

Future Research

The following topics require additional research:

- Effectiveness of motivational interviewing and related techniques, including the impact of brief motivational interviewing strategies delivered in primary care settings
- Effectiveness of physiological monitoring and biological marker feedback to motivate smokers to quit and increase abstinence rates

B. Medication Evidence

Recommendation: Clinicians should encourage all patients attempting to quit to use effective medications for tobacco dependence treatment, except where contraindicated or for specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents). (Strength of Evidence = A)

As with other chronic diseases, the most effective treatment of tobacco dependence requires the use of multiple clinical modalities. Medications are a vital element of a multicomponent approach. The clinician should encourage all patients initiating a quit attempt to use one or a combination of effective medications, although medication use may not be appropriate with some patient groups (e.g., those with medical contraindications, those smoking fewer than 10 cigarettes a day, pregnant/breastfeeding women, smokeless tobacco users, and adolescent smokers). The Guideline Panel identified seven first-line (FDA-approved) medications (bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline) and two second-line (non-FDA-approved for tobacco use treatment) medications (clonidine and nortriptyline) as being effective for treating smokers. Each has been documented to increase significantly rates of long-term smoking abstinence. These results are consistent with other independent reviews.^{158,297-300} No other medication treatments were consistently supported by the available scientific evidence.

In this update, the Panel conducted an inclusive meta-analysis of medications that complements the inclusive meta-analysis of psychosocial interventions that was conducted for the 2000 Guideline. For this meta-analysis, all medication trials with at least two studies of a particular medication,

at an appropriate dose and duration, were entered into one analysis. This inclusive medication meta-analysis allows for the comparison of particular medications to both placebo controls and other active medications (Table 6.26), and makes greater use of all information in the available studies. Note also that, although all of these studies were published in peer-reviewed journals, a number of the studies were supported by the pharmaceutical industry.

The medication meta-analysis included predominantly studies with “self-selected” populations (see Chapter 1, Overview and Methods). In addition, in medication studies both experimental and control subjects in the studies typically received substantial counseling. Both of these factors tend to produce higher abstinence rates than typically are observed among self-quitters.

The studies submitted to the inclusive medications meta-analysis were screened and categorized prior to analysis. Screening removed medications for which there were too few acceptable studies to submit to meta-analysis (e.g., the nicotine lozenge, selegiline), and removed study arms that were confounded (e.g., two different medication conditions had counseling adjuvants of different intensities). Decisions about cutscores for treatment duration and dose categories were designed to be consistent with package insert information and data on effectiveness (i.e., prior data indicated rough clinical equivalence of certain dosages). Therefore, although there was an attempt to achieve some uniformity across the medications, decisions about dose and duration categories necessarily were made on a medication-by-medication basis. It is important to note that some medication categories, and some medication recommendations, do not conform with manufacturers’ recommendations (e.g., the use of a nicotine patch dose > 25 mg per day). Table 6.25 shows the dosage and duration inclusion criteria for normal course, long-term, and high-dose medication classifications. In the case of medication combinations, the combinations typically comprised two standard-length medication regimens. In one combination, however, *ad libitum* NRT (gum or spray) was paired with long-term nicotine patch use (“patch [long-term] + *Ad Lib* NRT”). Different medications were grouped together into a single use category (e.g., grouping nicotine gum and spray together into the “Long-term *Ad Lib* NRT” condition) when the grouping was clinically and conceptually meaningful and when it permitted greater use of the available research evidence. Analyses were conducted for both 6- and 12-month outcomes, and the results of the

12-month analyses were very similar to the 6-month results shown in Table 6.26.

Table 6.25. Coding rules for medication duration and dose

Medication	Coding	Meaning
Nicotine Patch	Usual duration	6–14 weeks
	Long duration	> 14 weeks
	Usual dose/day	15 mg/16 hours/day 21 mg/24 hours/day
	High dose	> 25 mg/day
Nicotine Gum	Usual duration	6–14 weeks
	Long duration	> 14 weeks
Nicotine Inhaler and Nasal Spray	Usual duration	Up to 6 months
	Long duration	> 6 months
Bupropion SR	Usual duration	Up to 14 weeks
	Usual dose/day	150 mg once daily or twice daily
Varenicline	Usual duration	Up to 14 weeks
	Usual dose/day	1 mg daily or 1 mg twice daily (analyzed separately)

Recommendations Regarding Individual Medications: First-Line Medications

First-line medications are those that have been found to be safe and effective for tobacco dependence treatment and that have been approved by the FDA for this use, except in the presence of contraindications or with specific populations for which there is insufficient evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents). These first-line medications have an established empirical record of effectiveness, and clinicians should consider these agents first in choosing a medication. For the 2008 update, the first-line medications are listed in Table 6.26 by size of the odds ratio and in the text alphabetically by generic name.

