A Brief Review of Pharmacotherapies for Smoking Cessation

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Abstract
The U.S. Department of Health and Human Services’ Clinical Practice Guidelines have established both nicotine and nonnicotine-based pharmacotherapies as efficacious treatments for smoking cessation. Smokers attempting to quit smoking can significantly increase their chances by using one of several first-line agents, including nicotine transdermal patches, gum, nasal spray, inhalers, tablets, and the antidepressant bupropion. Those who cannot use either bupropion or nicotine replacement therapy because of contraindications or lack of effectiveness may benefit from the second-line treatment nortriptyline. This article also discusses several novel compounds for smoking cessation. (JNCCN 2006;4:583–589)

Background
Cigarette smoking is the principal cause of premature death and disability in the United States. Between 1995 and 1999, more than 440,000 Americans were estimated to die each year from a smoking-related disorder.1 According to a recent report published by the International Agency for Research on Cancer, tobacco smoking is causally linked to 13 different types of neoplastic disease.2 However, despite education about the health hazards of smoking and other tobacco control efforts, many smokers still find it extremely difficult to quit and remain tobacco-free long-term. In fact, only approximately 6% of all smokers who try to stop smoking every year quit successfully.3 Research on effective tobacco cessation treatments, both pharmacologic and behavioral, has been conducted and disseminated extensively over the past several decades. This article reviews the nicotine- and nonnicotine-based pharmacologic agents for tobacco cessation that are currently considered standard care, and other agents that are on the horizon.

Nicotine-Based Treatments
Nicotine replacement therapy (NRT) is considered a first-line treatment for tobacco dependence, and several forms have been approved by the U.S. Food and Drug Administration (FDA) over the past 2 decades.4 When smokers inhale cigarette smoke, they receive a bolus of nicotine that rapidly enters the brain and delivers immediate reinforcement to their drug-seeking behavior. NRTs are designed to provide a lower level and, in some cases, slower infusion of nicotine compared with cigarettes. NRTs wean smokers off nicotine by slowing and reducing the arterial and venous concentrations of the drug and can also relieve withdrawal and cravings among smokers attempting to quit. A recent meta-analysis that included data from more than 100 randomized trials that tested the effects of several forms of NRT reported that all commercially available agents, including nicotine gum, transdermal patches, nasal spray, inhalers, tablets, and the antidepressant bupropion, were effective for smoking cessation.5 These agents increase the odds of quitting long-term as much as two-fold and show no overall significant differences among them. In fact, when trials of all forms of NRT were pooled, results showed that 17% of smokers undergoing NRT therapy were able to quit compared with 10% of those treated with placebo, representing a 74% increase in the odds of abstinence after at least 6 months.6
Nicotine polacrilex (gum) has been available in the United States since 1985 and was approved for over-the-counter use in 1996. The gum is available in 2-mg and 4-mg dosages, with some evidence suggesting that the 4-mg variety may be more effective for heavy smokers (i.e., those who smoke 30 or more cigarettes per day).1-3 The gum is typically used episodically to control cravings and symptoms of withdrawal. A meta-analysis by Silagy et al.5 estimated that 17.4% of smokers who used nicotine gum to treat tobacco dependence in clinical trials remained abstinent 12 months later. The side effects often associated with nicotine gum include hiccoughs, gastrointestinal disturbances, jaw pain, and orodontal problems.7 Individuals with dentures or jaw pain may be unable to use nicotine gum.8 Furthermore, users may often underdose or neglect to follow the recommended dosing and chewing regimen, which could inhibit the agent’s efficacy in reducing withdrawal symptoms. Additionally, the absorption of nicotine from the gum may be impaired when taken concurrently with coffee and some acidic beverages.7 Nicotine gum is the only form of NRT that has been shown to reliably reduce weight gain often associated with smoking cessation, though these results may not persist after the gum is discontinued.8

