Strategies to Help a Smoker Who Is Struggling to Quit

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PATIENT PRESENTATION
A 50-year-old man (hypothetical scenario) with hypertension and a history of depression treated with fluoxetine smokes 15 to 20 cigarettes daily. When asked about his interest in quitting smoking, he says, “I know that I should, but I’ve tried everything. Nothing works.” He used a nicotine patch for 5 days but discontinued because he still wanted a cigarette. While taking bupropion for a month, he reduced to 5 cigarettes daily but never achieved abstinence. He has heard that varenicline might be dangerous. He asks you what you think about him using an electronic cigarette.

COMMENT
Why Addressing Tobacco Use Matters
Tobacco use is the leading preventable cause of death worldwide. Stopping tobacco use benefits virtually every smoker. Most of the 19% of US residents who smoke want to quit and have tried to do so. Most individual quit attempts fail, but two-thirds of smokers use no treatment when trying to quit. Treating tobacco dependence is one of the most cost-effective actions in health care. With a brief intervention, physicians can prompt smokers to attempt to quit and connect them to evidence-based treatment that includes pharmacotherapy and behavioral support (ie, counseling). Physicians can link smokers to effective counseling support offered by a free national network of telephone quit lines. Smokers who use nicotine replacement therapy (NRT), bupropion, or varenicline when trying to quit double their odds of success. The most effective way to use NRT is to combine the long-acting nicotine patch with a shorter-acting product (lozenge, gum, inhaler, or nasal spray) and extend treatment beyond 12 weeks. Observational studies have not confirmed case reports of behavior changes associated with varenicline and bupropion, and these drugs’ benefits outweigh potential risks. A chronic disease management model is effective for treating tobacco dependence, which deserves as high a priority in health care systems as treating other chronic diseases like diabetes and hypertension.

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into health care delivery systems and becomes integrated into routine health care.6 Tobacco use should be recognized as a relapsing disorder that starts in childhood, fits the definition of a chronic condition or disease, and needs a long-term management approach.7

**Changing Patterns of Tobacco Use**

The decades-long decline in US tobacco prevalence has recently stalled. Change is occurring in tobacco products and in patterns of tobacco use.12 Today’s smokers, like the man in the hypothetical case, average only 15 cigarettes daily; 22% of smokers do not smoke every day.3 Increasingly, tobacco users combine products, usually cigarettes with smokeless tobacco,9 or counteract the rising cost of cigarettes by buying cigarillos, cigarette-sized cigars exempt from tobacco excise taxes, or by rolling their own tobacco. Smoking tobacco in a water pipe has migrated from the Middle East to US young adults who mistakenly believe it to be less harmful than smoking cigarettes.5 These changes reflect the effect of tobacco control policies that raised tobacco excise taxes, expanded smoke-free areas, and funded mass media campaigns.1,16 These policies altered social norms and made smoking less acceptable. More change is likely now that the US Food and Drug Administration (FDA) can regulate tobacco products.1

In response, the tobacco industry has developed new marketing strategies and introduced new noncombustible tobacco products that reduce exposure to toxins in tobacco smoke.6 Another new product is the electronic cigarette (e-cigarette), a battery-powered device that aerosolizes nicotine for inhalation but does not burn tobacco.13 Because the devices are unregulated, little is known about their benefits, risks, or even how much nicotine they deliver. Electronic cigarettes are likely to be less harmful to an individual than continued cigarette smoking. Whether they will help smokers quit, reduce smoking cigarettes, or just maintain nicotine dependence in the presence of smoking bans is unknown. Electronic cigarettes should benefit individuals who cannot stop smoking cigarettes by reducing their exposure to tobacco toxins, but the products’ net population impact is unclear. Electronic cigarettes might distract smokers who might otherwise quit from trying, reduce the effect of smoking bans on promoting nonsmoking social norms, and encourage young people to experiment with and become addicted to nicotine and subsequently to tobacco products.