Table 6.26. Meta-analysis (2008): Effectiveness and abstinence rates for various medications and medication combinations compared to placebo at 6-months postquit (n = 83 studies)^a

Medication	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Placebo	80	1.0	13.8
Monotherapies			
Varenicline (2 mg/day)	5	3.1 (2.5–3.8)	33.2 (28.9–37.8)
Nicotine Nasal Spray	4	2.3 (1.7–3.0)	26.7 (21.5–32.7)
High-Dose Nicotine Patch (> 25 mg) (These included both standard or long-term duration)	4	2.3 (1.7–3.0)	26.5 (21.3–32.5)
Long-Term Nicotine Gum (> 14 weeks)	6	2.2 (1.5–3.2)	26.1 (19.7–33.6)
Varenicline (1 mg/day)	3	2.1 (1.5–3.0)	25.4 (19.6–32.2)
Nicotine Inhaler	6	2.1 (1.5–2.9)	24.8 (19.1–31.6)
Clonidine	3	2.1 (1.2–3.7)	25.0 (15.7–37.3)
Bupropion SR	26	2.0 (1.8–2.2)	24.2 (22.2–26.4)
Nicotine Patch (6–14 weeks)	32	1.9 (1.7–2.2)	23.4 (21.3–25.8)
Long-Term Nicotine Patch (> 14 weeks)	10	1.9 (1.7–2.3)	23.7 (21.0–26.6)
Nortriptyline	5	1.8 (1.3–2.6)	22.5 (16.8–29.4)
Nicotine Gum (6–14 weeks)	15	1.5 (1.2–1.7)	19.0 (16.5–21.9)
Combination therapies			
Patch (long-term; > 14 weeks) + <i>ad lib</i> NRT (gum or spray)	3	3.6 (2.5–5.2)	36.5 (28.6–45.3)
Patch + Bupropion SR	3	2.5 (1.9–3.4)	28.9 (23.5–35.1)
Patch + Nortriptyline	2	2.3 (1.3–4.2)	27.3 (17.2–40.4)
Patch + Inhaler	2	2.2 (1.3– 3.6)	25.8 (17.4–36.5)
Patch + Second generation antidepressants (paroxetine, venlafaxine)	3	2.0 (1.2–3.4)	24.3 (16.1–35.0)
Medications not shown to be effective			
Selective Serotonin Re-uptake Inhibitors (SSRIs)	3	1.0 (0.7–1.4)	13.7 (10.2–18.0)
Naltrexone	2	0.5 (0.2–1.2)	7.3 (3.1–16.2)

^a Go to www.surgeongeneral.gov/tobacco/gdlnrefs.htm for the articles used in this meta-analysis.

■ **Bupropion SR (Sustained Release)**

Recommendation: Bupropion SR is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

Bupropion SR was the first non-nicotine medication shown to be effective for smoking cessation and was approved by the FDA for that use in 1997. Its possible mechanisms of action include blockade of neuronal re-uptake of dopamine and norepinephrine and blockade of nicotinic acetylcholinergic receptors. It is contraindicated in patients with a seizure disorder, a current or prior diagnosis of bulimia or anorexia nervosa, use of a monoamine oxidase (MAO) inhibitor within the previous 14 days, or in patients taking another medication that contains bupropion. Bupropion SR is available exclusively as a prescription medication and can be used in combination with nicotine replacement therapies. Suggestions regarding the clinical use of bupropion SR are provided in Table 3.3.

Twenty-four studies generated the 26 arms that served as the basis for estimating the bupropion SR effect. The bupropion SR dose was 150 mg for 3 of these study arms, and 300 mg for the other 22 of these arms (one study did not report dose). As Table 6.26 reveals, bupropion SR approximately doubles the likelihood of long-term (> 5 month) abstinence from tobacco use as compared to placebo treatment. These results are consistent with other independent reviews.²⁹⁹

■ **Nicotine Replacement Therapies (NRTs)**

Nicotine replacement therapy (NRT) medications deliver nicotine with the intent to replace, at least partially, the nicotine obtained from cigarettes and to reduce the severity of nicotine withdrawal symptoms.

Nicotine Gum

Recommendation: Nicotine gum is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

Recommendation: Clinicians should offer 4 mg rather than 2 mg nicotine gum to highly dependent smokers. (Strength of Evidence = B)

Nicotine gum currently is available exclusively as an OTC medication and is packaged with important instructions on correct usage, including chewing (see Table 3.4 for information on the clinical use of nicotine gum). Nine studies generated the 15 study arms that served as the basis for estimating the effect of nicotine gum. In addition, another four studies generated the six arms that served as the basis for the estimation of effects of long-term gum use (directed use beyond 14 weeks). Two arms used gum for 52 weeks, and the other four arms used gum for 24–26 weeks. Table 6.26 reveals that regular course and long-term nicotine gum use increased the likelihood of long-term abstinence by about 50 percent compared to placebo treatment. These results are consistent with other independent reviews.³⁰⁰

Nicotine Inhaler

Recommendation: The nicotine inhaler is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

The nicotine inhaler currently is available exclusively as a prescription medication. The nicotine inhaler is not a true pulmonary inhaler, but rather deposits nicotine in the oropharynx, from which it is absorbed across the mucosa. See Table 3.5 for suggestions regarding the clinical use of the nicotine inhaler. Six studies generated the six arms that served as the basis for estimating the nicotine inhaler effect. As Table 6.26 shows, the inhaler approximately doubled smokers' likelihood of long-term abstinence from tobacco as compared to placebo treatment. These results are consistent with other independent reviews.³⁰⁰

Nicotine Lozenge

Recommendation: The nicotine lozenge is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = B)

Nicotine lozenge is available exclusively as an OTC medication and is packaged with important instructions for correct usage (see Table 3.6). Only one randomized controlled trial of the nicotine lozenge was available for review.³⁰¹ Therefore, the nicotine lozenge was not included in the inclusive meta-analysis (Table 6.26). The data from this study of more than 1,800 smokers found that the 2-mg lozenge for low-dependent smokers (smoke

a first cigarette 30 minutes or more after waking) approximately doubled and the 4-mg lozenge for highly dependent smokers (smoke a first cigarette within 30 minutes of waking) approximately tripled the odds of abstinence at 6 months postquit as compared to placebo treatment. See Table 6.27 for the study results. These results are consistent with other independent reviews.³⁰⁰

