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Strategies to Help a Smoker Who is Struggling to Quit

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Abstract

Tobacco use is the leading preventable cause of death worldwide. Stopping tobacco use benefits virtually every smoker. Most of the 19% of Americans 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 (i.e., counseling). Physicians can link smokers to effective counseling support offered by a free national network of telephone quitlines (1-800-QUIT-NOW). Smokers who use nicotine replacement (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, 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.

Case[a]

A 50 year-old male with hypertension and a history of depression treated with fluoxetine smokes 15–20 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 what you think about him using an electronic cigarette.

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[a]A hypothetical case representing common challenges seen in smokers whom the author has treated.

Why addressing tobacco use matters

Tobacco use is the leading preventable cause of illness and death worldwide.[1] In the U.S, it adds $96 billion in medical costs annually to health care spending and it contributes to unacceptable socioeconomic disparities in chronic disease burden because individuals with less education and lower incomes are more likely to smoke.[1,2] In 2010, 19.3% of U.S. adults, or 45 million people, smoked cigarettes.[2] Approximately half of them will die of a tobacco-related disease, losing an average of 10 years of life.[3]

Fortunately, smoking cessation benefits virtually all smokers, no matter how heavily or how long they have smoked or how ill or old they are when they stop.[5] After a myocardial infarction, for example, smokers' cardiovascular mortality falls by 36% over two years if they stop smoking.[6] Current evidence-based therapies to treat smokers are among the most cost-effective actions in health care.[5] Encouraging their use should be a high priority for physicians, health care systems, payers, and policymakers.

Making tobacco treatment an integral part of the delivery of high-quality health care is the challenge. It requires embedding tobacco treatment into the infrastructure of health care delivery systems so that it becomes routine care.[7] It also requires recognizing that tobacco use, as a relapsing disorder that starts in childhood, fits the definition of a chronic condition or disease and needs a long-term management approach.[8]

Changing patterns of tobacco use

The decades-long decline in U.S. tobacco prevalence has recently stalled, but change is occurring in tobacco products and in patterns of tobacco use.[1,2] Today's smokers average only 15 cigarettes daily and 22% of smokers do not smoke every day.[2] 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 cigarettes. Smoking tobacco in a waterpipe has migrated from the Middle East to U.S. young adults who mistakenly believe it to be less harmful than smoking cigarettes.[10] These changes reflect the impact of tobacco control policies that raised tobacco excise taxes, expanded smoke-free areas, and funded mass media campaigns.[1,11] They altered social norms and made smoking less acceptable. More change is likely now that the U.S. Food and Drug Administration (FDA) can regulate tobacco products.[1]

In response, the tobacco industry has developed new marketing strategies and introduced new smokeless tobacco products that reduce exposure to toxins in tobacco smoke.[9] Another new product is the electronic cigarette (e-cigarette), a battery-powered device that aerosolizes nicotine for inhalation but does not burn tobacco.[12] Because the devices are unregulated, little is known about their benefits, risks, or even how much nicotine theydeliver. 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. Principal concerns are that they will distract smokers who might otherwise quit from trying, reduce

the effect of smoking bans on promoting non-smoking 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.[4] Many try to do so, but few seek help and most quit attempts fail.[4] Yet, more than half of Americans who have ever smoked have now quit, suggesting that most smokers who keep trying eventually succeed.[2,13] In 2010, 69% of U.S. 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 one year later.[4] 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,[15] as are smokers who live with other smokers, have little social support for quitting and little confidence that they can succeed. 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 upregulates 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 U.S. Public Health Service (USPHS) and Cochrane Collaboration.[5,17] Two treatment modalities have strong evidence of efficacy, behavioral support (i.e., counseling) and pharmacotherapy. (Table 1) Each is effective by itself, but combinations of the two 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.[5] Neither hypnosis nor acupuncture has strong evidence of efficacy for smoking cessation.[5,17]

Behavioral Support and Counseling

Cognitive-behavioral therapy improves the success rate of smokers who are ready to quit.[5] 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. However, gradually reducing the number of cigarettes smoked may be as effective as abrupt cessation when smokers have a clear intention to quit.[18] 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.[5,19]

Behavioral support was developed for in-person delivery. Brief counseling by clinicians as part of routine care is effective, and an evidence-based approach is described in a subsequent section.[5,20] 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, strongest evidence base and is 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 U.S., telephone counseling is available free through a system of state-based quitlines accessible with one toll-free number (1-800-QUIT-NOW [1-800-784-8669]).[22, 23] Many state quitlines also provide free samples of nicotine replacement.[23] Quitlines welcome referrals from health care providers. Many offer fax-referral systems to permit clinicians to refer a smoker directly from the office to the quitline, 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 smaller evidence base.[24–26] The CDC Guide to Community Preventive Services recently judged mobile phone-based counseling as effective but web-based support as needing more evidence.[27] Smoking cessation applications for smart phones exist but have not yet been evaluated.[28]

