average of 3 to 5 kg.³⁰

Nicotine withdrawal. Patients are used to thinking that nicotine is calming, whereas in reality nicotine and smoking are anxiogenic, and cigarette smoking alleviates the anxiety that comes from nicotine withdrawal.³¹ Educate patients about nicotine withdrawal symptoms, which easily can be confused with early signs of a psychotic relapse but are much more time-limited:

- dysphoria and irritability
- anxiety
- insomnia
- reduced heart rate
- restlessness
- difficulty concentrating.

Clinical Point

For patients taking clozapine, reduce the dose by 10% in the first 4 days of abstinence; monitor for the need to make further reductions



Nicotine dependence

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Take care when prescribing bupropion in combination with clozapine because of an additive risk of causing seizures

Table 2

Suggested pharmacologic approaches for smoking cessation in patients with schizophrenia

Medication	Dosage	Specific instructions	Potential side effects
Bupropion SR	150 mg bid	Consider maintenance treatment if patient attains abstinence and tolerates medication well	Insomnia, anxiety, irritability (usually mild, time-limited); contraindicated in patients with a seizure disorder or who are at high risk for seizures; take care when prescribing in combination with clozapine
Varenicline	0.5 mg once daily for 3 days; 0.5 mg bid for 4 days; 1 mg bid ongoing	No published data in smokers with schizophrenia; several trials are underway	Nausea, headache (nausea can be managed in some patients with dose reduction)
NRT patch	21 mg/d to start	Consider combination treatment with short-acting preparation; consider maintenance treatment if patient attains abstinence and tolerates medication well	Rash, skin irritation, hypersensitivity reaction
Short-acting NRT (gum, lozenge, inhaler, spray)	≤20 mg/d as needed for craving, in 2-mg or 4-mg increments	Instruct in correct use, particularly with gum; for patients who attain abstinence, consider maintenance of as-needed short-acting NRT	

NRT: nicotine replacement therapy

Bupropion SR at 150 mg bid has been well-tolerated when added to antipsychotics and modestly effective for smoking cessation in this population. It has been associated with reduced negative symptoms and greater symptom stability during the cessation attempt—compared with placebo—and is well-tolerated when combined with NRT.^{20-22,27}

NRT in a variety of delivery forms has been well tolerated and modestly effective for smoking cessation in schizophrenia.^{23,27,28} Combinations of short-acting NRT (gum, lozenge, inhaler, or nasal spray) with the long-acting NRT patch improve long-term abstinence rates in smokers in the general population²⁶ and may improve abstinence rates in those with schizophrenia.²⁷ Maintaining the pharmacotherapy used to achieve abstinence may also improve sustained abstinence rates.

Varenicline is a partial nicotinic receptor agonist approved for treating tobacco de-

pendence. No reports have been published on its safety and efficacy for smoking cessation in persons with schizophrenia.

In our experience with open-label varenicline for nicotine dependence in schizophrenia, 8 of 9 patients quit smoking, reported reduced cravings, and remained clinically stable on the agent for 6 to 9 months. All had previously relapsed after discontinuing NRT, bupropion, or the combination.

Controlled trials are needed to discern this agent's place in the treatment hierarchy for smokers with schizophrenia, and several such trials are underway.

10-step office-based approach

CBT alone is not effective for smoking cessation in the schizophrenia population,^{22,28} but pharmacologic interventions have not been shown to succeed without concurrent behavioral treatment.

The 10 behavioral treatments described below and the tools listed in *Table 3* can be

covered in 1 or 2 visits and individualized for a relatively brief, office-based approach. Using the complete list may be ideal, but you can deliver a reasonable behavioral intervention by choosing tasks tailored to each patient's needs. After the initial session, review these interventions at follow-up appointments to reinforce skills.

1 Send a clear and simple message to your patients to quit smoking. If possible, provide a handout about health risks of smoking and benefits of quitting.

2 Elicit the *patient's* reasons for wanting to quit, and help him or her list these reasons as specifically as possible, such as:

- "I want to have more spending money."
- "I want to improve my health."
- "I want to make my sister proud."

Copy this list on index cards for the patient, and encourage him or her to carry 1 and post others around the house.

3 Prescribe pharmacotherapy, as supported by clinical trial results. Explain the rationale for its use, and encourage adherence. Review proper techniques for using NRT patches and gum, lozenge, inhaler, or nasal spray.

4 Teach the patient skills to cope with cravings. The "4 Ds" are a helpful mnemonic:

- Deep breathe.
- Drink fluids.
- Delay (smoking).
- Do something else.

Give the patient an index card listing the 4Ds, and help him or her memorize them.

5 Discuss the patient's smoking triggers and risky situations. These vary from patient to patient, but common triggers include:

- finishing a meal or drinking coffee
- seeing other people smoking
- psychological stressors or psychiatric symptoms such as anxiety or auditory hallucinations
- boredom, such as waiting for a bus.

Common risky situations include:

- going to a day treatment center where most patients and staff smoke

Table 3

CBT tools to help schizophrenia patients quit smoking

Create 'reasons to quit' card
Provide '4Ds' card of 'coping skills when I crave a cigarette' (deep breathe, drink fluids, delay (smoking), do something else)
Evaluate and practice problem-solving skills around 'triggers and risky situations'
Encourage patient to develop a '5 things I will do when I feel like smoking' card
Develop a detailed 'quit day' plan
Role-play cigarette refusal skills
Prepare a smoking cessation 'survival kit'

- visiting a family member who smokes
- dealing with a stressful situation.