Table 6.27. Effectiveness of the nicotine lozenge: Results from the single randomized controlled trial

Lozenge dose	N for active/N for placebo	Odds Ratio (95% C.I.)	Continuous abstinence rates at 6 months (Active/Placebo)
2 mg	459/458	2.0 (1.4–2.8)	24.2/14.4
4 mg	450/451	2.8 (1.9–4.0)	23.6/10.2

Nicotine Nasal Spray

Recommendation: Nicotine nasal spray is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

The nicotine nasal spray currently is available exclusively as a prescription medication. See Table 3.7 for suggestions regarding the clinical use of the nicotine nasal spray. Four studies generated the four study arms that served as the basis for estimating the nasal spray effect. As Table 6.26 reveals, the nasal spray more than doubles the likelihood of long-term abstinence from tobacco as compared to placebo treatment.

Nicotine Patch

Recommendation: The nicotine patch is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

Nicotine patches currently are available both as an OTC medication and as a prescription medication. Awareness of this prescription option is important for insurance plans that include coverage only for prescription medications. Suggestions for the clinical use of the nicotine patch are provided in Table 3.8.

Twenty-five studies generated the 32 study arms that served as the basis for estimating the nicotine patch effect. Of these 32 arms, the peak dose used was 14 or 15 mg in 6 study arms and 21–25 mg in 25 arms (one study did not report dose). As Table 6.26 shows, the nicotine patch almost doubled the likelihood of long-term abstinence compared to placebo treatment. These results are consistent with other independent reviews.³⁰⁰

The meta-analysis also addressed the effectiveness of long-term and high-dose nicotine patch therapy. As noted in Table 6.25, high-dose therapy was coded when the highest dose used exceeded 25 mg. This often was achieved by using two patches per day as a dosing regimen. Four studies generated four analyzable study arms with peak patch dosages of 30 mg (2 arms), 35 mg (1 arm), and 42 mg (1 arm). In some of these high-dose arms, patch use was of regular duration (14 weeks or less), although in other arms the duration of directed patch use exceeded 14 weeks.

Table 6.25 shows that long-term patch therapy was coded when the duration of directed patch use exceeded 14 weeks. All of the long-term patch studies used regular-dose patch regimens (15–25 mg). Eight studies generated 10 study arms that served as the basis for estimating the effect of long-term patch therapy. Table 6.26 shows that both long-term therapy and high-dose patch therapy approximately doubled the likelihood that a smoker would achieve long-term abstinence relative to placebo treatment. Thus, neither high-dose nor long-term patch therapy appeared to produce benefit above and beyond that of nicotine patch therapy at the regular duration (6–14 weeks) and dose (14–25 mg).

A time trend analysis of the nicotine patch studies based on data from the current meta-analysis revealed no significant change in the effectiveness of the nicotine patch during the approximately 15 years it has been available.

■ Varenicline

Recommendation: Varenicline is an effective smoking cessation treatment that patients should be encouraged to use. (Strength of Evidence = A)

Varenicline is a non-nicotine medication that was approved by the FDA for the treatment of tobacco dependence in 2006. Its mechanism of action is presumed to be due to its partial nicotine receptor agonist and antagonist effects. It is well tolerated in most patients. However, a recent publication

reported two case reports of exacerbations of existing psychiatric illness, schizophrenia and bipolar illness, in patients who took varenicline.^{302,303} In contrast, one recent smoking cessation study using varenicline included smokers with mental illness (depression, bipolar disorder, and/or psychosis) and reported no evidence that varenicline worsened the patients' mental illness.³⁰⁴ Importantly, the FDA noted that patients with psychiatric illness were not included in the studies conducted for the approval of this medication.

In February 2008, the FDA added a warning regarding the use of varenicline. Specifically, it noted that depressed mood, agitation, changes in behavior, suicidal ideation, and suicide have been reported in patients attempting to quit smoking while using varenicline. The FDA recommends (1) that patients tell their health care provider about any history of psychiatric illness prior to starting this medication; and (2) that clinicians monitor patients for changes in mood and behavior when prescribing this medication. In light of these FDA recommendations, clinicians should consider eliciting information on their patients' psychiatric history.

Because varenicline is eliminated almost entirely unchanged in the urine, it should be used with caution in patients with severe renal dysfunction (creatinine clearance < 30 ml per min). Varenicline is available exclusively as a prescription medication and is not recommended for use in combination with NRT because of its nicotine antagonist properties. One recent review²⁹⁷ found that varenicline increased odds of quitting over that of bupropion SR with a minimal to moderate side effect profile. Suggestions regarding the clinical use of varenicline are presented in Table 3.9.

The FDA dosing recommendation for varenicline is a total of 2 mg per day (1 mg twice daily). However, there is evidence that a dose of 1 mg per day also is effective.³⁰⁵ Therefore, the effectiveness of both doses was addressed in the inclusive meta-analysis. Four studies generated five study arms that served as the basis for estimating the effect of 2 mg varenicline. Two studies generated the three study arms that served as the basis for estimating the effect of 1 mg varenicline. As Table 6.26 shows, the 1 mg total daily dose of varenicline approximately doubles, and the 2 mg total daily dose of varenicline approximately triples, a smoker's likelihood of long-term abstinence from tobacco as compared to placebo treatment. This suggests that the 1 mg per day dose is a viable alternative to the 2 mg per day dose, should the patient experience dose-related side effects.