**Challenges to Stopping Tobacco Use**

Most smokers say that they want to quit smoking.13 Many try to do so, but few seek help and most quit attempts fail.15 Yet more than half of US residents who have ever smoked have now quit, suggesting that most smokers who keep trying eventually succeed.6,13 In 2010, 69% of US smokers said that they wanted to quit smoking and 52% of smokers had tried to quit in the past year, but only 6% of those who tried to quit were nonsmokers 1 year later.13 About half of quit attempts fail within the first week.14 Smokers with other substance use, psychiatric disorders, and strong nicotine dependence are less likely to succeed in a quit attempt.13 Smokers who live with other smokers, have little social support for quitting, and have little confidence that they can succeed also tend to fail in smoking cessation attempts. Smoking the day’s first cigarette within 30 minutes of awakening is a clinically useful measure of stronger nicotine dependence.

The addictiveness of nicotine is a major reason why quit attempts fail. Inhaling cigarette smoke delivers nicotine rapidly to the brain, where it binds to midbrain nicotinic cholinergic receptors.16 This triggers the release of dopamine and other neurotransmitters that reinforce smoking and activities associated with smoking. Repeated smoking up-regulates nicotine receptors, producing tolerance to higher nicotine doses and nicotine withdrawal when levels fall.16 Except for cigarette craving, nicotine withdrawal symptoms (anxiety, depressed mood, irritability, restlessness, and insomnia) are nonspecific and often not recognized as nicotine withdrawal. When smoking a cigarette relieves these symptoms, smokers think that cigarettes reduce stress. To quit smoking, a smoker must overcome pharmacologic nicotine dependence, cope with nicotine withdrawal, and also extinguish strong behavioral associations with smoking.

Another reason why quit attempts fail is that only one-third of smokers who try to quit use any assistance.2 Population smoking cessation rates could be substantially improved by ensuring that evidence-based treatments were more often used by smokers trying to quit. This is a gap that clinicians and the health care delivery system are well positioned to fill.

**Tobacco Treatment Methods**

Effective methods for treating tobacco use have been identified from systematic evidence reviews conducted by the US Public Health Service and Cochrane Collaboration.4,17 Two treatment modalities have strong evidence of efficacy: behavioral support (ie, counseling) and pharmacotherapy (TABLE 1). Each is effective by itself, but combinations of the 2 are more effective than either alone because they assist smokers in different ways. Pharmacotherapy eases the physical discomfort of nicotine withdrawal and quells urges to smoke. Behavioral support enhances a smoker’s motivation and confidence and teaches practical quitting skills. A clear dose-response relationship exists between treatment intensity and quit success, but even brief interventions are effective.4 Neither hypnosis nor acupuncture has strong evidence of efficacy for smoking cessation.4,17

**Behavioral Support and Counseling**

Cognitive behavioral therapy improves the success rate of smokers who are ready to quit.4 Programs typically enhance motivation, bolster social support, and teach smokers to identify and manage nicotine withdrawal symptoms, cravings, and tempting situations. Smokers are usually advised to set a quit date in the near future. How-
ever, when smokers have a clear intention to quit, there is evidence that gradually reducing the number of cigarettes smoked (cut down to quit) may be as effective as abrupt cessation.20 Less is known about what to offer to smokers who are not ready to make a quit attempt, but motivational interviewing techniques have efficacy and are widely recommended.21

Behavioral support was developed for in-person delivery. Brief counseling by clinicians as part of routine care is effective (Table 1). An evidence-based approach is described in a subsequent section.4,22 More intensive counseling programs are more effective but attract few smokers. To broaden the reach and cost-effectiveness of behavioral support, in-person techniques were adapted for delivery by other channels, including telephones (voice and text), Internet, and social media.

Smoking cessation counseling by telephone has the longest history, has the strongest evidence base, and is the most widely used.21 It offers accessibility, convenience, and privacy to smokers. To be effective, it must be proactive, meaning that counselor-initiated calls are scheduled to fit a smoker's quit plan. In the United States, telephone counseling is available free through a system of state-based quit lines accessible with 1 toll-free number (1-800-QUITNOW).24,25 Many state quit lines also provide free samples of nicotine replacement.22 Quit lines welcome referrals from health care providers. Many offer fax-referral systems to permit clinicians to refer a smoker directly from the office to the quit line, which proactively calls the smoker to offer assistance.