Transdermal nicotine patches are available in various shapes and sizes, can be worn for 16-hour or 24-hour durations, and deliver between 7 mg and 22 mg of nicotine to the user.10 Unlike the other forms of NRT, the patch is not intended for episodic use but rather to provide a slow but consistent release of nicotine throughout the day. The patch successfully circumvents many of the side effects associated with nicotine gum, but can result in (usually mild) skin sensitivity and irritation.10 Perhaps because of the convenience of applying the patch only once a day, compliance rates with this form of NRT are typically high,10 although the patch provides no oral stimulation. A meta-analysis suggests that an 8-week course of therapy with the patch is as efficacious as longer courses (e.g., up to 28 weeks) and that no treatment difference exists between the 24-hour and 16-hour patches.11 Several studies suggest that a high-dose nicotine patch (i.e., 44 mg) produces slightly higher abstinence rates in heavy smokers (i.e., those who smoke 30 or more cigarettes per day)12-13 and may be especially useful for heavy smokers who report persistent craving and other withdrawal symptoms during cessation.5 Although concern exists about the safety of the patch and other forms of NRT for patients with cardiovascular disease, a recent review showed that in at least 2 trials, the occurrence of adverse cardiac events was no more common in those using the patch compared with those treated with placebo.1

Nicotine nasal spray and the nicotine inhaler are available by prescription and have been found to nearly double a smoker's odds of successfully quitting.1 The nicotine nasal spray is believed to more closely mimic the pharmacokinetics of nicotine delivery through a cigarette than are other forms of NRT.14 The meta-analysis by Silagy et al.5 showed that the overall odds of sustained smoking cessation at 6 to 12 months follow-up were greatest for these 2 forms of NRT, although fewer studies exist for these newer agents and the few studies directly comparing various forms of NRT did not show significant differences. Studies suggest that use of the nicotine inhaler can reduce self-reported withdrawal symptoms, such as craving and restlessness,15 although individuals may experience difficulty complying with the recommended dosage.11 Both inhaler and nasal spray have been associated with local irritation at the site of administration. More specifically, nicotine inhaler users reported side effects such as throat irritation, coughing, and oral burning,11 whereas those using the nasal spray often complained of nasal irritation and runny nose.7

Several forms of nicotine tablets were developed recently, including oral lozenges that deliver 2-mg or 4-mg dosages of nicotine during an approximately 30-minute dissolution period.16 Based on their meta-analysis, Silagy et al.5 reported that the nicotine lozenges resulted in an odds ratio (OR) for abstinence of 2.05 (95% confidence interval [CI], 1.62 to 2.59) and an overall cessation rate of 17% after 12 months. Compared with nicotine gum, lozenges may deliver more nicotine to the user than nicotine gum and are not associated with jaw pain or dental problems.16 Additionally, the lozenge may be particularly effective for smokers who were unable to retain abstinence after using other cessation pharmacotherapies.17 However, associated side effects include hiccoughs, burning sensations in the mouth, sore throat, coughing, dry lips, and mouth ulcers.16 A sublingual nicotine tablet has been marketed in Europe, but is not currently available in the United States.18

Only a few well-designed studies have examined combined forms of NRT, such as comparing the use of
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Gum and the patch versus the patch alone, the patch and inhaler versus either one independently, and nasal spray and the patch versus the patch alone. Results of the meta-analysis by Silagy et al. suggest that combining 2 forms of NRT may have a modest benefit, although further research is required before definitive recommendations can be made. In general, smokers who have been unable to remain abstinent using a single form of NRT may benefit from a combined regimen. However, combining therapies does not necessarily lead to increased efficacy. For example, one large trial showed bupropion to have superior efficacy compared with the nicotine patch, and that combined treatment with the patch and bupropion was not more effective than bupropion alone. Additionally, preliminary data suggest that beginning NRT before an individual's quit date may increase long-term abstinence rates, though self-reported withdrawal symptoms were not decreased relative to those who began NRT on the quit date.