Evidence indicates that varenicline is well-tolerated for periods up to 1 year³⁰⁶ and that extended treatment may prove useful in reducing the likelihood of relapse.³⁰⁷ More research is needed, however, to evaluate varenicline as a relapse prevention medication, to assess its long-term effects, and to evaluate its effectiveness in specific populations.

■ **Interactions of First-Line Tobacco Use Medications With Other Drugs**

The goal of treating tobacco use and dependence is abstinence from tobacco products. In achieving this goal, the metabolic effects of tobacco abstinence must be understood with respect to potential changes in homeostasis that occur in response to quitting and, eventually, the elimination of nicotine from the body. This is particularly important for smokers who are on other medications for chronic disease state management because they essentially are in a homeostatic metabolic condition and the titration of their chronic disease medications may have been influenced by their smoking status.

The polycyclic aromatic hydrocarbons in tobacco smoke are metabolic inducers of some isoforms of the hepatic cytochrome P450.³⁰⁸ Thus, when smokers quit and the P450 system returns to its basal level of functioning, the concentration of drugs metabolized by these particular CYP isoforms may increase. As a result, smokers who quit can experience side effects from supratherapeutic drug levels of caffeine, theophylline, fluvoxamine, olanzapine, and clozapine. This can have serious consequences for selective drugs such as clozapine, with its associated agranulocytosis.³⁰⁹

Although nicotine is metabolized by CYP2A6, it does not appear to induce, in a clinically significant way, CYP enzymes. Thus, when a smoker is switched from cigarettes to a nicotine replacement product, changes in drug metabolism are similar to those seen when quitting without NRT.

Nicotine produces sympathetic activation that may reduce the sedative effects of benzodiazepines, and the vasoconstrictive effects of nicotine may decrease subcutaneous absorption of insulin. Nicotine also may attenuate the ability of beta-blockers to lower blood pressure and heart rate and may lessen opioid analgesia. When nicotine replacement products are withdrawn, adjustments in these types of medications may be necessary.

The metabolism of bupropion is mediated primarily by CYP2B6. Three categories of drugs could have clinically significant interactions with bupropion: drugs affecting CYP2B6, drugs metabolized by CYP2D6, and general enzyme inducers/inhibitors.³¹⁰ Drugs that affect CYP2B6 metabolism, such as cyclophosphamide and orphenadrine, potentially could alter bupropion metabolism. Bupropion and its metabolites inhibit CYP2D6^{311,312} and could affect the impact of agents metabolized by this enzyme (e.g., tricyclic antidepressants, antipsychotics, type 1C antiarrhythmics, or certain beta-blockers). Due to the extensive metabolism of bupropion, enzyme inducers (e.g., carbamazepine, phenobarbital, phenytoin) and inhibitors (e.g., valproate, cimetidine) may alter its plasma concentration. Bupropion can lower seizure threshold. It should be used with caution with medications that can also lower seizure threshold.^{310,313} Specifically, use of bupropion within 14 days of discontinuation of therapy with any MAO inhibitor is contraindicated.

Varenicline is eliminated unchanged by kidney excretion and thus is believed to pose no metabolic effects. Cimetidine inhibits the renal secretion of varenicline, although the magnitude of the interaction is small. No significant drug-drug interactions are known.³¹⁴

Recommendations Regarding Second-Line Medications

Second-line medications are medications for which there is evidence of effectiveness for treating tobacco dependence, but they have a more limited role than first-line medications because: (1) the FDA has not approved them for a tobacco dependence treatment indication; and (2) there are more concerns about potential side effects than exist with first-line medications. Second-line medications should be considered for use on a case-by-case basis after first-line medications (either alone or in combination) have been used without success or are contraindicated. The listing of the second-line medications is alphabetical by generic name.

■ Clonidine

Recommendation: Clonidine is an effective smoking cessation treatment. It may be used under a physician's supervision as a second-line agent to treat tobacco dependence. (Strength of Evidence = A)

Three studies generated three analyzable study arms that served as the basis for estimating clonidine's effects on long-term abstinence. These studies all were conducted prior to 1997. Table 6.26 reveals that the use of clonidine approximately doubles abstinence rates when compared to a placebo. These studies varied the clonidine dose from 0.1 to 0.75 mg per day. The drug was delivered either transdermally or orally. It should be noted that abrupt discontinuation of clonidine can result in symptoms such as nervousness, agitation, headache, and tremor, accompanied or followed by a rapid rise in blood pressure and elevated catecholamine levels.

Clonidine is used primarily as an antihypertensive medication and has not been approved by the FDA as a medication for treating tobacco use and dependence. Therefore, clinicians need to be aware of the specific warnings regarding this medication as well as its side-effect profile. Additionally, a specific dosing regimen for the use of clonidine in smoking cessation has not been established. The Guideline Panel chose to recommend clonidine as a second-line as opposed to first-line agent because of the warnings associated with clonidine discontinuation, variability in dosages used to test this medication, and lack of FDA approval. As such, clonidine should be considered for treating tobacco use under a physician's monitoring with patients unable to use first-line medications because of contraindications or with patients who were unable to quit when using first-line medications. An independent review²⁹⁸ indicated that clonidine is effective in promoting smoking abstinence, but prominent side effects limit its usefulness. Suggestions regarding clinical use of clonidine are provided in Table 3.10.

