Published in final edited form as:
CA Cancer J Clin. 2009 ; 59(5): 314–326. doi:10.3322/caac.20031.

Treating Tobacco Dependence in a Medical Setting

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Abstract

The US Public Health Service Guideline for Treating Tobacco Use and Dependence 2008 Update emphasizes tobacco use as a chronic medical disorder; highlights both behavioral counseling and the use of 1 or more of the 7 approved medications; and points out the utility, efficacy, and reach of telephone quitlines. The treatment of users of smokeless tobacco continues to be less than optimal. Although providing evidence-based treatment for tobacco-dependent patients is a challenge for busy physicians, a team approach including trained and certified tobacco treatment specialists (TTS) provides an efficient treatment model. TTS represent a new and growing part of the health care team and hold great potential for expanding the collective tobacco treatment expertise in the medical setting. The effective treatment of tobacco dependence frequently requires tailoring, and often intensifying, interventions (both counseling and pharmacotherapy) to meet the needs of the individual patient.

Introduction

The US Public Health Service Guideline for Treating Tobacco Use and Dependence 2008 Update

In 2008, the US Public Health Service (USPHS) released a comprehensive update of its 2000 Guideline for Treating Tobacco Use and Dependence.[1] This evidence-based Guideline was updated by a panel of experts who have distilled a literature of greater than 8,700 peer-reviewed articles and performed comprehensive meta-analyses. The Guideline emphasizes that tobacco dependence is a chronic medical condition that often requires repeated intervention and multiple attempts to stop. In the United States, approximately 70% of smokers want to stop smoking and 44% attempt to stop smoking every year. Unfortunately, these efforts are usually unaided and unsuccessful; only approximately 4% to 7% of smokers who attempt to stop smoking are able to do so on their own. The authors of the 2008 Guideline note that substantial progress has been made since the first Guideline was published in 1996. The Guideline points to the increased coverage of tobacco dependence treatments by health plans, Medicare, and Medicaid. The Joint Commission now requires tobacco dependence interventions for hospitalized smokers with a diagnosis of acute myocardial infarction, congestive heart failure, or pneumonia (available at: http://

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No other conflict of interest relevant to this article was reported. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

www.coreoptions.com/new_site/jcahocore.html). In addition, the Guideline highlights that progress has been made in disseminating treatment options. Telephone quitlines have been particularly effective in providing wide access to counseling, and many quitlines provide nicotine replacement therapy (NRT) at no cost to the smoker.[2]

Each Guideline recommendation is supported by a meta-analysis of scientific studies to provide a strong base of evidence that will encourage clinicians to advise effective tobacco dependence counseling and medications to their patients who use tobacco. The Guideline also recommends that health systems, insurers, and purchasers assist clinicians in making such effective treatments available. For this to occur, clinicians and health care delivery systems need to consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting. The Guideline recommends that an office-wide system should be implemented to ensure that every patient at every clinic visit is queried regarding their tobacco use status and documented. One easy way to accomplish this is to expand the vital signs to include tobacco use.

Clinicians should encourage every patient who is willing to make an attempt to stop using tobacco and direct them toward effective counseling and medications. For the patient who is unwilling to set a quit date, the Guideline recommends using the technique of motivational interviewing to maintain patient engagement in the treatment process. Even brief tobacco counseling interventions are effective for improving tobacco abstinence outcomes compared with no intervention or self-help materials. Because there is a dose response for counseling interventions, longer or more intensive treatments result in better smoking abstinence outcomes compared with brief behavioral therapy. This is true regardless of the format used for the counseling intervention (ie, individual, group, or telephone counseling). Two components of counseling are especially effective and clinicians should use these when counseling patients to stop tobacco use: 1) Practical counseling. This problem-solving and skills training approach is used to help the patient recognize thoughts, behaviors, and situations that may lead to increased smoking or relapse and help the patient identify and practice coping or problem-solving skills to deal with them. Practical counseling also includes providing basic information concerning the neurobiology of tobacco dependence and withdrawal symptoms that might be experienced. 2) Intratreatment support. The clinician engaged with the patient can provide support in a variety of ways, which begin with encouraging the patient to make an attempt to stop. The clinician should communicate in a caring, nonjudgmental manner and also encourage the patient to openly discuss perceived barriers to stopping smoking. Telephone counseling and return visits are a clear demonstration of intratreatment support.

The Guideline also recommends that the 7 first-line medications should be used either individually or in combinations. These medications include 5 nicotine medications (nicotine gum, a nicotine vapor inhaler, nicotine lozenges, nicotine nasal spray, and nicotine patches) and 2 non-nicotine medications (bupropion and varenicline). The Guideline highlights that counseling and medication are effective when used by themselves, but the combination of counseling and medication is more effective than either used alone. Every patient who is willing to make an attempt to stop smoking should be offered counseling and medications.[1]

The Guideline emphasizes that telephone quitline counseling is effective with diverse populations and has a broad reach. In the United States, telephone quitlines are available in every state; therefore, both clinicians and health care delivery systems should ensure patient access to quitlines and promote quitline use. The national quitline number is 1-800-QUITNOW, which connects smokers to a routing system that redirects them to their state quitline service.

Finally, as highlighted in the Guideline, counseling and pharmacotherapy are proven effective strategies to help smokers stop smoking. Higher taxes for cigarettes and smoke-free workplace policies are 2 effective public health policies that may prompt a smoker to make an attempt to stop and often help them stop.

Basic Neurobiology of Tobacco Dependence

A major barrier for most smokers who try to quit is the neurobiology of tobacco dependence, which is fed by the most efficient delivery device of nicotine that exists—the cigarette. Cigarette smoking delivers high concentrations of nicotine to the central nervous system (CNS) within seconds of the first puff. The primary target for nicotine in the CNS is the $\alpha 4\beta 2$ nicotinic acetylcholine receptor, which, when activated by nicotine binding, results in the release of dopamine in the brain's "reward center" and provides the positive reinforcement observed with cigarette smoking.

Smoking 1 cigarette results in a high level of occupancy of the $\alpha 4\beta 2$ nicotinic acetylcholine receptors in the CNS, and 3 cigarettes completely saturate these receptors for as long as 3 hours.[3] Craving results when the receptor occupancy declines over time, and reducing that craving requires achieving virtually complete receptor saturation. Clinicians need to understand this important concept that places into context 2 important facts regarding treatment for tobacco use and dependence: 1) the efficient and rapid delivery of nicotine by cigarettes is a key factor in the development of tobacco dependence; and 2) the nicotine replacement products commonly used to treat tobacco dependence are relatively inefficient in delivering nicotine, and deliver much lower concentrations compared with cigarettes.