Pharmacotherapy

Pharmacotherapy aids quitting by relieving nicotine withdrawal symptoms. The USPHS guideline identified three categories of pharmacotherapy as first line: nicotine replacement therapy (NRT), bupropion (an atypical antidepressant), and varenicline (a selective nicotine receptor partial agonist)(Tables 1 and 2).[5] 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.[5] Nortriptyline and clonidine also have evidence of efficacy but lack FDA approval for this indication and are second-line agents (Table 1).[5] SSRI antidepressants or antianxiety agents have not demonstrated efficacy for treating tobacco use.[5]

Promising strategies to improve the efficacy of current drugs are to combine products, identify optimal dosing schedules, and improve medication adherence.[29] These strategies improved the treatment success for other chronic diseases like hypertension or HIV infection. There is good evidence that combining drugs improves quit rates and treating for longer durations may also improve outcomes.[30–33]

Nicotine replacement therapy (NRT)

NRT delivers nicotine in a non-inhaled form to alleviate nicotine withdrawal symptoms while a smoker stops using cigarettes. Five products are sold in the U.S.: three nonprescription products (skin patch, gum, and lozenge) and two 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 (Figure). Therefore, NRT's dependence potential is low. Nonetheless, fears that NRT is addictive or causes cancer are common barriers to smokers' use of the products.[34]

Because NRT products have two 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 four 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 (5–10 minutes to peak nicotine level) but its use is limited by local irritation from spraying nicotine onto nasal mucosa. Nicotine in the gum, lozenge, and oral inhaler is absorbed through the oropharynx, reaching peak levels in 20–30 minutes. The user can regulate nicotine blood levels by adjusting the administration of these shorter-acting products, but usersoften 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).[5,32–33, 35–36] The USPHS clinical guideline recommends combinations.[5] Evidence is accumulating that other novel ways of administering NRT can improve quit rates. This includes prolonging treatment beyond the standard 8-week duration[30,31] and continuing rather than discontinuing NRT use after a slip (smoking a cigarette).[37] Some (but not all) studies find better efficacy for starting NRT two weeks ahead of the quit day rather than on the quit day.[35,38] 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.[39] 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 UK, NRT is licensed for combination use and for reducing smoking prior to cessation.

Bupropion

Bupropion, an atypical antidepressant that increases dopamine levels in CNS mesolimbic pathways also activated by other drugs of dependence, increases smoking cessation rates independent of its antidepressant effect.[5,40] Bupropion is associated with an increased risk of seizure, occurring in 0.1% of smokers.[40] It is contraindicated in smokers with a seizure disorder.[40] A potentially helpful property of bupropion is its ability to temporarily blunt post-cessation weight gain. Weight is regained after stopping the drug. Nonetheless, this property makes it useful for smokers with weight concerns. There is inconclusive evidence that adding bupropion to NRT increases long-term cessation, but it is done in practice (Table 3).[40]

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 controlled trials,[41] had better long-term efficacy than bupropion in two head-to-head randomized trials,[42,43] and had marginally better long-term efficacy than the nicotine patch in one open-label randomized trial.[44] 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.[45,46]

Concerns about varenicline's safety arose from post-marketing 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."[47] 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 over 3000 smokers did not detect these side effects, but the studies excluded smokers with depression and other mental illness who might be more vulnerable to developing psychiatric side effects on varenicline.[48] Varenicline was well tolerated in two subsequent small trials which together enrolled 240 smokers with schizophrenia.[49,50] 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 to NRT.[5,51] 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.[52,53] While 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.[47,52]

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.[54] The FDA subsequently issued a warning that varenicline might increase the risk of cardiovascular events in patients with cardiovascular disease.[55] However, the meta-analysis had methodologic limitations,[56] and a subsequent meta-analysis found no significant association.[57] Meanwhile, clinicians and patients must decide whether and in which patients to use varenicline (or bupropion). As with all drugs, this decision requires balancing risks and benefits. Varenicline and bupropion are two of very few effective drugs available to treat tobacco dependence, an undoubtedly hazardous behavior. The FDA's most recent statement, from October 2011, was, "the Agency continues to believe that varenicline's benefits outweigh the risks and the current warnings in the Chantix drug label are appropriate."[52] Clinicians who prescribe varenicline should monitor patients' behavior and mood, especially those 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.[5,21], Brief counseling is more effective than advice alone, and cessation rates rise with increasing counseling intensity (duration or frequency).[5,21] (Table 1) Brief counseling during prenatal care visits is effective but cessations rates are modest.[58] Using smoking cessation medication in pregnancy is controversial because the evidence of efficacy and safety is limited and inconclusive.[58]