■ Nortriptyline

Recommendation: Nortriptyline is an effective smoking cessation treatment. It may be used under a physician's supervision as a second-line agent to treat tobacco dependence. (Strength of Evidence = A)

Four studies generated the five analyzable study arms that served as the basis for estimating the effect of nortriptyline on long-term abstinence. Nortriptyline dosages were 75 mg per day (3 arms) and 100 mg per day (2 arms), with treatment lasting from 6 to 13 weeks across the five arms. As Table 6.26 shows, nortriptyline almost doubles a smoker's likelihood of achieving long-term abstinence from tobacco as compared to placebo treatment. A recent independent review¹⁵⁸ also indicated that nortriptyline is effective in treating tobacco dependence. Suggestions regarding the

clinical use of nortriptyline are provided in Table 3.11. Nortriptyline is used primarily as an antidepressant and has not been evaluated or approved by the FDA as a medication for treating tobacco use and dependence. Clinicians need to be aware of the specific warnings regarding this medication as well as its side-effect profile. Because of the side-effect profile and the lack of FDA approval for tobacco dependence treatment, nortriptyline is recommended as a second-line rather than a first-line agent. As such, nortriptyline should be considered for treating tobacco use under a physician's direction with patients unable to use first-line medications because of contraindications or with patients who were unable to quit using first-line medications.

Combination Medications

Recommendation: Certain combinations of first-line medications have been shown to be effective smoking cessation treatments. Therefore, clinicians should consider using these combinations of medications with their patients who are willing to quit. Effective combination medications are:

- **Long-term (> 14 weeks) nicotine patch + other NRT (gum and spray)**
- **The nicotine patch + the nicotine inhaler**
- **The nicotine patch + bupropion SR (Strength of Evidence = A)**

The number and variety of analyzable articles was sufficient to assess the effectiveness of five combinations of medications relative to placebo. Only the patch + bupropion combination has been approved by the FDA for smoking cessation.

■ Nicotine Patch + Bupropion SR

Three studies yielded three analyzable study arms that served as the basis for estimating the effect of the nicotine patch + bupropion SR on long-term abstinence. Both the patch and bupropion SR were used at standard durations and doses (see Table 6.25).

■ Nicotine Patch + Nicotine Inhaler

Two studies generated two arms that served as the basis for estimating the effect of the nicotine patch + the nicotine inhaler. The 15-mg patch was used in both studies at a regular treatment duration. The directed duration of use of the inhaler was 12 weeks in one arm and 26 weeks in the other arm.

■ Long-Term Nicotine Patch Use + *Ad Libitum* NRT

Three studies yielded three analyzable study arms that served as the basis for estimating the effect of long-term nicotine patch use + *ad libitum* NRT use. All arms involved nicotine patch therapy that exceeded 14 weeks, with durations that ranged from 18 to 24 weeks. The *ad libitum* NRT condition involved nicotine gum in two arms and the nicotine nasal spray in one arm. The two gum arms both used 2-mg gum, with directed use lasting 26 weeks in one arm and 52 weeks in another arm. The third arm involved nicotine nasal spray, with directed use lasting 52 weeks.

■ Nicotine Patch + Nortriptyline

Two studies generated three analyzable arms that served as the basis for estimating the effects of the nicotine patch + nortriptyline. The 21-mg nicotine patch served as the highest patch dose in all study arms, and the nortriptyline dose was 75 mg per day in one arm and 100 mg per day in the other arm. Both medications were used for standard durations (8–14 weeks).

■ Nicotine Patch + Second Generation Antidepressants

Three studies yielded three analyzable arms that served as the basis for estimating the effects of second generation antidepressants + the nicotine patch. The antidepressants used included the specific serotonin re-uptake inhibitor paroxetine (20 mg per day for 9 weeks for 2 arms), and the atypical antidepressant venlafaxine (22 mg per day for 21 weeks). The 21- or 22-mg patch served as the highest patch dose, with the duration of patch therapy being 6 or 8 weeks.

■ Effectiveness of Medication Combinations

Table 6.26 displays the 2008 meta-analytic results describing the effectiveness data for the five medication combinations. The data reveal that the nicotine patch + bupropion SR, the nicotine patch + inhaler, the long-term nicotine patch + *ad libitum* NRT, the nicotine patch + nortriptyline, and the nicotine patch + second generation antidepressants all significantly increased a smoker's likelihood of abstinence relative to placebo treatment. A meta-analysis using 12-month abstinence rates had similar results. The first three medication combinations involve only first-line medications and therefore are recommended for use as first-line treatments.

Decisions about use of a medication combination may be based on considerations other than abstinence. Evidence indicates, for instance, that a combination of medication may result in greater suppression of tobacco withdrawal symptoms than does the use of a single medication.^{148,315,316}

Patient preferences also may play a role, because some combinations of medications may produce more side effects and cost more than individual medications.^{315,317,318}

Relative Effectiveness of Medications

Information on the relative effectiveness of medications may help the clinician and patient select an appropriate medication intervention. To this end, all medication conditions in Table 6.26 were compared with the nicotine patch. The nicotine patch was selected as a comparison condition because more study arms were available for this condition than for any other, and because this condition was of moderate effectiveness relative to other conditions (see Table 6.26; OR = 1.9). Contrasts between all treatments were not conducted because of concerns about Type I error due to multiple testing. Also, a conservative Hochberg³¹⁹ adjustment to the alpha level was used so that only treatments that were substantially different in effectiveness would be found to be significantly different. These comparisons of the different medications should be viewed as suggestive rather than definitive. For instance, the studies of one type of medication may differ from studies evaluating a different medication on numerous bases such as year of publication, type of population, and newness of the medication. It is possible that such differences could have affected the relative size of the odds ratios obtained for the different medications. Existing studies that provide head-to-head comparisons of medications

(which were included in this meta-analysis) provide an additional source of information on this topic.