Nicotine has complex and wide-ranging effects on the CNS. Nicotine binds to and causes conformational changes in nicotinic acetylcholine receptors. Nicotinic acetylcholine receptors are located in all areas of the human brain and, when stimulated, cause the release of dopamine, norepinephrine, glutamate, vasopressin, serotonin, γ-aminobutyric acid, β-endorphins, and other neurotransmitters. High concentrations of $\alpha 4\beta 2$ nicotinic acetylcholine receptors exist in the mesolimbic dopamine system and locus ceruleus.[4] The former is important for pleasure and reward and the latter is significant for cognitive function. Although to our knowledge not completely understood, upregulation of the high affinity $\alpha 4\beta 2$ nicotinic acetylcholine receptor is critical for the development of tolerance to and dependence on nicotine.[5] Repeated exposure to high concentrations of nicotine causes upregulation of the $\alpha 4\beta 2$ nicotinic acetylcholine receptors, leading to an absolute increase in their numbers.[5,6] Neuroadaptation of the mesolimbic system in smokers and its target neurons in the nucleus accumbens may be longer lasting than previously believed, which could explain the observation that the craving to smoke lasts for months after a smoker stops smoking.[7]

In laboratory animals, self-administered intravenous nicotine increases the sensitivity of brain reward systems and imprints an indelible memory of its effects in these reward systems, an action that appears unique to nicotine among drugs of abuse.[8] This may partially explain the rapid return to former levels of smoking that frequently follows a relapse after a prolonged period of smoking abstinence.

Pharmacotherapy for Tobacco Dependence

Nicotine Replacement Products

One approach to the therapeutic use of NRT for the treatment of tobacco dependence is to determine the patient's level of nicotine exposure. Once the degree of exposure is determined, a nicotine replacement dose approximating the dose the individual receives

from smoking can be prescribed. However, several factors make this task difficult. Smokers exposed to the same amount of nicotine through inhaled tobacco smoke have marked interindividual differences in venous nicotine concentrations.[9,10] Furthermore, there are significant, genetically determined variations in nicotine metabolism (ie, slow versus fast metabolizers of nicotine).[11] Cigarette smoking produces initial arterial nicotine concentrations that are several-fold higher than concomitant venous nicotine levels.[12] In addition, nicotine has a short half-life (ie, 120 minutes) and, with smoking, tends to have peaks and troughs in both venous and arterial concentrations. For these reasons, cotinine, the major metabolite of nicotine, provides a better estimate of nicotine exposure.

Cotinine has a half-life of 18 to 20 hours and can be used to quantify an individual's exposure to nicotine. Venous nicotine concentrations are less than arterial concentrations and reflect acute nicotine exposure, whereas cotinine reflects nicotine exposure over a period of several days. Minor tobacco alkaloids such as nornicotine, anatabine, and anabasine can also be measured in the urine of tobacco users as qualitative assessments of nicotine and tobacco exposure.[13–15] The tobacco alkaloid anabasine is not a metabolic product of nicotine, but is present in the urine of tobacco users and not in the urine of patients using only NRT. Anabasine may be useful in distinguishing abstinent tobacco users who are using NRT from those who are continuing to use tobacco. This has become especially important for adjudicating tobacco abstinence in situations that require abstinence from tobacco use to pursue advanced medical or surgical therapy, such as lung and/or heart transplantation.

To date, the US Food and Drug Administration (FDA) has approved 5 nicotine replacement products: nicotine gum, nicotine patches, nicotine nasal spray, a nicotine vapor inhaler, and nicotine lozenges. Nicotine gum, patches, and lozenges are available as over-the-counter (OTC) products, whereas the nasal spray and vapor inhaler are available by prescription only. Because 6 of the products used in the pharmacotherapy for nicotine dependence have been reviewed extensively in a recent publication in this journal,[16] we will briefly review these medications here, but will substantially update the section regarding varenicline. We will discuss how we use all of the medications later in this article.

In general, physicians who prescribe NRT for tobacco dependence should individualize the dose and duration of treatment and schedule follow-up office visits or telephone calls to monitor patient response. The dose and duration of therapy should be based on the patient's response to treatment, including the subjective relief of withdrawal symptoms and cravings.

NRT can be divided into 2 groups: short-acting NRT (nicotine gum, nicotine lozenges, nicotine nasal spray, and nicotine vapor inhaler) and longer-acting (nicotine patches). If NRT is selected for treatment, a combination therapy of nicotine patches and short-acting NRT is usually preferred over monotherapy with a short-acting NRT product. Short-acting NRT is best used for the acute management of nicotine withdrawal symptoms and cravings in combination with longer-acting medications such as nicotine patches, bupropion, or varenicline.[17]

Nicotine gum is available as an OTC product, in both the 2-mg and 4-mg doses. Patients should be instructed in its proper use to “chew and park” and to avoid acidic beverages that lower the intra-oral pH and thereby reduce nicotine absorption. Nicotine gum can be used as monotherapy or in combination with other NRT or bupropion.

The nicotine lozenge is available in the United States as an OTC product. The nicotine lozenge is available in 2-mg and 4-mg doses, with the latter indicated for use in “high”-dependence smokers (ie, time to first cigarette of the day of less than 30 minutes after

arising).[18] The method of delivery (ie, transbuccal) is similar to that of nicotine gum, and it can be used alone or in combination with other NRT or bupropion.

Nicotine nasal spray delivers nicotine directly to the nasal mucosa and has been observed to be effective for achieving smoking abstinence as monotherapy.[19] This device delivers nicotine more rapidly than other therapeutic nicotine replacement delivery systems and reduces withdrawal symptoms more quickly than nicotine gum.[20,21] The reduction in withdrawal symptoms may be partially attributable to the rapidity with which nicotine is absorbed from the nasal mucosa and the resulting arterial venous differences in the plasma concentration of nicotine.[10]

The nicotine vapor inhaler has also been shown to be effective as monotherapy for increasing smoking abstinence.[22] The device delivers nicotine in vapor form that is absorbed across the oral mucosa. Although the device is called an inhaler, this is a misnomer because little of the nicotine vapor reaches the pulmonary alveoli, even with deep inhalations.[23]

Nicotine patch therapy was introduced in 1991 and delivers a steady dose of nicotine for 24 hours after a single application. The once-daily dosing requires little effort on the part of the patient, which enhances compliance. Nicotine patches are available without a prescription in doses of 7 mg, 14 mg, and 21 mg. To our knowledge, in nearly every randomized clinical trial performed to date, the nicotine patch has been shown to be effective compared with placebo, usually with a doubling of the smoking abstinence rate.

Standard-dose (21 mg/24 hours) nicotine patch therapy achieves a median serum cotinine level of only 54% of the cotinine concentrations achieved through smoking.[9,24] There is a dose response for nicotine patch therapy, particularly among lighter smokers who have lower baseline cotinine concentrations, suggesting that their nicotine replacement needs are more adequately met with standard doses than those of heavier smokers.[25]

Because of the observation that many patients are underdosed with a standard nicotine patch dose, studies have been conducted assessing the efficacy of higher doses. The use of high doses of nicotine patch therapy (ie, doses of greater than 21 mg/day) are appropriate for heavy smokers, those who previously failed standard-dose patch therapy, and/or for those whose nicotine withdrawal symptoms are not relieved sufficiently with standard-dose therapy.[26] This approach can be especially important for heavy smokers because they will be significantly underdosed with standard-dose patch therapy.[9] High-dose nicotine patch therapy has been shown to be safe and well-tolerated in patients who smoke more than 20 cigarettes per day.[9,27] The 2008 USPHS Guideline Panel concluded that “high-dose” nicotine patch therapy (greater than 21 mg/day) did not appear to produce benefit above and beyond that of standard-dose nicotine patch therapy. The panel concluded that if the patient is highly dependent, the clinician may consider doses higher than those recommended by the FDA and that higher doses have been shown to be effective in highly dependent smokers. The panel also notes that there is no evidence of increased cardiovascular risk with any of the NRT medications.