Some researchers suggest that efficacy of the various NRTs may vary with individual differences such as gender or genetic predisposition, although these hypotheses are largely untested and deserve further analysis. At least 2 trials have investigated the pharmacogenetic effects of NRT involving genes related to dopamine receptor sensitivity (DRD2). One study examined genes involved in nicotine metabolism (CYP2A6) and the other study investigated genes involved in opiate receptor function (OPRM1). Although promising, these results are preliminary and will undoubtedly be on the forefront of upcoming NRT research.

The benefits of NRT are apparent at 6- to 12-month follow-up despite the significant relapse rates. Although the effects of NRT seem to be largely independent of the treatment setting, effectiveness has been found to vary by target population and treatment intensity. Across all forms of NRT, overall ORs for abstinence were higher for smokers in the community who volunteered for treatment than for those who were hospital inpatients or referred by their primary care physician. Although a recent meta-analysis showed that the effectiveness of NRT was largely independent of the intensity of additional support offered (i.e., increased abstinence was reported to be associated with higher-intensity support strategies, but the CIs overlapped, suggesting that this may have occurred coincidentally), individual study data suggest that higher quit rates may be achieved as the intensity of a behavioral intervention increases, particular in those using nicotine gum.

Nonnicotine-Based Treatments

Antidepressants

In addition to NRTs, antidepressant medications, including tricyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and atypical antidepressants, have been widely studied as nonnicotine pharmacotherapy for smoking cessation. Researchers examined the effectiveness of antidepressant medications in smoking cessation for several reasons, such as the hypothesis that nicotine may have an antidepressant effect in humans. Furthermore, a strong association exists between smoking and depression. Smokers are more likely than nonsmokers to report a history of depression, and attempts at smoking cessation may also precipitate depression. Among antidepressants, bupropion and nortriptyline modulate noradrenergic neurotransmission, although bupropion may also inhibit the reuptake of dopamine and act as a partial nicotine antagonist. A meta-analysis has shown that these medications double the chance for long-term abstinence compared with placebo.

Bupropion, an atypical antidepressant, was approved as a nonnicotine-based pharmacotherapy for smoking cessation in 1997. As a dopamine and noradrenaline reuptake inhibitor, it has been found to increase the dopamine and norepinephrine concentrations in the mesolimbic dopaminergic and the noradrenergic systems, respectively. Because bupropion may also act as a nicotinic acetylcholine receptor antagonist, it may be useful in preventing relapse by blocking the reinforcing properties of nicotine if one resumes smoking. Bupropion is typically prescribed as bupropion SR 150 mg daily or twice daily. In a meta-analysis based on 19 clinical trials studying the effects of bupropion alone, Hughes et al. found that smokers treated with bupropion were twice as likely as those treated with placebo to achieve long-term abstinence at either 6- or 12-month follow-up visits (pooled OR 2.06; 95% CI, 1.77–2.40). For instance, one of the first clinical trials showed abstinence rates for placebo averaging 19.0% at the end of treatment and 12.4% at the end of 1 year versus abstinence rates of 44.2% and 23.1%, respectively, for 300 mg of bupropion. However, extending the use of bupropion did not
enhance relapse prevention. Two studies\(^38,39\) that asked smokers who had achieved abstinence in the initial treatment phase to continue bupropion therapy for an additional 12 months showed no significant benefit in preventing relapse with the extended treatment (pooled OR 1.25; 95% CI, 0.86–1.81).\(^32\)

Earlier studies examining the effectiveness of bupropion reported a dose–response relationship that showed a higher cessation rate at the end of treatment among smokers who received a higher dose. However, recent findings found no significant difference in cessation rate between the 150-mg and 300-mg doses at long-term (12-month) follow-up (pooled OR 1.07; 95% CI, 0.87–1.32).\(^31\) Research combining bupropion with the nicotine patch has also shown mixed results. One study found that adding bupropion to the nicotine patch enhanced the abstinence rate compared with that of nicotine patch alone (OR 2.65; 95% CI, 1.22–3.53).\(^23\) However a second unpublished study failed to find significant incremental benefits in smoking abstinence by adding bupropion to nicotine patch.\(^40\)