The *a posteriori* tests resulted in three treatment conditions being statistically different from the effectiveness of the nicotine patch when it is used at regular doses and durations. The 2 mg per day varenicline and the combination of long-term patch use + *ad libitum* NRT (gum or spray) were both found to produce significantly greater likelihood of long-term abstinence than the patch by itself (see Table 6.28). Two treatments produced a lower likelihood of long-term abstinence: selective serotonin re-uptake inhibitors (SSRIs) and naltrexone. The analyses presented in Table 6.28 represent 6-month abstinence rates. Similar conclusions were reached in a meta-analysis of 12-month abstinence rates.

Table 6.28. Meta-analysis (2008): Effectiveness of and abstinence rates of medications relative to the nicotine patch (n = 83 studies)^a

Medication	Number of arms	Estimated odds ratio (95% C. I.)
Nicotine Patch (reference group)	32	1.0
Monotherapies		
Varenicline (2 mg/day)	5	1.6 (1.3–2.0)
Nicotine Nasal Spray	4	1.2 (0.9–1.6)
High-Dose Nicotine Patch (> 25 mg; standard or long-term)	4	1.2 (0.9–1.6)
Long-Term Nicotine Gum (> 14 weeks)	6	1.2 (0.8–1.7)
Varenicline (1 mg/day)	3	1.1 (0.8–1.6)
Nicotine Inhaler	6	1.1 (0.8–1.5)
Clonidine	3	1.1 (0.6–2.0)
Bupropion SR	26	1.0 (0.9–1.2)
Long-Term Nicotine Patch (> 14 weeks)	10	1.0 (0.9–1.2)
Nortriptyline	5	0.9 (0.6–1.4)
Nicotine Gum	15	0.8 (0.6–1.0)
Combination therapies		
Patch (long-term; > 14 weeks) + NRT (gum or spray)	3	1.9 (1.3–2.7)
Patch + Bupropion SR	3	1.3 (1.0–1.8)

Table 6.28. Meta-analysis (2008): Effectiveness of and abstinence rates of medications relative to the nicotine patch (n = 83 studies)^a (continued)

Medication	Number of arms	Estimated odds ratio (95% C. I.)
Combination therapies		
Patch + Nortriptyline	2	0.9 (0.6–1.4)
Patch + Inhaler	2	1.1 (0.7–1.9)
Second-generation antidepressants & Patch	3	1.0 (0.6–1.7)
Medications not shown to be effective		
Selective Serotonin Re-uptake Inhibitors (SSRIs)	3	0.5 (0.4–0.7)
Naltrexone	2	0.3 (0.1–0.6)

^a Go to www.surgeongeneral.gov/tobacco/gdlnrefs.htm for the articles used in this meta-analysis.

■ Precessation NRT Use

Recent studies have investigated the use of NRT prior to a quit attempt. Some of these studies involved smokers who are planning to quit, and others involved smokers who were not willing to quit but who were willing to reduce their smoking. The use of NRT while smoking contradicts NRT package inserts. The existence of multiple studies on this prequit medication strategy led the Panel to review this topic as part of this Guideline update. The results of this review (see below) suggest that NRT prior to quitting may be effective in increasing abstinence rates, but the Panel chose not to recommend this intervention (see below). If this strategy is used clinically, patients should be advised to cease NRT use if they develop symptoms of nicotine toxicity (e.g., nausea, vomiting, dizziness).

Precessation Use of NRT Among Patients Making a Quit Attempt. Two randomized controlled studies examined the effect of initiating the use of NRT prior to a quit attempt among patients making a quit attempt. One study examined the use of nicotine patches, either active or placebo, 2 weeks prior to quitting, after which all participants received active patches for 12 weeks following the quit day.³²⁰ Results revealed no differences in adverse events, and smokers who had received the active patches during the prequit period were more likely to be abstinent at 6 months postquit. In a second study, Rose and colleagues³²¹ found that precessation patch use significantly increased abstinence rates at 4 weeks postquit but not at 6 months.

Finally, a small pilot study found that prequit patch use was well tolerated by smokers wanting to quit.³²² Given the limited data on this strategy, the Panel declined to recommend precessation use of NRT among patients making a quit attempt. However, this topic warrants further research.

Use of NRT Among Patients Unwilling to Make a Quit Attempt at This Time.

Research has examined the use of NRT in patients who are not currently willing to make a quit attempt but who state that they are willing to reduce their smoking. In general, these studies found that NRT used in this way increased the likelihood that smokers will make a quit attempt and succeed in quitting. Sufficient studies were available to meta-analyze this topic for the Guideline update. Five studies generated five arms that met criteria for the analysis of the effect of NRT compared to placebo with smokers not willing to quit (but who were willing to reduce the number of cigarettes smoked and use a nicotine replacement medication). As Table 6.29 shows, the use of NRT more than doubled the likelihood that a smoker would be abstinent at 12 months, despite the smoker's unwillingness to make a quit attempt at the time of initial assessment. The nicotine replacement products in these studies included nicotine gum (2 or 4 mg for 6–12 months), the nicotine inhaler (10 mg for 6–24 months), the nicotine patch (16-hour 15-mg patch for up to 6 months), or the choice of a combination of these medications.