Smoking rate can be used to determine the initial nicotine patch dose at a dose of approximately 1 mg of nicotine for each cigarette smoked per day (CPD). Thus, less than 10 CPD warrant a 7-mg to 14-mg dose, 10 to 20 CPD warrant a 14-mg to 21-mg per day dose, 21 to 40 CPD warrant a 21-mg to 42-mg per day dose, and greater than 40 CPD warrant a dose of 42 mg per day or more. Adequacy of the initial dose is determined by assessing the patient's withdrawal symptoms and relief from cravings.

When available, clinicians can use serum cotinine concentrations to tailor the nicotine replacement dose so that it approaches 100%. A baseline cotinine concentration is obtained

while the smoker is smoking at the usual rate. An initial nicotine patch dose based on the baseline cotinine concentration (or CPD) is prescribed. A 14-mg to 21-mg nicotine patch dose should be prescribed if the baseline cotinine level is less than 200 mg/mL, a 21-mg to 42-mg patch dose should be prescribed for a patient with a baseline cotinine level of 200 to 300 mg/mL, and a greater than 42-mg patch dose should be prescribed if the baseline cotinine level is greater than 300 mg/mL. After the patient reaches steady state (more than 3 days of nicotine patch therapy and still not smoking), the serum cotinine concentration is rechecked and the replacement dose adjusted to achieve a steady-state cotinine level that approaches the baseline level (ie, 100% replacement). Higher percentage replacement has been shown to reduce nicotine withdrawal symptoms,[9] but to the best of our knowledge the efficacy of such an approach for long-term smoking abstinence has not been clearly established to date.[9,28–30] Smokers who did not get adequate relief of withdrawal symptoms from a single nicotine patch dose on a prior attempt should be considered for a higher nicotine patch dose plus supplemental, short-acting NRT.

After the initiation of nicotine patch therapy on the stop date, the patient should have a follow-up visit or a telephone counseling session within the first 2 weeks and periodically thereafter. Abstinence from smoking during the first 2 weeks of patch therapy has been shown to be highly predictive of long-term abstinence.[25,31] Thus, the first 2 weeks after treatment initiation appear to be critical in setting the stage for long-term smoking abstinence. Alterations in therapy at follow-up depend on relief of withdrawal symptoms and cravings and how well the patient is maintaining smoking abstinence. If the patient continues to smoke at all during the first 2 weeks, the treatment plan may need to be changed either by changing the nicotine patch dose, adding additional pharmacotherapy, or intensifying behavioral counseling. Nicotine patch doses should be increased for patients experiencing pronounced withdrawal symptoms such as irritability, anxiety, loss of concentration, or cravings, or for patients who do not achieve 100% replacement based on the second serum cotinine concentration. Most patients use the nicotine patch for 4 to 8 weeks, but it is safe for longer use if needed to maintain smoking abstinence. To our knowledge, the optimal length of treatment has not been determined, but longer-term treatment (more than 14 weeks) appears to provide benefit over standard lengths of treatment when combining nicotine patches and nicotine gum.[1] Furthermore, long-term treatment of up to 6 months with triple combination therapy (nicotine patches, bupropion, and a nicotine vapor inhaler) appears superior to standard-dose nicotine patch therapy given over a 10-week period.[32]

Non-Nicotine Medications

Sustained-Release Bupropion—Bupropion is a monocyclic antidepressant that inhibits the reuptake of both norepinephrine and dopamine.[33] Dopamine release in the mesolimbic system and the nucleus accumbens is believed to be the basis for the reinforcing properties of nicotine and other drugs of addiction.[34–36] The efficacy of bupropion in treating smokers is hypothesized to stem from its dopaminergic activity on the pleasure and reward pathways in the mesolimbic system and nucleus accumbens. Bupropion also has been shown to have an antagonist effect on nicotinic acetylcholine receptors.[37,38] Thus, its mechanism of action likely is multifactorial.

Sustained-release bupropion (bupropion SR) has been shown to be effective and exhibits a significant dose-response effect.[39] In addition, weight gain attenuation occurs during the treatment phase for subjects who are continuously abstinent while receiving the 300-mg/day dose. However, the attenuation of weight gain does not persist at 1 year of follow-up for smokers who received short-term treatment (7 weeks). Weight gain attenuation has been observed with 52 weeks of bupropion SR compared with subjects who received placebo, and

the weight gain attenuation in these subjects persisted for the 1 year follow-up after the medication was discontinued.[40] Bupropion SR has also been shown to be effective in subpopulations of smokers, including those with coronary artery disease or chronic obstructive pulmonary disease, or those who have previously failed to achieve long-term smoking abstinence after an initial course of bupropion SR.[41–43] Treatment with bupropion SR alone or in combination with the nicotine patch resulted in a significantly higher long-term rate of abstinence from smoking than did use of either the nicotine patch alone or placebo.[44] The 2008 USPHS Guideline recommends the combined use of bupropion SR and nicotine patch therapy.[1] In July 2005, the US FDA issued a public health advisory for bupropion. All patients being treated with bupropion should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation behavior and attempted suicide. Patients should stop taking bupropion and contact a health care provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior.

Varenicline—Varenicline is a partial nicotine agonist/antagonist that selectively binds to the $\alpha 4\beta 2$ nicotinic acetylcholine receptor. Varenicline both blocks nicotine from binding to the receptor (antagonist effect)[45] and partially stimulates (agonist effect) receptor-mediated activity, leading to the release of dopamine, which reduces cravings and nicotine withdrawal symptoms. Varenicline is not metabolized but it is excreted virtually unchanged in the urine and has a half-life of approximately 17 hours.

Pivotal trials in healthy smokers comparing varenicline at a dose of 1 mg twice daily to placebo or bupropion SR have demonstrated that varenicline is more effective compared with placebo or bupropion SR, with end-of-treatment (12 weeks) continuous smoking abstinence rates of 44% versus 30% for bupropion SR and 18% for placebo.[46,47] The end-of-treatment, 7-day point prevalence smoking abstinence rates were approximately 50% for varenicline versus 35% for bupropion SR and 20% for placebo. An additional 12 weeks of varenicline has been shown to be effective in maintaining smoking abstinence in smokers who had stopped smoking after 12 weeks of open-label varenicline treatment.[48] In this study, 70% of subjects treated with varenicline were continuously abstinent from smoking from Weeks 13 to 24 compared with 50% of smokers assigned to placebo ($P < .001$).[48]

Varenicline is initiated at a dose of 0.5 mg once daily for 3 days followed by 0.5 mg twice daily for 4 days. The target quit date is Day 8, when the maintenance dose of 1 mg twice daily begins. Length of treatment should be at least 12 weeks and can be extended for an additional 12 weeks. From a practical standpoint, we frequently recommend longer treatment for abstinent smokers who are not secure and are concerned about smoking relapse.