Furthermore, in a recent study in which successful quitters (4-week continuous abstinence) were randomized into 1 of 4 maintenance pharmacotherapies (bupropion plus nicotine gum, bupropion plus placebo gum, placebo medication plus nicotine gum, and placebo medication plus placebo gum), the results showed that only those who received bupropion plus placebo gum had significantly longer time to relapse than those in the placebo/placebo arm.\(^41\) The most common side effects of bupropion are insomnia, dry mouth, headache, and nausea. Results from clinical trials showed that, typically, between 7% and 12% of smokers who received bupropion could not tolerate the side effects and discontinued the medication.\(^32\)

Unlike most forms of NRT and bupropion, which have been rated as first-line pharmacotherapy options for smoking cessation by the U.S. Department of Health and Human Services Clinical Practice Guidelines, nortriptyline is recommended as an effective but second-line medication for smoking cessation.\(^4\) According to these guidelines, a second-line agent is used when a patient cannot use a first-line medication because of either contraindications or lack of effectiveness. Nortriptyline is a tricyclic antidepressant that has highly specific effects on inhibiting the reuptake of norepinephrine.\(^42\) Four trials that used nortriptyline without the nicotine patch\(^43-46\) showed that nortriptyline doubled the odds of long-term abstinence compared with placebo (pooled OR 2.79; 95% CI, 1.70–4.59).\(^32\) In 2 other studies, nortriptyline as an adjunctive therapy to the nicotine patch\(^47,48\) did not show a significant effect compared with the nicotine patch and placebo (pooled OR 1.53; 95% CI, 0.90–2.61).\(^32\)

Hall et al.\(^49\) found bupropion and nortriptyline to be similarly effective (OR 1.85; 95% CI, 0.60–5.02). The typical dose of nortriptyline for smoking cessation treatment ranges from 75 to 150 mg. The common side effects are dry mouth, drowsiness, lightheadedness, and constipation. In 2 clinical trials, between 4% and 9% of smokers were unable to tolerate these side effects and dropped out of the studies.\(^32\) As with other TCAs, nortriptyline, when overdosed, can be lethal and should be used with caution in patients with cardiovascular disease. The possibility of significant adverse events might have warranted nortriptyline’s classification as a second-line medication.\(^49\) However, no serious adverse events were reported in any of the 6 clinical trials for smoking cessation.

Several studies found that neither bupropion nor nortriptyline showed superior efficacy for smokers with a past history of depression compared with those without. Furthermore, despite clinical trials showing that some selective serotonin reuptake inhibitors (SSRIs) such as venlafaxine and fluoxetine were effective in treating smoking cessation in light smokers\(^50\) and smokers with minor depression,\(^51\) respectively, other trials failed to support the efficacy of various other types of SSRIs and other antidepressants as helpful agents for smoking cessation. Together, these findings suggest that the effectiveness of bupropion and nortriptyline as smoking cessation aids may be independent of their antidepressant effect. Although the mechanisms of action remain unclear, researchers believe that the dopaminergic and noradrenergic actions and bupropion’s nicotine receptor antagonistic properties may contribute to the success of these drugs as smoking cessation aids.\(^32,49\)