Systematic identification of smoking status increases clinicians' delivery of advice and counseling.[5] Health systems must now identify patients' smoking status to meet U.S. government criteria for the "meaningful use" of electronic health records.[59] A practical evidence-based five-step strategy to guide healthcare providers' efforts at an office visit, the "5A's,"direct clinicians to ***ask*** all patients about smoking status, ***advise*** all smokers to quit and ***assess*** readiness to quit, ***assist*** quitting, and ***arrange*** follow-up.[5] It may be as or more effective to simply offer to help every smoker use available, effective smoking cessation treatments rather than first asking about a smoker's interest in quitting.[60]

Only 48% of smokers who saw a physician in 2010 recalled receiving advice to stop smoking.[4] 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, and recommending 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 quitlines is the most accessible external resource; quitlines welcome referrals from clinician offices and may offer free samples of NRT.[22,23]

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 one year improved short and long-term smoking cessation rates over standard visit-based treatment in one randomized trial.[61] 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.[62] 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, tobacco use deserves as high a priority in health care as treating diabetes, hypertension, and other major chronic diseases.

Case, revisited

The case illustrates a common scenario: a smoker who wants to quit, has little self-confidence that he can do so because past quit attempts failed, and 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 your office to a free telephone quitline. I would discourage 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. Alternately, he could try varenicline, which is appropriate if his psychiatric status is stable, careful follow-up is insured, 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 SSRIs. 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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Table 1

Efficacy of Methods Used to Treat Tobacco Dependence: Meta-analyses from the Cochrane Database of Systematic Reviews [a]

Non-pharmacologic interventions	**Risk ratio vs. minimal treatment/usual care** ***(95% Confidence interval)***	**Number of trials in meta-analysis**
Smoking cessation counseling		
In person		
Individual	1.39 (1.24–1.57)	22
Group	1.98 (1.60–2.46)	13
Telephone quitline	1.37 (1.26–1.50)	9
Physician intervention		
Brief advice to quit		
vs. no advice or usual care	1.66 (1.42–1.94)	17
Brief counseling		
vs. no advice or usual care	1.84 (1.60–2.13)	11
vs. brief advice	1.37 (1.20–1.56)	
Pharmacologic interventions	**Risk ratio vs. placebo or no treatment** ***(95% Confidence interval)***	
1st line drugs[b]		
Bupropion (sustained release)	1.69 (1.53–1.85)	36
Varenicline	2.27 (2.02–2.55)	14
Nicotine replacement		
Nicotine patch	1.66 (1.53–1.81)	41
Nicotine gum	1.43 (1.33–1.53)	53
Nicotine lozenge	2.00 (1.63–2.45)	6
Nicotine inhaler	1.90 (1.36–2.67)	4
Nicotine nasal spray	2.02 (1.49–3.73)	4
2nd line drugs [c]		
Nortriptyline [d]	2.03 (1.48–2.78)	6
Clonidine [e]	1.63 (1.22–2.18)	6

[a] Source: http://summaries.cochrane.org/

[b] 1st line drugs are all approved by the U.S. Food and Drug Administration as smoking cessation aids and recommended as first-line drugs by the 2008 U.S. Public Health Service guideline.[5]

[c] Drugs classified as 2nd line by the 2008 U.S. Public Health Service guideline have evidence of efficacy in a systematic review but are not approved by the U.S. Food and Drug Administration as smoking cessation aids and have more concerns about potential side effects than 1st line drugs.[5]

[d] Nortriptyline was used at doses of 75–100 mg/d for 6–12 weeks in smoking cessation trials.[5]

[e] Studies of clonidine for smoking cessation are older, have potential sources of bias, and found a high incidence of dose-dependent side effects (dry mouth and sedation).[63]

Table 2

Drugs Used to Treat Tobacco Dependence [a]