Nausea is the most frequent adverse effect of varenicline and was reported by approximately 30% of the subjects in the clinical trials. Nausea was most often mild to moderate, and participant dropouts related to nausea were infrequent (less than 3%). Vivid dreams (reported in approximately 15% of subjects) are the next most common adverse event, but do not often lead to discontinuation of the medication. In July 2009, the US FDA issued an updated public health advisory because of postmarketing surveillance reports. All patients being treated with varenicline should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation behavior and attempted suicide. Patients should stop taking varenicline and contact a health care provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. Patients should also be advised to use

caution when driving, operating machinery, or engaging in other potentially hazardous activities until they know how varenicline may affect them. However, a large study demonstrated that a past history of depression in smokers taking varenicline to stop smoking did not lead to new or worsening depression symptoms compared with smokers without a past history of depression.[49] More research is needed in smokers with pre-existing psychiatric problems.

Combination Pharmacotherapy

The 2008 USPHS Guideline states that certain combinations of first-line medications have been shown to be more effective than monotherapy, with long-term (greater than 14 weeks) nicotine patch therapy combined with nicotine gum or nicotine nasal spray, nicotine patch therapy plus nicotine vapor inhaler, and nicotine patch therapy plus bupropion SR cited as examples. Combining bupropion with the nicotine vapor inhaler is reported to provide a better treatment effect than either alone.[50] However, the expert panel points out that the use of combinations of medications may be based on considerations other than smoking abstinence. Control of withdrawal symptoms is an important consideration, as is patient past experience and/or preference. Whether the superiority of combination therapy is because of the use of 2 types of delivery systems or to the finding that 2 delivery systems tend to produce higher blood nicotine levels remains unclear. Combination pharmacotherapy or higher-dose NRT appears to relieve nicotine withdrawal symptoms more effectively, especially in more dependent smokers.

Clinical Decision Making Surrounding Pharmacotherapy

In clinical medicine, we base our clinical decision making for medication selection and dosing on the published literature, but also on our clinical experience. It has long been recognized by clinicians that there are limitations to standard-dose or fixed-dose regimens with most drugs used in clinical practice today. As a result, clinicians use their clinical skills and knowledge of pharmacotherapy to individualize drug dosing for patients. These same skills and knowledge should be applied to those medications used to treat tobacco dependence. Much of this clinical decision making is based on the patient's past experience and preference. Although complex algorithms and questionnaires are available to assess the severity of tobacco dependence, a simple question such as the time of the first cigarette in the morning is a practical question that provides real insight into the level of dependence of the smoker. A smoker who smokes within the first 5 minutes of arising is more dependent than a smoker who smokes within 30 minutes of arising.

Although each of the FDA-approved medications has been shown to be effective compared with placebo in randomized clinical trials, we rarely use short-acting NRT (nicotine gum, nicotine vapor inhaler, nicotine lozenges, or nicotine nasal spray) alone. The exception is for the patient who previously stopped smoking using a short-acting NRT as monotherapy. The same would be true for monotherapy with nicotine patches, bupropion, or varenicline. From a practical standpoint, we view nicotine patch therapy, bupropion SR, or varenicline as the foundation on which to begin building a patient's pharmacotherapeutic regimen and may use 1 of these longer-acting medications either as monotherapy or in combination with a short-acting NRT product. We often combine the medications. Depending on the patient's past experience and desires, we may use nicotine patch therapy in combination with bupropion SR. A short-acting NRT product may also be added to any regimen as needed to control withdrawal symptoms or cravings. Because varenicline and bupropion have different mechanisms of action, we sometimes use them in combination, particularly in smokers who have previously stopped smoking using bupropion monotherapy but struggled during the process. A pilot study of this combination demonstrated excellent efficacy and suggests that the combination of bupropion and varenicline was well-tolerated.[51]

For patients with more severe tobacco dependence, such as those treated in our residential treatment program, we commonly use combination therapy and often use 3 or more products simultaneously.[52] For patients with a partial response to initial medication therapy (ie, a decreased smoking rate but not abstinence from smoking), further tailoring of the medication regimen may be necessary to reach the desired therapeutic goal of smoking abstinence. For example, if a patient has reduced smoking using varenicline at a dose of 1 mg twice daily and has tolerated the medication without substantial nausea, we may increase the dose to 1 mg taken 3 times daily. Another situation requiring creativity (ie, the art of medicine) is a smoker who has stopped smoking using nicotine patch therapy and a short-acting NRT but notices increased withdrawal symptoms in the early evening. Adding a 14-mg patch in the late afternoon may decrease evening withdrawal. We have used nicotine patch therapy in our residential treatment program for smokers who want to initiate varenicline therapy at the time of admission.[17] Because patients stop smoking on admission to our residential treatment program and varenicline requires several days to reach steady-state concentrations, withdrawal symptoms will be poorly controlled during the initiation of varenicline treatment. Thus, we are better able to control nicotine withdrawal symptoms that may be disruptive to the patient's treatment experience.

Treating Smokeless Tobacco Users

Smokeless tobacco (ST) is tobacco consumed orally and not burned. A variety of ST types are consumed throughout the world. In the United States, the principal types of ST are chewing tobacco (cut tobacco leaves) and snuff (moist ground tobacco). According to the National Toxicology Program Report, ST use is estimated to be the greatest exogenous source of human exposure to nitrosamines.[53] The available literature suggests that ST is associated with periodontal disease[54,55] and precancerous oral lesions.[56] Long-term ST use is associated with an increased risk for oral cancer[57] and cancers of the kidney[58,59] and pancreas.[60] Long-term ST use is also associated with death from coronary heart disease and stroke.[61]

The prevalence of ST use among Americans has increased significantly from 2004 to 2006 (3.0% vs 3.3%; $P < .05$).[62] In 2007, approximately 8.1 million (3.2%) of US adults aged 12 years of age or older were current (within the past month) ST users.[63] In response to changing market pressures and public health policies such as smoke-free workplaces, 2 of the world's largest cigarette manufacturers, Reynolds America and Philip Morris USA, have entered the ST market. R.J. Reynolds Tobacco Company purchased Conwood Sales Company, LLC (maker of the Grizzly and Kodiak brands of moist tobacco) for $3.5 billion in 2006[64] and Altria Group Inc (of which Philip Morris USA is the US tobacco division) purchased UST Inc (maker of the Copenhagen and Skoal brands of dipping tobacco) for more than $10 billion.[64] R.J. Reynolds launched “Camel Snus”[65] and Philip Morris USA launched “Marlboro Snus.” Both products have been designed to appeal to smokers and are being promoted for use when smoking is not allowed.[65] At the same time, ST is also being promoted by some as a harm reduction strategy for cigarette smokers, which is creating controversy in the tobacco control field.[66,67] The impact of these factors on the prevalence of ST use remains unclear, but suggest an urgency for developing effective treatments for ST users.