Problem-solve with patients about how to cope with smoking triggers (*Table 4, page 72*). For example, switch from coffee to tea or "decaf," listen to music to cope with auditory hallucinations, use nicotine gum or lozenges while waiting for the bus, or surf the Internet at day treatment instead of going outside to smoke during breaks. Have patients make an index card with a list of "5 things I will do when I feel like smoking."

6 Set a quit date with a detailed "quit day" plan. When the patient has some mastery over triggers and risky situations, work with him or her to prepare for quit day (such as throw out cigarettes and lighters, tell family he or she will be quitting).

Plan the day, often hour by hour, to help the patient make new choices (such as go to the park in the morning instead of the convenience store, do a puzzle while watching TV at night). Schedule in some rewards and pleasant activities to substitute for cigarettes.

7 Work on 'refusal skills.' Patients will likely need to practice saying no to cigarettes offered to them in their social environments. Discuss these skills, and role-play to increase patients' likelihood of success.

8 Provide a 'survival kit' for use during the first week without cigarettes. Include

Clinical Point

To help the patient cope with craving, provide a card listing '4Ds': deep breathe, drink fluids, delay (smoking), or do something else



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Discuss rewards patients can give themselves (a new concept to many) to help them depend less on cigarettes for gratification

Table 4
6-step problem-solving skills to help prevent smoking relapse

Step (with sample therapist question)	Sample patient response
1. Identify the problem (What is the situation that is making it difficult for you to stay quit?)	I am tempted to buy cigarettes every time I walk by the convenience store in my neighborhood
2. Brainstorm solutions (What are some possible solutions?)	<ol style="list-style-type: none"> 1. Walk a different way to the bus so I don't pass the convenience store 2. Tell the people at the convenience store that I quit smoking 3. Don't carry extra money so I can't buy cigarettes
3. Evaluate pros and cons (What are the good things and the not-so-good things about each possible solution?)	Walking a different route to the bus: Pros: less temptation, more exercise Cons: longer trip, different routine Don't carry money: Pros: can't buy cigarettes Cons: can't buy other things; might need money in an emergency
4. Pick a solution (Which solution or combination of solutions looks the best?)	Walk a different way to the bus so I don't pass the store
5. Make a plan (What do you need to do to try it out?)	I need to test out other routes to the bus, set alarm earlier so have enough time for longer route
6. Rate the solution (How well did it work? Do you need to try something else?)	Since I planned my route in advance, I don't feel nervous about it. I think about cigarettes less in the morning now

tools to help with cravings and provide distractions, such as a small bag with sugarless gum or candy, toothpicks and straws to chew, rubber bands to keep hands busy, a water bottle, cough drops, healthy snacks, and a card with the 4 Ds.

9 Discuss rewards patients can give themselves instead of cigarettes. This concept will be new to many but is important to help patients depend less on cigarettes for gratification.

10 Call patients on their quit date or the day after to make sure they are on track.

CASE CONTINUED

An improving picture

With CBT, Mr. V grasped that he had to make important changes to quit smoking and reduce his risk of relapse. He embraced the "4 Ds" and successfully adhered to the plan for his quit date. He maintained abstinence through the 12-month relapse prevention treatment period with the same bupropion and NRT dosage he had used to quit smoking (and tapered CBT sessions).

After 12 months, Mr. V's bupropion dosage was tapered to 150 mg/d for 2 weeks and then discontinued, and the NRT patch was tapered to 14 mg/d for 2 weeks, 7 mg/d for 2 weeks, then discontinued. At the same time, he gradually decreased his use of short-acting nicotine gum.

Mr. V realized early in treatment that if he quit smoking he could save \$1,000 per year in the price of cigarettes. The camera he bought with the money he saved served as a motivator and helped alleviate the boredom that had kept him smoking.

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Bottom Line

Multifaceted treatment with pharmacotherapy and a 10-step cognitive-behavioral intervention increases the likelihood of smoking cessation in patients with schizophrenia. To reduce nicotine dependence, consider combining bupropion SR with patch and short-acting NRT. Develop a 'quit day' plan, teach coping skills, build in self-rewards, and provide cues written on index cards to reinforce abstinence.

Related Resources

- U.S. Public Health Service. Clinical practice guideline. Treating tobacco use and dependence. www.surgeongeneral.gov/tobacco/tobaqrg.htm.
- Agency for Healthcare Research and Quality. Treating tobacco use and dependence: clinician's packet. A how-to guide for implementing the Public Health Service Clinical Practice Guideline. www.ahrq.gov/clinic/tobacco.
- Massachusetts Department of Public Health. www.trytostop.org.
- Centers for Disease Control and Prevention. Tobacco Information and Prevention Source (TIPS). www.cdc.gov/tobacco.

Drug Brand Names

Benztrapine mesylate • Cogentin	Nicotine/polacrilex
Bupropion SR • Zyban	• Nicorette
Clozapine • Clozaril	Perphenazine • various
Lorazepam • Ativan	Varenicline • Chantix
Nicotine/transdermal	Ziprasidone • Geodon
• Nicotrol, Prostep	Zonisamide • Zonegram
Nicotine/nasal spray	
• Nicotrol NS	

Disclosures

Dr. Gottlieb reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Evins receives research support from Janssen Pharmaceutica.

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Clinical Point

Call patients on their quit date or the day after to make sure they are on track