Delivering behavioral support via newer modalities such as mobile phone text messaging or the Internet has a stronger evidence base.26-28 The Centers for Disease Control and Prevention Guide to Community Preventive Services recently judged mobile phone–based counseling as effective but web-based support as needing more evidence.29 Smoking cessation applications for smart phones exist but have not yet been evaluated.30

### Pharmacotherapy

Pharmacotherapy aids quitting by relieving nicotine withdrawal symptoms. The US Public Health Service guideline identified 3 categories of pharmacotherapy as first line: nicotine replacement therapy (NRT), bupropion (an atypical antidepressant), and varenicline (a selective nicotine receptor partial agonist; Table 1 and Table 2).29 Each is approved by the FDA as a smoking cessation aid. Smokers who use any first-line drug when making a quit attempt roughly double their odds of achieving long-term abstinence.4 Nortriptyline and clonidine also have evidence of efficacy but lack FDA approval for this indication and are second-line agents (Table 1).22 Selective serotonin reuptake inhibitor antidepressants or antianxiety agents have not demonstrated efficacy for treating tobacco use.4

Promising strategies to improve the efficacy of current drugs are to combine products, identify optimal dosing schedules, and improve medication adherence.33 These strategies improved the treatment success for other chronic diseases like hypertension or human immunodeficiency virus infection. There is good evidence that combining drugs improves quit rates and treating for longer durations may also improve outcomes.32,33,36,37

NRT. Nicotine replacement therapy delivers nicotine in a noncombustible form to alleviate nicotine withdrawal symptoms while a smoker stops using cigarettes. Five products are sold in the United States: 3 nonprescription prod-

#### Table 1. Efficacy of Methods Used to Treat Tobacco Dependence: Meta-analyses From the Cochrane Database of Systematic Reviews

<table>
<thead>
<tr>
<th>Method</th>
<th>Nonpharmacologic Methods vs Minimal or Usual Care, Risk Ratio (95% CI)</th>
<th>No. of Trials in Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonpharmacologic methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking cessation counseling</td>
<td>1.39 (1.24-1.57)</td>
<td>22</td>
</tr>
<tr>
<td>Individual</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group</td>
<td>1.98 (1.60-2.46)</td>
<td>13</td>
</tr>
<tr>
<td>Telephone quit line</td>
<td>1.57 (1.26-1.50)</td>
<td>9</td>
</tr>
<tr>
<td>Physician intervention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief advice to quit vs no advice or usual care</td>
<td>1.66 (1.42-1.94)</td>
<td>17</td>
</tr>
<tr>
<td>Brief counseling vs No advice or usual care</td>
<td>1.84 (1.60-2.13)</td>
<td>11</td>
</tr>
<tr>
<td>Brief advice</td>
<td>1.37 (1.20-1.56)</td>
<td></td>
</tr>
<tr>
<td>Pharmacologic methods vs Placebo or No Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>1.69 (1.53-1.85)</td>
<td>36</td>
</tr>
<tr>
<td>Varenicline</td>
<td>2.27 (2.02-2.55)</td>
<td>14</td>
</tr>
<tr>
<td>Nicotine replacement therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td>1.66 (1.53-1.81)</td>
<td>41</td>
</tr>
<tr>
<td>Gum</td>
<td>1.43 (1.33-1.53)</td>
<td>53</td>
</tr>
<tr>
<td>Lozenge</td>
<td>2.00 (1.63-2.45)</td>
<td>6</td>
</tr>
<tr>
<td>Inhaler</td>
<td>1.90 (1.36-2.67)</td>
<td>4</td>
</tr>
<tr>
<td>Nasal spray</td>
<td>2.02 (1.49-3.73)</td>
<td>4</td>
</tr>
<tr>
<td>Second-line drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>2.03 (1.48-2.78)</td>
<td>6</td>
</tr>
<tr>
<td>Clonidine</td>
<td>1.63 (1.22-2.18)</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviation: SR, sustained release.