A need for efficacious interventions exists, because approximately 64% of ST users report the desire to quit.[68] Behavioral interventions have been shown to be effective for increasing ST abstinence rates.[69,70] Among ST users, bupropion SR attenuates weight gain and tobacco cravings but does not increase ST abstinence rates compared with placebo.[71] Among heavy ST users (greater than 3 cans/pouches per week), a dose-response relation exists between nicotine patch dose and withdrawal symptom relief such that higher doses result in a greater

attenuation of withdrawal symptoms.[72] In an open-label pilot study, the 4-mg nicotine lozenge was associated with an end-of-treatment (12 weeks) ST abstinence rate of 53% (95% confidence interval [95% CI], 34–72%) and an ST abstinence rate of 47% (95% CI, 28–66%) at 6 months.[73] Randomized clinical trials of the nicotine lozenge, varenicline, and high-dose nicotine patch therapy for ST users are currently underway. As pointed out in the USPHS Guideline, no pharmacotherapy to date has been shown to be effective in treating ST users. Consequently, clinicians will have to use their understanding of the pharmacology in conjunction with the patient's past experience and desires to shape the clinical decision making for each individual patient.

Other Noncigarette Tobacco Use

The use of other noncigarette tobacco products, such as cigars, pipes, and water pipes, also poses health threats to users. In 2007, approximately 13.3 million Americans (5.4% of the US population aged 12 years or older) smoked cigars and 2.0 million (0.8% of that same population) smoked pipes,[63] and the prevalence of water pipe use in the United States appears to be increasing.[74] Cigar smokers have risks of developing oral and esophageal cancers that are similar to those of cigarette smokers,[75] and pipe smoking confers a risk of death from cancers of the lung, oropharynx, esophagus, colon and rectum, pancreas, and larynx that is equivalent to or exceeds those associated with smoking cigars.[6] A World Health Organization (WHO) Study Group published a scientific advisory note suggesting that during a typical 1-hour session, a water pipe smoker will inhale as much smoke as a cigarette smoker inhales consuming 100 to 200 cigarettes and that water pipe smoking poses serious health hazards.[77] However, to the best of our knowledge, effective treatment strategies for users of non-cigarette tobacco products have not been established to date. General principles of therapy could include nicotine patches, bupropion SR, and varenicline for daily users and ad lib NRT for nondaily users.

Tobacco Treatment Specialists

In the past 20 years, clinicians have been encouraged to actively treat tobacco dependence. Brief interventions were promoted using first the 4 A's and then the 5 A's (Ask, Advise, Assess, Assist, and Arrange). Brief interventions by physicians have been shown to be effective, but it is well known that there is a dose response for behavioral counseling. Overall, engagement by clinicians in the provision of brief interventions has been limited.[78] Despite evidence that more intensive interventions are more effective, they are rarely provided, except by clinicians who have special expertise in treating tobacco dependence.

A growing number of clinicians have developed the specialized knowledge and skills required to effectively treat tobacco dependence. Despite this growing expertise among physicians, the time they are able to devote to tobacco dependence interventions remains limited in most health care settings. As a result, a new model of care using trained and certified tobacco treatment specialists (TTS) has been developed.[79] This is a new and growing part of the health care team. Certified TTS typically hold a Bachelor's or Master's degree in a health care or related field such as counseling or social work. TTS play several important roles on the health care team: 1) primary care providers can refer tobacco users to a TTS, especially those patients who have failed previous treatments; 2) TTS are agents for disseminating new treatment approaches; 3) TTS provide advocacy for the effective treatment of tobacco users and policy changes that promote the use of effective treatments; 4) TTS often spearhead quality improvement efforts in tobacco dependence treatment; and 5) TTS legitimize dissemination within their primary professions.[79] The USPHS Guideline 2008 Update defines TTS as health care providers from various professional backgrounds who view tobacco dependence treatment as a primary professional role.[1] In addition to

having the knowledge, skills, and ability to provide treatment through modalities across a range of intensities, TTS contribute to tobacco control efforts by: 1) providing a resource to nonspecialists in treating tobacco dependence; 2) developing, implementing, and evaluating procedures for treating tobacco dependence in the office, clinic, or hospital; and 3) developing and evaluating innovative strategies to increase effectiveness in the use of tobacco dependence treatment. TTS are trained in the breadth of interventions for treating tobacco dependence, including motivational interviewing techniques. Thus, TTS are not constrained to providing treatment to those already motivated to stop smoking, but also help unmotivated smokers to move through the change process toward an attempt to stop smoking.[80] Health care providers with counseling backgrounds are ideally suited to be trained as TTS, but they would then need to work under the supervision of a prescribing physician. Trained and certified practitioners, such as physician assistants and nurse practitioners, may be trained as TTS and are able to be more independent because they have prescribing capabilities in most states in the United States. They also are able to bill independently of physician involvement and may care for patients in both the outpatient and inpatient settings. Labeling tobacco dependence treatment as a clinical activity rather than a prevention effort helps to promote TTS, who are then viewed as being essential to developing an adequate system of treatment for tobacco dependence.[79]

TTS offer intensive treatment interventions or services in the context of a medical setting or through telephone quitlines. They are able to provide cost-effective and more intensive interventions than physicians by providing comprehensive consultations, multiple counseling sessions, and group interventions. Working in concert with physicians, TTS can provide a unique referral resource for the physician, who then can practice with 2 A's and an R—the Ask, Advise, and Refer approach to treating tobacco users. This model fits well with the time constraints common in modern medical practice. TTS may be useful for developing, evaluating, and implementing changes in the office or clinic to increase the rate of tobacco user identification and triage. Because tobacco dependence treatment is their primary professional role, TTS possess the skills, knowledge, and training to provide effective intervention across a range of intensities.

Systematic Approach to Treating Tobacco Dependence in a Medical Center

We started our Nicotine Dependence Center Treatment Program in 1988. Our treatment approach was based on the prevailing addictions treatment model at that time, incorporating counselor-provided treatment services under physician supervision.[81] The intervention is based on the concepts of behavioral treatment, addictions treatment, pharmacotherapy, and relapse prevention, but is provided in an empathetic fashion through the technique of motivational interviewing. We created a treatment service that was integrated with the larger medical practice by making the services convenient for clinicians and patients through easy-to-make referrals, and appropriate documentation in the unified medical record. The general clinical data collection form used to gather patient intake information at the Mayo Clinic identifies (Ask) all tobacco users for the physician. Physicians can provide complete treatment through advising (Advise) the patient to stop smoking and providing treatment (Assess and Assist) and follow-up (Arrange). At a minimum, we encourage our physicians to identify (Ask) tobacco users, advise (Advise) the patient to stop smoking, and refer (Refer) the patient to a telephone quitline or to 1 of our TTS for further evaluation and treatment. We have TTS counselors available to see referred patients; thus, we ask our physicians to refer any patient they desire. We have developed systems and procedures to support the referral process that make it as easy for the physician to refer (Refer) for a TTS consult as it is to schedule a simple laboratory test.

In the outpatient clinic, our counselor TTS sees the patient (whether physician-referred or self-referred) for an initial 45-minute to 60-minute evaluation, during which an assessment is made of the patient's level of nicotine dependence, prior attempts to stop, tobacco-caused medical problems, and any psychiatric or substance abuse comorbidity. The TTS uses scaling questions to assess the patient's level of motivation and confidence in their ability to stop smoking. A treatment plan is developed including recommendations for pharmacotherapy, all of which is recorded in the medical record. The latter are reviewed with the physician, who then provides prescriptions for the medications. Follow-up visits are very important, but when distance is a barrier, the TTS arranges for follow-up by telephone.