Drug	How Sold	Dose	Duration	Common side effects	Advantages	Disadvantages and Warnings
Bupropion sustained release	• Prescription only • Generic, Zyban, Wellbutrin SR	• 150 mg daily × 3 d, then 150 mg twice daily. • Start 1 wk before quit date	3–6 mo [b]	• Insomnia, • Vivid or abnormal dreams • Dry mouth	• Blunts post-cessation weight gain while being used • Oral agent	• Increases seizure risk • FDA boxed warning about psychiatric side effects [c]
Nicotine patch 21mg, 14mg, 7mg	• OTC,[d] prescription • Generic, Nicotrol, Nicoderm CQ	• Apply 1 new patch daily 21mg for ≥10 cig/day, 14mg for <10 cig/day. • Taper to lower dose after 4–6 wk	2–3 mo or more [e]	• Skin irritation, • insomnia	• Provides steady nicotine level • Easiest nicotine product to use	• Nicotine released slowly. • User cannot alter nicotine level in case of craving
Nicotine gum 2mg, 4mg	• OTC[d], prescription • Generic, Nicorette	• 1 piece every hour 2mg for <25 cig/day 4mg for ≥25 cig/day • Up to 24 pieces/day	3 mo or more [e]	• Mouth irritation • Jaw soreness • Heartburn	• User controls nicotine dose • Oral substitute for cigarettes	• Proper chewing technique required [f] • Can damage dental work • Difficult for denture wearers to use • No food or drink for 30min before use and during use
Nicotine lozenge 2mg, 4mg	• OTC[d] • Generic, Commit	• 1 piece every 1–2 hr 2mg if 1st cigarette ≥30 min after waking 4mg if 1st cigarette	3–6 mo	• Hiccups • Heartburn	• User controls nicotine dose • Can be used by smokers with poor	• No food or drink for 30min before use and during use

Drug	How Sold	Dose	Duration	Common side effects	Advantages	Disadvantages and Warnings
		<30 min after waking <30 min after waking <30 min after waking			dentition or dentures	
Nicotine inhaler 4 mg/ cartridge	• Prescription only • Nicotrol inhaler	• Inhale as needed, • Use 6–16 cartridges daily	Up to 6mo	• Mouth and throat irritation	• User controls nicotine dose • Oral substitute for cigarettes	• Frequent puffing required • Device visible when being used
Nicotine nasal spray	• Prescription only • Nicotrol NS	• Apply once to each nostril 1–2 times/hour. • Up to 40 applications daily	3–6 mo	• Nasal irritation • Sneezing, cough, • Teary eyes	• User controls nicotine dose • Most rapid delivery of nicotine	• Local irritation to nasal mucosa is difficult for many to tolerate
Varenicline	• Prescription only • Chantix [g]	• 0.5 mg daily × 3 d, then 0.5 mg twice daily × 4 d, then 1 mg twice daily. • Start 1 wk before quit date	3 –6 mo [b]	• Nausea • Insomnia • Vivid or abnormal dreams	• Dual action: relieves nicotine withdrawal and blocks reward from smoking • Oral agent	• FDA boxed warning about psychiatric side effects [c] • FDA communication about potential CVD risk [h] • Reduce dose in moderate to severe renal insufficiency

[a] All drugs are approved by the U.S. Food and Drug Administration as smoking cessation aids and recommended as first-line drugs by the U.S. Public Health Service guidelines.[5]

[b] If smoker is abstinent at end of 12 weeks, he/she can extend use to 6 months

[b] Public Health Advisory: FDA Requires New Boxed Warnings for the Smoking Cessation Drugs Chantix and Zyban. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169986.htm

[d] OTC = over-the-counter (non-prescription) sale

[e] Two trials suggest a benefit from extending nicotine patch treatment to 6 months.[30,31] Clinically, nicotine gum use is also often extended beyond 3 months.

[f] 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 min of chewing.

[g] Brand name outside US is Champix

[h] FDA Drug Safety Communication: Chantix (varenicline) drug label now contains updated efficacy and safety information http://www.fda.gov/Drugs/DrugSafety/ucm264436.htm

Table 3

Potential Medication Combinations for Treating Tobacco Use

Medication Combination	Rationale	Well Tolerated?	More Effective than Single Agent?	FDA approval
≥ 1 Nicotine replacement product: Nicotine Patch + (Nicotine gum, lozenge, inhaler or spray)	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.	Yes[5,31]	Yes,[29–31]	No but endorsed by 2008 USPHS Clinical Guideline[5]
Bupropion + Nicotine replacement	Different and complementary mechanisms of action in CNS	Yes[5,35]	Evidence mixed[5,35]	Yes
Bupropion + Varenicline	Different and complementary mechanisms of action in CNS	Yes[41]	Under study	No
Varenicline + Nicotine replacement	Uncertain. Varenicline dose may not saturate all CNS 4β2 nicotinic receptors.	Yes[40]	Unknown	No