The data from this table are based on studies in the Cochrane database.19

First-line drugs are all approved by the US Food and Drug Administration (FDA) as smoking cessation aids and recommended as first-line drugs by the 2008 US Public Health Service guideline.4

Second-line drugs classified as second-line by the 2008 US Public Health Service guideline have evidence of efficacy in a systematic review but are not approved by the FDA as smoking cessation aids and have more concerns about potential adverse effects than first-line drugs.4

Nortriptyline was used at doses of 75 to 100 mg/d for 6 to 12 weeks in smoking cessation trials.4

Studies of clonidine for smoking cessation are older, have potential sources of bias, and found a high incidence of dose-dependent adverse effects (dry mouth and sedation).4

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STRAIGHT TO QUIT SMOKING

ucts (skin patch, gum, and lozenge) and 2 prescription-only products (oral inhaler and nasal spray). Because no NRT product is absorbed through the lungs, none reproduces a cigarette’s rapid delivery of nicotine to the arterial circulation, which contributes to the addictiveness of cigarettes. Therefore, NRT dependence potential is low. Nevertheless, fears that NRT is addictive or causes cancer are common barriers to smokers’ use of the products.38 Because NRT products have 2 distinct patterns of nicotine delivery, there is a rationale for combining them to improve efficacy. The patch has a slow onset, but produces steady nicotine levels for 16 or 24 hours. It offers prolonged withdrawal relief without requiring frequent administration, is the simplest product to use, and has the best adherence. However, the user has no control of nicotine levels once the patch is applied and no way to respond to cigarette cravings by administering more nicotine as cigarette smokers do throughout a day to maintain comfort and avoid nicotine withdrawal.

The other 4 NRT products have a more rapid onset but shorter duration of action, requiring repeated administration to maintain stable nicotine blood levels and withdrawal relief. The nasal spray has the most rapid onset of action (3-10 minutes to peak nicotine level), but its use is limited by local ir-

Table 2. Drugs Used to Treat Tobacco Dependence

<table>
<thead>
<tr>
<th>Drug</th>
<th>How Sold</th>
<th>Dose</th>
<th>Duration, mo</th>
<th>Common Adverse Effects</th>
<th>Advantages</th>
<th>Disadvantages and Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Prescription only; brand: Wellbutrin SR</td>
<td>150 mg/d for 3 days, then 150 mg/2d Start 1 wk before quit date</td>
<td>3-6b</td>
<td>Insomnia, vivid or abnormal dreams, or dry mouth</td>
<td>Blunts postcessation weight gain while being used Oral agent</td>
<td>Increases suicide risk FDA boxed warning about adverse psychiatric effects32</td>
</tr>
<tr>
<td>Nicotine patch</td>
<td>OTC: Prescription: generic; nicotrol; brand: Nicoderm CQ</td>
<td>Apply new patch daily 21 mg for ≥10 cig/d, 14 mg for &lt;10 cig/d Taper to lower dose after 4-6 wk</td>
<td>≥2-3d</td>
<td>Skin irritation, insomnia</td>
<td>Provides steady nicotine level Easiest nicotine product to use</td>
<td>Nicotine released slowly User cannot alter nicotine level in case of craving</td>
</tr>
<tr>
<td>Nicotine gum</td>
<td>OTC: Prescription: generic; brand: Nicorette</td>
<td>1 piece every hour 2 mg for &lt;25 cig/d, 4 mg for ≥25 cig/d ≤24 pieces/d</td>
<td>≥3d</td>
<td>Mouth irritation, jaw soreness, or heartbeat</td>
<td>User controls nicotine dose Oral substitute for cigarettes</td>
<td>Proper chewing technique required Can damage dental work Difficult for denture wearers to use No food or drink for 30 min before use and during use</td>
</tr>
<tr>
<td>Nicotine lozenge</td>
<td>OTC: generic; brand: Commit</td>
<td>1 piece every 1-2 h 2 mg if first cigarette ≥30 min after waking 4 mg if first cigarette &lt;30 min after waking</td>
<td>3-6</td>
<td>Hiccups or heartburn</td>
<td>User controls nicotine dose Can be used by smokers with poor dentition or dentures</td>
<td>No food or drink for 30 min before use and during use</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>Prescription only; Nicotrol inhaler</td>
<td>Inhaler as needed Like 6-16 cartridges daily</td>
<td>≤6</td>
<td>Mouth and throat irritation</td>
<td>User controls nicotine dose Oral substitute for cigarettes</td>
<td>Frequent puffing required Device visible when being used</td>
</tr>
<tr>
<td>Nicotine NS</td>
<td>Prescription only; Nicotrol NS</td>
<td>Apply once to each nostril 1-2/h ≤40 applications daily</td>
<td>3-6</td>
<td>Nasal irritation, sneezing, cough, or teary eyes</td>
<td>User controls nicotine dose Most rapid delivery of nicotine</td>
<td>Local irritation to nasal mucosa is difficult for many to tolerate</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Prescription only; Chantix</td>
<td>0.5 mg/d for 3 days, then 0.5 mg 2d for 4 days, then 1 mg 2d Start 1 wk before quit date</td>
<td>3-6b</td>
<td>Nausea, insomnia or vivid or abnormal dreams</td>
<td>Dual action: relieves nicotine withdrawal and blocks reward from smoking Oral agent</td>
<td>FDA boxed warning about adverse psychiatric effects FDA communication about potential CVD risk Reduce dose in moderate to severe renal insufficiency</td>
</tr>
</tbody>
</table>