For hospitalized smokers, we provide care through our Nurse Tobacco Use Intervention Protocol.[82] Patients who have been smokers within the 6 months prior to hospital admission receive a brief behavioral intervention by the bedside nurse. Under the protocol, the bedside nurse can order nicotine patch therapy and also can refer for a TTS consultation. The hospital TTS are midlevel practitioners (nurse practitioner or physician assistant) who have been TTS trained and certified. These midlevel practitioners can provide the initial and follow-up counseling in the hospital, prescribe the range of medications that we use, and bill for patient services with minimal direct physician supervision. The advantages and disadvantages to these 2 types of TTS providers include a lower cost for care provided by a counselor TTS, but they are unable to bill for services independently. A midlevel TTS can provide a broader range of services in both the inpatient and outpatient settings, but they are more costly. However, midlevel TTS can be cost-neutral if they see an appropriate volume of patients.

Finally, a small fraction of patients will need and are able to be treated in our residential treatment program. This 8-day program is the most intensive treatment available.[83] A physician oversees the program, performs an initial examination on each patient, and provides tailored pharmacotherapy. The TTS provide the behavior counseling. The team makes daily rounds, during which issues are discussed and pharmacotherapy is altered depending on the patient's response. Program components include a daily education session, group therapy, individual therapy, skills training, exercise, and tailored pharmacotherapy. At the time of admission, we obtain a serum cotinine level to assess the patient's level of tobacco use, and to determine the initial nicotine patch dose in appropriate patients. A second serum cotinine is drawn in 4 days to determine the adequacy of nicotine replacement. The nicotine patch dose is increased if the percentage of nicotine replacement is less than 100%. Compared with our typical outpatient, residential treatment patients are generally older (mean age, 53 years), heavier smokers (mean CPD, 35), have substantial tobacco-caused medical illnesses (80%), and are more commonly (40%) in recovery from alcohol or drug dependence. Table 1 shows the components of our treatment program.

Treatment Outcomes

Outcomes for our various treatment options have been systematically assessed over the 2 decades our program has existed. We have always used an “intent-to-treat” analysis, whereby every patient who received treatment services is included in the denominator but only patients who are contacted and report themselves to be abstinent from tobacco are included in the numerator as treatment successes. Patients we are unable to contact or who decline to report their outcome are counted as treatment failures. For patients receiving our outpatient services, the 6-month smoking abstinence rates have been reported to range from 22% to 25%.[81,84] The 6-month smoking abstinence rate from hospitalized smokers who receive counseling from a counselor or midlevel TTS is 32%. The 1-year smoking abstinence rate for patients who enter our residential treatment program is reported to be 52%.[83]

Conclusions

The USPHS Guideline for Treating Tobacco Use and Dependence 2008 Update emphasizes tobacco use as a chronic medical disorder; highlights both behavioral counseling and the use of 1 or more of the 7 approved medications; and points out the utility, efficacy, and reach of telephone quitlines.[1] The treatment of ST users continues to be less than optimal. Although providing evidence-based treatment for tobacco-dependent patients is a challenge for busy physicians, a team approach including trained and certified TTS provides an efficient treatment model. TTS represent a new and growing part of the health care team and hold great potential for expanding the collective tobacco treatment expertise in the medical setting. Effective tobacco dependence treatment frequently requires tailoring, and often intensifying, the interventions (both counseling and pharmacotherapy) to meet the needs of the individual patient.

Acknowledgments

Disclosures: Supported in part by Award Numbers R01 CA 12115 and R21 CA 132621 from the National Cancer Institute. Dr. Richard D. Hurt serves on the Advisory Board for Pfizer, Inc, and Dr. J. Taylor Hays has received a research grant from Pfizer, Inc.

References

1. Fiore, M.; Baker, T.; Jaen, C., et al. Clinical Practice Guideline. Rockville, Md: US Department of Health & Human Services, Public Health Service; 2008. Treating Tobacco Use and Dependence: 2008 Update.
2. Swartz SH, Cowan TM, Klayman JE, et al. Use and effectiveness of tobacco telephone counseling and nicotine therapy in Maine. Am J Prev Med. 2005; 29:288–294. [PubMed: 16242591]
3. Brody AL, Mandelkern MA, London ED, et al. Cigarette smoking saturates brain alpha 4 beta 2 nicotinic acetylcholine receptors. Arch Gen Psychiatry. 2006; 63:907–915. [PubMed: 16894067]
4. Watkins SS, Koob GF, Markou A. Neural mechanisms underlying nicotine addiction: acute positive reinforcement and withdrawal. Nicotine Tob Res. 2000; 2:19–37. [PubMed: 11072438]
5. Balfour, DJK. The neurochemical mechanisms underlying nicotine tolerance and dependence. In: Pratt, JA., editor. The Biological Basis of Drug Tolerance and Dependence. London, UK: Academic Press; 1991. p. 121-151.
6. Perry DC, Davila–Garcia MI, Stockmeier CA, et al. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. J Pharmacol Exp Ther. 1999; 289:1545–1552. [PubMed: 10336551]
7. Hope BT, Nagarkar D, Leonard S, et al. Long-term upregulation of protein kinase A and adenylate cyclase levels in human smokers. J Neurosci. 2007; 27:1964–1972. [PubMed: 17314292]
8. Kenny PJ, Markou A. Conditioned nicotine withdrawal profoundly decreases the activity of brain reward systems. J Neurosci. 2005; 25:6208–6212. [PubMed: 15987950]
9. Dale LC, Hurt RD, Offord KP, et al. High-dose nicotine patch therapy. Percentage of replacement and smoking cessation. JAMA. 1995; 274:1353–1358. [PubMed: 7563559]
10. Gourlay SG, Benowitz NL. Arteriovenous differences inplasma concentration of nicotine and catecholamines and related cardio-vascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin Pharmacol Ther. 1997; 62:453–463. [PubMed: 9357397]
11. Ho M, Mwenifumbo J, Al Koudsi N, et al. Association of nicotine metabolite ratio and CYP2A6 genotype with smoking cessation treatment in African-American light smokers. Clin Pharmacol Ther. 2009; 85:635–643. [PubMed: 19279561]
12. Henningfield JE, Stapleton JM, Benowitz NL, et al. Higher levels ofnicotinein arterial than in venous blood after cigarette smoking. Drug Alcohol Depend. 1993; 33:23–29. [PubMed: 8370337]
13. Jacob, Pr; Yu, L.; Shulgin, AT., et al. Minor tobacco alkaloids as biomarkers for tobacco use: comparison of users of cigarettes, smokeless tobacco, cigars, and pipes. Am J Public Health. 1999; 89:731–736. [PubMed: 10224986]