Because of the selective participant inclusion criteria and other aspects of this research, it is unclear that the results described above would be relevant to the broader population of smokers unwilling to quit. For instance, most patients in the studies included in the analysis in Table 6.29 were not offered a cessation intervention prior to study induction. It is possible that some of the participants would have opted for a free cessation treatment had it been offered. Also, in some instances, the recruitment material may have made it clear that treatment was available only for those uninterested in quitting. It is unclear how this perceived contingency affected the sample. Further, it is not clear if the results would be true for only those interested in reducing their smoking and not for uninterested patients, in general. Additionally, there was concern that if clinicians routinely asked about interest in cutting down, this might suggest to tobacco users that reduction confers health benefits, is a recommended strategy for persons trying to quit, or is a recommended goal of treatment (rather than quitting smoking)—and that these perceptions might decrease the proportion of smokers willing to make a quit attempt. Because of such concerns, the Panel

decided not to recommend medication use as a standard intervention for smokers unwilling to quit. A recent Cochrane analysis³²³ found that NRT significantly increased quit rates among smokers not initially motivated to quit. The authors concluded, however, that there was insufficient evidence to recommend this as a standard treatment approach with this population. The Panel believes that this topic warrants further research.

Table 6.29. Meta-analysis (2008): Effectiveness of and abstinence rates for smokers not willing to quit (but willing to change their smoking patterns or reduce their smoking) after receiving NRT compared to placebo (n = 5 studies)^a

Intervention	Number of arms	Estimated odds ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Placebo	5	1.0	3.6
Nicotine replacement (gum, inhaler, or patch)	5	2.5 (1.7–3.7)	8.4 (5.9–12.0)

^a Go to www.surgeongeneral.gov/tobacco/gdlnhrefs.htm for the articles used in this meta-analysis.

Medications Not Recommended by the Guideline Panel

■ Antidepressants Other Than Bupropion SR and Nortriptyline

Smoking is significantly more prevalent among individuals with a past history of depression, and these individuals have more difficulty quitting smoking than do smokers without a past history of depression.^{324–328} One antidepressant, bupropion SR, has been documented as effective for treating tobacco use and approved by the FDA for this use (see Bupropion SR [sustained release], page 110). Nortriptyline also has been documented to be effective (see Nortriptyline, page 117), although the FDA has not evaluated this medication for treatment of tobacco dependence. The Panel's review of the extant literature revealed a sufficient body of research to evaluate one class of antidepressants that is dissimilar from both bupropion SR and nortriptyline: selective serotonin re-uptake inhibitors (SSRIs).

■ **Selective Serotonin Re-Uptake Inhibitors (SSRIs)**

Two studies yielded three analyzable arms that served as the basis for estimating the effects of SSRIs. Sertraline (200 mg per day) served as the medication in one arm, and fluoxetine (30 to 60 mg per day) served as the medication in the other two arms. The treatment duration was 10 weeks in all arms. Results showed that treatment with SSRIs did not significantly increase the likelihood of abstinence relative to placebo treatment. These results are consistent with other independent reviews²⁹⁹ (see Table 6.26).

■ **Anxiolytics/Benzodiazepines/Beta-Blockers**

A few trials have evaluated anxiolytics and other agents that reduce the somatic signs or the symptoms of anxiety. Early individual trials of propranolol, a beta-blocker,³²⁹ and diazepam, an anxiolytic,³³⁰ did not reveal a beneficial effect for these drugs compared with control interventions. Likewise, of the early studies assessing the anxiolytic buspirone that met inclusion criteria, only one revealed evidence of effectiveness relative to placebo.³³¹ Further studies of buspirone have failed to replicate this effect.³³²⁻³³⁴ These results are consistent with other independent reviews.³³³ Because of a lack of data, no meta-analyses were conducted, and no conclusions were drawn regarding the effectiveness of anxiolytics in smoking cessation.

■ **Opioid Antagonists/Naltrexone**

Two studies yielded the analyzable study arms that served as the basis for estimating the effects of the opiate antagonist naltrexone. Table 6.26 reveals that naltrexone treatment did not increase the likelihood of abstinence relative to placebo treatment. These results are consistent with other independent reviews.³³⁵ Two studies^{336,337} also examined whether naltrexone added to the effectiveness of the nicotine patch. The studies used different naltrexone and patch dosing regimens. The patch use regimen in one study did not meet meta-analysis inclusion criteria. Therefore, these patch + naltrexone studies could not be submitted to meta-analysis. Neither study reported significant benefit from adding naltrexone to the nicotine patch.

■ Silver Acetate

Due to limitations of the literature available regarding silver acetate, this agent was not included in the inclusive meta-analysis. Several randomized clinical trials³³⁸⁻³⁴⁰ of silver acetate, however, revealed no beneficial effects for smoking cessation; a Cochrane review concurs with this finding.³⁴¹

■ Mecamylamine

In the single study that compared mecamylamine alone to placebo, no effectiveness was noted.³⁴² Another early study compared a combination of mecamylamine plus the nicotine patch to placebo and found a significant effect for this combination.³⁴³ A more recent study comparing nicotine patch alone to nicotine patch plus mecamylamine found no significant differences.³⁴⁴ These findings are consistent with other independent reviews.³⁴⁵ Because of these findings, the Panel drew no conclusions regarding mecamylamine as a monotherapy.