Clonidine, an \(\alpha_2\) agonist that acts as a peripheral vascular stabilizer, has been recommended as a second-line treatment for smoking cessation in the NCCN Clinical Practice Guidelines.\(^4\) It is primarily used as an antihypertensive agent but has also been used to treat opiate and alcohol withdrawal, Tourette’s syndrome, chronic pain, and menopausal flushing. The efficacy of clonidine as a smoking cessation agent has not been conclusively shown. One meta-analysis
that looked at 12 double-blind studies found a trend for increased smoking cessation with clonidine compared with placebo. However, a more recent meta-analysis looked at 6 studies that reported abstinence data at 3 months after the end of drug treatment and found that clonidine was effective (pooled OR 1.89; 95% CI, 1.30–2.74) compared with placebo, despite only 1 of the 6 studies reporting statistically significant findings. Data from clinical trials indicated that a large number of patients taking clonidine reported side effects (median 14%) and that approximately 14% of patients discontinued the drug because of side effects. Common side effects include fatigue, sedation, dry mouth, dizziness, and postural hypotension.

**Novel Agents**

Two new compounds, varenicline and rimonabant, have recently received considerable attention in the treatment of smoking cessation. Several phase III clinical trials involving these agents have been completed. Varenicline is a partial agonist of the β4α2 nicotinic acetylcholine receptor that combines both agonist and antagonist properties. Thus, varenicline may have the potential to provide relief from withdrawal (agonist effect) and block the rewarding effects of nicotine (antagonist effect). Two clinical trials comparing varenicline (2 mg), bupropion (300 mg), and placebo showed overall continuous abstinence rates of 22.1%, 16.4%, and 8.4%, respectively, between 9 and 52 weeks after quitting. Varenicline more than doubled the odds of quitting over placebo (OR 2.82; 95% CI, 2.06–3.66) and performed significantly better than bupropion (OR 1.56; 95% CI, 1.19–2.06). Compared with smokers treated with placebo, those treated with varenicline reported significantly fewer cravings and withdrawal symptoms throughout the trials. Side effects of varenicline may include nausea and abnormal dreams.

Rimonabant, a selective cannabinoid receptor blocker, is purported to help smokers quit and prevent postcessation weight gain. In a multicenter, double-blind, placebo-controlled trial, in which smokers underwent treatment with either rimonabant, 20 mg or 5 mg, or placebo, smokers treated with rimonabant, 20 mg (14.6%) were significantly more likely to maintain continuous abstinence at 1 year (between 2 and 48 weeks postquit) than were those treated with placebo (7.3%; OR 2.21; P = .008). In another clinical trial, smokers were treated with either rimonabant 20 mg or placebo for an initial 10-week period. Participants who abstained for at least 7 days during the initial treatment period were rerandomized to undergo a 20-mg, 5-mg, or placebo maintenance regimen for another 42 weeks. Results showed that smokers who underwent the 20-mg/20-mg and the 20-mg/5-mg treatment/maintenance regimens experienced significantly lower relapse rates than those who underwent the 20-mg/placebo regimen (OR 1.49; 95% CI, 1.10–2.04, and OR 1.51; 95% CI, 1.11–2.07, respectively). Compared with those who underwent the 20-mg/5-mg and 20-mg/placebo regimens, smokers who underwent the 20-mg/20-mg regimen also experienced significant reduction in postcession weight gain. Rimonabant’s side effects may include upper respiratory tract infections, nasopharyngitis, and headaches. The FDA has recently declined an approval for rimonabant as a pharmacotherapy for smoking cessation. However, additional analyses examining the efficacy of rimonabant are planned and new results may soon emerge.

**Summary**

After more than 2 decades of research and development, an arsenal of efficacious pharmacotherapies to treat smoking cessation are now available. These agents (e.g., NRTs, bupropion, nortriptyline) often double the odds for quitting compared with placebo. Many smokers have benefited from these treatments and quit successfully. However, despite these advances, many smokers relapse and the long-term abstinence rates among smokers who are interested in quitting smoking remain low. Tobacco researchers are working on novel smoking cessation therapies to enhance both initial cessation and long-term abstinence. For instance, 2 promising new compounds designed specifically to block the rewarding properties of nicotine are on the horizon, and pharmacogenetic studies are using genetic information to better tailor existing treatment agents to smokers.

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**References**


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