14. Moyer TP, Charlson JR, Enger RJ, et al. Simultaneous analysis of nicotine, nicotine metabolites, and tobacco alkaloidsinserum or urine by tandem mass spectrometry, with clinically relevant metabolic profiles. Clin Chem. 2002; 48:1460–1471. [PubMed: 12194923]
15. Jacob P 3rd, Hatsukami D, Severson H, et al. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. Cancer Epidemiol Biomarkers Prev. 2002; 11:1668–1673. [PubMed: 12496059]
16. Henningfield JE, Fant RV, Buchhalter AR, et al. Pharmacotherapy for nicotine dependence. CA Cancer J Clin. 2005; 55:281–299. quiz 322–325. [PubMed: 16166074]
17. Ebbert JO. Combination treatment with varenicline and nicotine replacement therapy. Nicotine Tob Res. 2009; 11:572–576. [PubMed: 19351781]
18. Shiffman S, Dresler CM, Hajek P, et al. Efficacy of a nicotine lozenge for smoking cessation. Arch Intern Med. 2002; 162:1267–1276. [PubMed: 12038945]
19. Schneider NG, Olmstead R, Mody FV, et al. Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. Addiction. 1995; 90:1671–1682. [PubMed: 8555958]
20. Hurt RD, Offord KP, Croghan IT, et al. Temporal effects of nicotine nasal spray and gum on nicotine withdrawal symptoms. Psychopharmacology (Berl). 1998; 140:98–104. [PubMed: 9862408]
21. Schneider NG, Lunell E, Olmstead RE, et al. Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. Clin Pharmacokinet. 1996; 31:65–80. [PubMed: 8827400]
22. Leischow SJ, Nilsson F, Franzon M, et al. Efficacy of the nicotine inhaler as an adjunct to smoking cessation. Am J Health Behav. 1996; 20:364–371.
23. Bergstrom M, Nordberg A, Lunell E, et al. Regional deposition of inhaled 11C-nico-tine vapor in the human airway as visualized by positron emission tomography. Clin Pharm Ther. 1995; 57:309–317.
24. Hurt RD, Dale LC, Offord KP, et al. Serum nicotine and cotinine levels during nicotine-patch therapy. Clin Pharm Ther. 1993; 54:98–106.
25. Hurt RD, Dale LC, Fredrickson PA, et al. Nicotine patch therapy for smoking cessation combined with physician advice and nurse follow-up. One-year outcome and percentage of nicotine replacement. JAMA. 1994; 271:595–600. [PubMed: 8301791]
26. Hughes JR. Treatment of nicotine dependence. Is more better? JAMA. 1995; 274:1390–1391. [PubMed: 7563566]
27. Fredrickson PA, Hurt RD, Lee GM, et al. High dose transdermal nicotine therapy for heavy smokers: safety, tolerability and measurement of nicotine and cotinine levels. Psychopharmacology (Berl). 1995; 122:215–222. [PubMed: 8748390]
28. Hughes JR, Lesmes GR, Hatsukami DK, et al. Are higher doses of nicotine replacement more effective for smoking cessation? Nicotine Tob Res. 1999; 1:169–174. [PubMed: 11072398]
29. Jorenby DE, Smith SS, Fiore MC, et al. Varying nicotine patch dose and type of smoking cessation counseling. JAMA. 1995; 274:1347–1352. [PubMed: 7563558]
30. Tonnesen P, Paoletti P, Gustavsson G, et al. Higher dosage nicotine patches increase one-year smoking cessation rates: results from the European CEASE trial. Collaborative European Anti-Smoking Evaluation. European Respiratory Society. Eur Respir J. 1999; 13:238–246. [PubMed: 10065662]
31. Kenford SL, Fiore MC, Jorenby DE, et al. Predicting smoking cessation. Who will quit with and without the nicotine patch. JAMA. 1994; 271:589–594. [PubMed: 8301790]
32. Steinberg MB, Greenhaus S, Schmelzer AC, et al. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. Ann Intern Med. 2009; 150:447–454. [PubMed: 19349630]
33. Ascher JA, Cole JO, Colin JN, et al. Bupropion: a review of its mechanism of antidepressant activity. J Clin Psychiatry. 1995; 56:395–401. [PubMed: 7665537]
34. Clarke PB. Nicotine dependence—mechanisms and therapeutic strategies. Biochem Soc Symp. 1993; 59:83–95. [PubMed: 8192688]

35. DiChiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci U S A. 1988; 85:5274–5278. [PubMed: 2899326]
36. Pontieri FE, Tanda G, Orzi F, et al. Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature. 1996; 382:255–257. [PubMed: 8717040]
37. Fryer JD, Lukas RJ. Noncompetitive functional inhibition at diverse, human nicotinic acetylcholine receptor subtypes by bupropion, phencyclidine and ibogaine. J Pharmacol Exp Ther. 1999; 288:88–92. [PubMed: 9862757]
38. Slemmer JE, Martin BR, Damaj MI. Bupropion is a nicotinic antagonist. J Pharmacol Exp Ther. 2000; 295:321–327. [PubMed: 10991997]
39. Hurt R, Sachs D, Glover E, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. N Engl J Med. 1997; 337:1195–1202. [PubMed: 9337378]
40. Hays JT, Hurt RD, Rigotti NA, et al. Sustained-release bupropion for pharmacologic relapse prevention after smoking cessation: a randomized, controlled trial. Ann Intern Med. 2001; 135:423–433. [PubMed: 11560455]
41. Gonzales DH, Nides MA, Ferry LH, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo-controlled study. Clin Pharmacol Ther. 2001; 69:438–444. [PubMed: 11406741]
42. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. Lancet. 2001; 357:1571–1575. [PubMed: 11377644]
43. Tonstad S, Farsang C, Klaene G, et al. Bupropion SR for smoking cessation in smokers with cardiovascular disease: a multicentre, randomised study. Eur Heart J. 2003; 24:946–955. [PubMed: 12714026]
44. Jorenby DE, Leischow SJ, Nides M, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Engl J Med. 1999; 340:685–691. [PubMed: 10053177]
45. Rollema H, Chambers LK, Coe JW, et al. Pharmacological profile of the alpha4beta2 nicotinic acetylcholine receptor partial agonist varenicline, an effective smoking cessation aid. Neuropharmacology. 2007; 52:985–994. [PubMed: 17157884]
46. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:56–63. [PubMed: 16820547]
47. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA. 2006; 296:47–55. [PubMed: 16820546]
48. Tonstad S, Tonnesen P, Hajek P, et al. Effect of maintenance therapy with varenicline on smoking cessation: a randomized controlled trial. JAMA. 2006; 296:64–71. [PubMed: 16820548]
49. McClure JB, Swan GE, Jack L, et al. Mood, side-effects and smoking outcomes among persons with and without probable lifetime depression taking varenicline. J Gen Intern Med. 2009; 24:563–569. [PubMed: 19238488]
50. Croghan IT, Hurt RD, Dakhil SR, et al. Randomized comparison of a nicotine inhaler and bupropion for smoking cessation and relapse prevention. Mayo Clin Proc. 2007; 82:186–195. [PubMed: 17290726]
51. Ebbert JO, Croghan IT, Sood A, et al. Varenicline and bupropion sustained-release combination therapy for smoking cessation. Nicotine Tob Res. 2009; 11:234–239. [PubMed: 19246427]
52. Hays JT, Ebbert JO. Bupropion sustained release for treatment of tobacco dependence. Mayo Clin Proc. 2003; 78:1020–1024. quiz 1024. [PubMed: 12911050]
53. National Toxicology Program. Report on Carcinogens. 11th. Washington, DC: US Department of Health and Human Services, Public Health Service, National Toxicology Program;
54. Ernster VL, Grady DG, Greene JC, et al. Smokeless tobacco use and health effects among baseball players. JAMA. 1990; 264:218–224. [PubMed: 2355443]
55. Fisher MA, Taylor GW, Tilashalski KR. Smokeless tobacco and severe active periodontal disease, NHANES III. J Dent Res. 2005; 84:705–710. [PubMed: 16040726]