Abbreviations: CQ, committed quitter; FDA, US Food and Drug Administration; NS, nasal spray; OTC, over-the-counter (nonprescription) sale; SR, sustained release.

*All drugs are approved by the FDA as smoking cessation aids and recommended as first-line drugs by the US Public Health Service guidelines.32

*If smoker is abstinent at end of 12 weeks, he/she can extend use to 6 mo.

*FDA requires boxed warnings for the Chantix and Zyban.31

*Two trials suggest a benefit from extending nicotine patch treatment to 6 mo.32,33 Clinically, nicotine gum use is also often extended beyond 3 mo.

*User chews gum slowly until taste change indicates nicotine is being released, then places gum between cheek and gum until taste disappears. Gum is chewed intermittently, just enough to maintain nicotine release. Discard gum after 30 minutes of chewing.

*Brand name outside the United States is Champix.

*FDA updates to drug labels.32

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ritation from spraying nicotine onto nasal mucosa. Nicotine in the gum, lozenge, and oral inhaler is absorbed through the oropharynx, reaching peak levels in 20 to 30 minutes. The user can regulate nicotine blood levels by adjusting the administration of these shorter-acting products, but users often fail to administer the products often enough to produce stable nicotine blood levels or reliable levels of withdrawal relief. Furthermore, short-acting products except the lozenge require training for proper use, which reduces adherence.

Combining the patch with the shorter-acting NRT products is safe and more effective than using a single NRT product (Table 3). The US Public Health Service clinical guideline recommends combinations.

Evidence is accumulating that other novel ways of administering NRT can improve quit rates. This includes prolonging treatment beyond the standard 8-week duration and continuing rather than discontinuing NRT use after a setback (ie, smoking a cigarette). Some (but not all) studies find better efficacy for starting NRT 2 weeks ahead of the quit day rather than on the quit day. Preliminary evidence even suggests that offering NRT to smokers who want to cut down but not to quit might lead some of them to quit. Despite this evidence, the FDA label for NRT products still warns smokers against combining products, starting NRT before the quit date, and smoking while using NRT. These restrictions reflect early concerns about causing nicotine overdose or sustaining dependence that proved unfounded. These outdated restrictions can dissuade smokers from the most effective uses of NRT. In the United Kingdom, NRT is licensed for combination use and for reducing smoking prior to cessation.

**Bupropion**. Bupropion, an atypical antidepressant that increases dopamine levels in mesolimbic pathways in the central nervous system that are also activated by other drugs of dependence, increases smoking cessation rates independent of its antidepressant effect. Bupropion is associated with an increased risk of seizure, occurring in 0.1% of smokers. It is contraindicated in smokers with a seizure disorder. A potentially helpful property of bupropion is its ability to temporarily blunt postcessation weight gain. Weight is regained after stopping the drug. Nevertheless, this property makes it attractive to smokers with weight concerns. There is inconclusive evidence that adding bupropion to NRT increases long-term cessation; nevertheless, it is done in practice (Table 3).