■ Extended Use of Medications

For some patients, it may be appropriate to continue medication treatment for periods longer than is usually recommended. Results of the inclusive meta-analysis indicated that long-term patch and gum use are effective. Evidence indicates that the long-term use of gum may be more effective than a shorter course of gum therapy (Table 6.26). The Lung Health Study, of almost 4,000 smokers with evidence of early COPD, reported that approximately one-third of long-term quitters still were using nicotine gum at 12 months,³⁴⁶ and some for as long as 5 years, with no serious side effects.³⁴⁷ Other studies also have found that, among patients given free access to nicotine gum, 15 to 20 percent of successful abstainers continue to use the gum for a year or longer.³⁴⁸ Thus, it may be that certain groups of smokers may benefit from long-term medication use. Although weaning should be encouraged for all patients using medications, continued use of such medication clearly is preferable to a return to smoking with respect to health consequences. This is because, unlike smoking, these medications do not (a) contain non-nicotine toxic substances (e.g., “tar,” carbon monoxide, formaldehyde, benzene); (b) produce sharp surges in blood nicotine levels; and/or (c) produce strong dependence.^{349,350} Finally, it should be noted that the medication treatment that produced the largest effects on abstinence rates, of those analyzed, involved long-term nicotine patch therapy + *ad libitum* NRT (Table 6.26).

■ Use of NRT in Cardiovascular Patients

Soon after the nicotine patch was released, the media reported a possible link between the use of this medication and cardiovascular risk. This question has been studied systematically since that time. Separate analyses now have documented the lack of an association between the nicotine patch and acute cardiovascular events,³⁵¹⁻³⁵⁶ even in patients who continued to smoke while on the nicotine patch,³⁵⁷ although a recent study raised questions regarding NRT use in intensive care units.³⁵⁸ Because of inaccurate media coverage in the past, it may be important to inform patients who are reluctant to use NRTs that there is no evidence of increased cardiovascular risk with these medications. Note that package inserts recommend caution in patients with acute cardiovascular diseases (see Tables 3.3–3.11).

■ Future Research

The following pharmacotherapeutic topics require additional research:

- Relative effectiveness and safety of the seven FDA-approved medications, in general and for specific subpopulations (e.g., women; adolescents; older smokers; smokeless tobacco users; individuals with psychiatric disorders, including substance use disorders; postmyocardial infarction patients) and for long-term treatment
- Use of combined tobacco dependence medications in general and for specific subpopulations (e.g., highly dependent smokers)
- Effectiveness of long-term medications
- Effectiveness of prequit NRT use in increasing abstinence rates
- Strategies to address widespread misconceptions about effective smoking cessation medications and common barriers to their appropriate use
- Effectiveness of MAO inhibitors, especially for those with depression

Use of Over-the-Counter Medications

Recommendation: Over-the-counter nicotine patch therapy is more effective than placebo, and its use should be encouraged. (Strength of evidence = B)

No new studies were identified for the 2008 update that examined the effectiveness of nicotine patch versus placebo patch in an OTC setting. Based on the 2000 Guideline, there were three placebo-controlled studies with six arms that met selection criteria for the meta-analysis of medication interventions in OTC settings. These three studies specifically examined the effect of patch versus placebo. The only additional treatments in these studies were a self-help manual, instructions contained in the package, or written directions for using the patch. As shown in Table 6.30, the use of the nicotine patch in OTC settings nearly doubles abstinence rates when compared to a placebo. These results are consistent with a more recent (2003) meta-analysis of active versus placebo patch in an OTC setting that found an odds ratio of 2.5 (95% C.I. = 1.8–3.6) for active nicotine patch.³⁵⁹ A study that did not meet inclusion criteria for meta-analysis reported low abstinence rates when the nicotine patch was used in the OTC setting.³⁶⁰ Too few studies were done in the OTC setting to permit meta-analysis of the OTC effect of any other medication. The “B” strength of evidence rating reflects the Panel’s concern about the external validity of the studies designed to reflect the OTC context.

The FDA has approved nicotine gum, the nicotine lozenge, and the nicotine patch for OTC use. The patches and gum are identical to those previously available only via prescription. Although the OTC status of these medications has increased their availability and use,³⁶¹ this does not reduce the clinician’s responsibility to intervene with smokers or insurers/managed care organizations/payers to cover the costs of such treatment. Moreover, OTC availability may enhance the capacity of a broad array of clinicians to intervene comprehensively when treating tobacco dependence.

All clinicians have specific responsibilities regarding these products, such as encouraging their use when appropriate, identifying patients with specific contraindications, providing counseling and followup, encouraging total abstinence during a quit attempt, offering instruction on appropriate use, addressing common patient misconceptions, and providing prescriptions

when needed for select populations to ensure reimbursement (e.g., Medicaid patients). Additionally, patients should be urged to read the package insert and consult with their pharmacist. Finally, the clinician should advise patients regarding the selection and use of medications, whether purchased OTC or by prescription. Debate has arisen in the field regarding the effectiveness of OTC NRT use. For instance, a population-based study found no long-term effects of OTC nicotine patch use.³⁴ However, cross-sectional surveys have methodological constraints (e.g., patients may self-select certain treatments based on dependence or perceived difficulty of quitting).³⁶²

Table 6.30. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for OTC nicotine patch therapy (n = 3 studies)^a

OTC therapy	Number of arms	Odds Ratio (95% C.I.)	Estimated abstinence rate (95% C.I.)
Placebo	3	1.0	6.7
OTC nicotine patch therapy	3	1.8 (1.2–2.8)	11.8 (7.5–16.0)

^a Go to www.surgeongeneral.gov/tobacco/gdlnrefs.htm for the articles used in this meta-analysis.

■ Future Research

Important topics for future research are:

- Effectiveness of nicotine patch, gum, and lozenge when access is OTC
- Extent to which individuals use medications appropriately when access is OTC
- Extent to which the effectiveness of OTC medication is enhanced by other treatments (e.g., pharmacist counseling, telephone counseling, computer self-help resources, clinician interventions)
- Extent to which OTC status increases or reduces the use of medications by poor or minority populations
- Strategies for improving the accessibility and appropriate use of OTC medications