56. Mattson ME, Winn DM. Smokeless tobacco: association with increased cancer risk. Natl Cancer Inst Monogr. 1989; (8):13–16.
57. Stockwell HG, Lyman GH. Impact of smoking and smokeless tobacco on the risk of cancer of the head and neck. Head Neck Surg. 1986; 9:104–110. [PubMed: 3623935]
58. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. Am J Epidemiol. 1986; 124:926–941. [PubMed: 3776975]
59. Muscat JE, Hoffmann D, Wynder EL. The epidemiology of renal cell carcinoma. A second look. Cancer. 1995; 75:2552–2557. [PubMed: 7736400]
60. Muscat JE, Stellman SD, Hoffmann D, et al. Smoking and pancreatic cancer in men and women. Cancer Epidemiol Biomarkers Prev. 1997; 6:15–19. [PubMed: 8993792]
61. Henley SJ, Thun MJ, Connell C, et al. Two large prospective studies of mortality among men who use snuff or chewing tobacco (United States). Cancer Causes Control. 2005; 16:347–358. [PubMed: 15953977]
62. Substance Abuse and Mental Health Services Administration. [Accessed November 6, 2007] Results from the 2006 National Survey on Drug Use and Health: National Findings. Available at: http://www.oas.samhsa.gov/NSDUH/2k6NSDUH/2k6results.cfm#4.4
63. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Results from the 2007 National Survey on Drug Use and Health: National Findings. Rockville, Md: Department of Health and Human Services, Substance Abuse and Mental Health Services Administration, Office of Applied Studies; 2007. Available at: http://www.oas.samhsa.gov/NSDUH/2k7NSDUH/2k7Results.cfm#Ch4 [Accessed November 6, 2007]
64. Foley, S. [Accessed November 4, 2007] BAT's US subsidiary puts its faith in chewing tobacco. The Independent. Apr 26. 2006 Available at: http://www.independent.co.uk/news/business/news/bats-us-subsidiary-puts-its-faith-in-chewing-tobacco-475621.html
65. Campaign for Tobacco Free Kids. [Accessed December 15, 2007] R J Reynolds Entry Into Smokeless Tobacco Market Cause For Major Concern. Available at: http://www.tobaccofreekids.org/Script/DisplayPressRelease.php3?Display=911
66. McNeill A. Harm reduction. BMJ. 2004; 328:885–887. [PubMed: 15073074]
67. NIH State-of-the-Science Panel. National Institutes of Health State-of-the-Science conference statement: tobacco use: prevention, cessation, and control. Ann Intern Med. 2006; 145:839–844. [PubMed: 16954353]
68. Severson, H. NIH Pub No 93-3461. Bethesda, Md: National Institutes of Health; 1992. Enough Snuff: ST Cessation From the Behavioral, Clinical, and Public Health Perspectives.
69. Ebbert JO, Montori V, Vickers KS, et al. Interventions for smokeless tobacco use cessation. Cochrane Database Syst Rev. 2007; (4):CD004306. [PubMed: 17943813]
70. Severson HH. What have we learned from 20 years of research on smokeless tobacco cessation? Am J Med Sci. 2003; 326:206–211. [PubMed: 14557736]
71. Dale LC, Ebbert JO, Glover ED, et al. Bupropion SR for the treatment of smokeless tobacco use. Drug Alcohol Depend. 2007; 90:56–63. [PubMed: 17353101]
72. Ebbert JO, Dale LC, Patten CA, et al. Effect of high-dose nicotine patch therapy on tobacco withdrawal symptoms among smokeless tobacco users. Nicotine Tob Res. 2007; 9:43–52. [PubMed: 17365735]
73. Ebbert JO, Dale LC, Severson H, et al. Nicotine lozenges for the treatment of smokeless tobacco use. Nicotine Tob Res. 2007; 9:233–240. [PubMed: 17365754]
74. Smith-Simone S, Maziak W, Ward KD, et al. Waterpipe tobacco smoking: knowledge, attitudes, beliefs, and behavior in two U.S. samples. Nicotine Tob Res. 2008; 10:393–398. [PubMed: 18236304]
75. National Cancer Institute, National Institutes of Health. NCI Monograph 9. Bethesda, Md: National Cancer Institute, National Institutes of Health, Cancer Control and Population Sciences; 1998. Cigars: Health Effects and Trends.
76. Henley SJ, Thun MJ, Chao A, et al. Association between exclusive pipe smoking and mortality from cancer and other diseases. J Natl Cancer Inst. 2004; 96:853–861. [PubMed: 15173269]

77. World Health Organization. TobReg-Advi-sory Note Waterpipe Tobacco Smoking: Health Effects, Research Needs and Recommended Actions by Regulators. Geneva: World Health Organization; 2005.

78. Quinn VP, Hollis JF, Smith KS, et al. Effectiveness of the 5-As tobacco cessation treatments in nine HMOs. J Gen Intern Med. 2009; 24:149–154. [PubMed: 19083066]

79. Hughes JR. Tobacco treatment specialists: a new profession. J Smoking Cessation. 2007; 2(suppl): 2–7.

80. Rubak S, Sandbaek A, Lauritzen T, et al. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005; 55:305–312. [PubMed: 15826439]

81. Hurt RD, Dale LC, McClain FL, et al. A comprehensive model for the treatment of nicotine dependence in a medical setting. Med Clin North Am. 1992; 76:495–514. [PubMed: 1312657]

82. Zarling K, Burke M, Gaines K, et al. Registered nurse initiation of a tobacco intervention protocol: leading quality care. J Cardiovasc Nurs. 2008; 23:443–448. [PubMed: 18728517]

83. Hays JT, Wolter TD, Eberman KM, et al. Residential (inpatient) treatment compared with outpatient treatment for nicotine dependence. Mayo Clin Proc. 2001; 76:124–133. [PubMed: 11213299]

84. Croghan IT, Ebbert JO, Hurt RD, et al. Gender differences among smokers receiving interventions for tobacco dependence in a medical setting. Addict Behav. 2009; 34:61–67. [PubMed: 18814974]

Table 1
Mayo Clinic Nicotine Dependence Center Treatment Program Components

Hospital Patients
Nurse Tobacco Use Intervention Protocol
Nurse practitioner TTS
Outpatients
Counselor TTS
Physician
Residential Treatment Program
Physician
TTS
Multicomponent

TTS indicates tobacco treatment specialist.