**Varenicline**. Varenicline is a selective partial agonist at the α4β2 nicotinic receptor subtype that mediates nicotine dependence. As a partial agonist, it relieves nicotine withdrawal symptoms while blocking the reinforcement of smoking by preventing nicotine from binding to the α4β2 receptor. Varenicline demonstrated efficacy for smoking cessation in multiple placebo-controlled randomized trials, had better long-term efficacy than bupropion in 2 head-to-head randomized trials and had marginally better long-term efficacy than the nicotine patch in one open-label randomized trial. Varenicline and combination NRT have not been directly compared in a clinical trial. Combining varenicline with bupropion or NRT might improve its efficacy and is being studied (Table 3). Combinations were tolerable in preliminary studies.

Concerns about varenicline’s safety arose from postmarketing case reports of behavior changes in smokers taking varenicline. In 2009, the FDA reviewed case reports for all smoking cessation drugs and reported that varenicline and bupropion, but not NRT, were “associated with reports of changes in behavior such as hostility, agitation, depressed mood, and suicidal thoughts or actions.” Both bupropion and varenicline were required to add black-box warnings to their labels.

Stopping smoking produces nicotine withdrawal symptoms that include depressed mood, anxiety, and irritability. Case reports of these symptoms in a smoker who is taking a smoking cessation drug cannot distinguish whether the cause is nicotine withdrawal or the drug. Pooled analysis of 10 randomized double-blind placebo-controlled varenicline trials enrolling more than 3000 smokers did not detect these adverse effects, but the studies excluded smokers with depression and other mental illness who might

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**Table 3. Potential Medication Combinations for Treating Tobacco Dependence**

<table>
<thead>
<tr>
<th>Medication Combination</th>
<th>Rationale</th>
<th>Well Tolerated</th>
<th>Efficacy Over Single Agent</th>
<th>FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 nicotine replacement product: nicotine patch + nicotine gum, lozenge, inhaler or spray</td>
<td>Combining products with different nicotine delivery profiles produces better relief of nicotine withdrawal. Patch has a slow-onset, long-acting pattern. Other products have a faster-onset, shorter-acting pattern.</td>
<td>Yes</td>
<td>Yes</td>
<td>No but endorsed by USPHS Clinical Guideline</td>
</tr>
<tr>
<td>Bupropion + nicotine replacement</td>
<td>Different and complementary mechanisms of action in CNS</td>
<td>Yes</td>
<td>Evidence mixed</td>
<td>Yes</td>
</tr>
<tr>
<td>Bupropion + varenicline</td>
<td>Different and complementary mechanisms of action in CNS</td>
<td>Yes</td>
<td>Under study</td>
<td>No</td>
</tr>
<tr>
<td>Varenicline + nicotine replacement</td>
<td>Uncertain: Varenicline dose may not saturate α4β2 nicotinic receptors</td>
<td>Yes</td>
<td>Unknown</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; USPHS, US Public Health Service.

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be more vulnerable to developing adverse psychiatric effects while taking varenicline.51 Varenicline was well tolerated by participants in 2 subsequent small trials that together enrolled 240 smokers with schizophrenia.52,53 A retrospective analysis of the UK General Practice Research Database found no excess risk of suicides, suicidal thoughts or attempts, or new antidepressant prescriptions in patients starting varenicline or bupropion compared with NRT.4,54 Similar analyses using the US Veterans Administration and Military Health System databases detected no difference in rates of psychiatric hospitalization for 30 days after smokers started varenicline or NRT.55,56 Although reassuring, these observational studies were limited by the small number of psychiatric events and potential residual confounding. A large clinical trial to further evaluate the risk is ongoing.31,55

In 2011, a meta-analysis of varenicline trials reported an association of varenicline with increased cardiovascular events, though the absolute risk and risk difference were small.57 The FDA subsequently issued a warning that varenicline might increase the risk of cardiovascular events in patients with cardiovascular disease.58 However, the meta-analysis had methodological limitations,59 and a subsequent meta-analysis found no significant association.60

Meanwhile, clinicians and patients must decide whether and which patients should take varenicline (or bupropion). As with all drugs, this decision requires balancing risks and benefits. Varenicline and bupropion are 2 of very few effective drugs available to treat tobacco dependence, an undoubtedly hazardous behavior. The FDA said in October 2011, its most recent statement: "The Agency continues to believe that varenicline’s benefits outweigh the risks and the current warnings in the Chantix drug label are appropriate." Clinicians who prescribe varenicline should monitor patients’ behavior and mood, especially participants with current or past psychiatric diagnoses. Combination NRT is an alternative for individuals in whom varenicline is considered potentially risky.

Incorporating Tobacco Treatment Into the Health Care System
Addressing tobacco use in health care settings has a strong evidence base. Clinician advice to stop smoking prompts smokers to make quit attempts and increases quit rates.3–23 Brief counseling is more effective than advice alone, and cessation rates rise with increasing counseling intensity (duration or frequency).3–23 Brief counseling during prenatal care visits is effective butcessations rates are modest.61 Using smoking cessation medication during pregnancy is controversial because the evidence of efficacy and safety is limited and inconclusive, but NRT or bupropion is sometimes used for pregnant smokers who do not quit with nonpharmacologic methods alone (Table 1).61 Systematic identification of smoking status increases clinicians’ delivery of advice and counseling.4 Health systems must now identify patients’ smoking status to meet US government criteria for the “meaningful use” of electronic health records.58 A practical evidence-based 5-step strategy to guide health care providers’ efforts during an office visit, the “5 As,” direct clinicians to ask all patients about smoking status, advise all smokers to quit, assess readiness to quit, assist quitting, and arrange for follow-up.4 Some clinicians argue that it is as or more effective to simply offer effective smoking cessation treatments to every smoker rather than first asking about a smoker’s interest in quitting.63 Only 48% of smokers who saw a physician in 2010 recalled receiving advice to stop smoking.12 The competing demands on a clinician’s limited time at an office visit are an obstacle to better performance. To compensate, newer models distribute the 5A tasks across the health care team, allowing physicians to focus on their special role: providing advice to quit, encouraging a quit attempt, making tailored treatment recommendations, and recommending specific treatment resources. Identifying smoking status and providing treatment and follow-up can be delegated to other practice-based staff, to a health system–based tobacco coordinator, or to community resources. The national network of free telephone quit lines is the most accessible external resource; quit lines welcome referrals from clinician offices and may offer free samples of NRT.24,25 These strategies focus on actions triggered by a single visit. A better strategy for treating the chronic relapsing condition of tobacco dependence might be a longitudinal chronic care management model like those used to manage other chronic diseases. In this model, treatment offered during an office visit or hospitalization would be sustained and coordinated over time and across settings of care. A longitudinal model that offered telephone counseling and NRT to smokers repeatedly over 1 year improved short- and long-term smoking cessation rates over standard visit-based treatment in 1 randomized trial.64 A population management strategy that proactively offered barrier-free treatment to known smokers independent of their health care visits was promising in another randomized trial.65 These are examples of how treating tobacco dependence can be incorporated into new models of health care delivery. As the leading preventable cause of death, treating tobacco use deserves as high a priority in health care as treating diabetes, hypertension, and other major chronic diseases.

CONCLUSION
This case scenario is typical: a smoker who wants to quit has little self-confidence that he can do so because past quit attempts failed and he believes that he has “tried everything.” In fact, he has not tried everything. He has never used behavioral support, combination pharmacotherapy, or varenicline, and his trial of NRT was inadequate. Behavioral support is essential in view of his low self-confidence. It could be encouraged and arranged by referral from the clinician’s office to a
free telephone quit line. I would discourage his use of the electronic cigarette because of the absence of scientific data on its safety or efficacy for cessation and the existence of FDA-approved effective options that he has not tried. In place of an unapproved nicotine delivery device, he could combine the nicotine patch with his choice of lozenge, gum, or inhaler. Alternatively, he could try varenicline, which is appropriate if his psychiatric status is stable, careful follow-up is ensured, and his concerns about using varenicline can be allayed. Combining bupropion and NRT is another option since he had partial success with bupropion in the past, and bupropion can be used in individuals taking selective serotonin reuptake inhibitors. Whatever his next step, it is important to encourage him to keep trying, assure him that he can succeed, monitor his progress, and continue to offer help at each visit.

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