## Clinical Practice Guideline

# Treating Tobacco Use and Dependence: 2008 Update


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# Chapter 6 Evidence and Recommendations

## Background

The recommendations summarized in Chapters 2, 3, 4, and 5 are the result of a review and analysis of the existing tobacco treatment literature. This chapter reports that review and analysis and describes the effectiveness of various treatments, assessments, and implementation strategies. This chapter also addresses which treatments or assessments are effective, how they should be used, and how they should be implemented within a health care system.

The Panel identified topics that warranted new analyses for the 2008 update based on several criteria: they were important, supported by substantial new literature, and/or addressed issues not considered in prior Guidelines. The number of topics selected for new analyses was limited by the Public Health Service Guideline Update contract parameters. The 2008 Guideline Update Panel selected 11 topics for new analysis (see Table 1.1), based in part on input from tobacco control researchers and practitioners. These 11 topics and related categories are represented in Table 6.1. Type of outcome analyses varied across the different topics. In most analyses, long-term abstinence (6 months or more) was the outcome measure of interest; in others, it was the rate of smoker identification or intervention delivery. In addition to these new topics, Table 6.2 lists the topics that previously were analyzed for the 1996 and 2000 Guidelines. Importantly, the Guideline Update Panel reviewed all recommendations from the 1996 and 2000 Guidelines that did not undergo updated meta-analyses. For these prior recommendations, the Panel reviewed relevant literature since 1999 to determine whether the prior recommendation merited retention, modification, or deletion. See Appendix D for comparison of 2000 and 2008 Guideline recommendations.

The analyses reported in this chapter almost exclusively addressed treatments for cigarette smoking, as opposed to the use of other forms of tobacco, as the small number of studies on the use of noncigarette tobacco products, other than smokeless tobacco, precluded their separate analysis.

Finally, the Panel attempted to analyze treatment and assessment strategies that constitute distinct approaches that exist in current clinical practice.

The Panel chose categories within each analyzed topic according to three major criteria. First, some categories reflected generally accepted dimensions or taxonomies. An example of this is the categorical nature of the clinician types (physician, psychologist, nurse, and so on). Second, information on the category had to be available in the published literature. Many questions of theoretical interest had to be abandoned simply because the requisite research literature was not available. Third, the category had to occur with sufficient frequency to permit meaningful statistical analysis. Therefore, the cutpoints of some continuous variables (e.g., total amount of contact time) were determined so there were a sufficient number of studies within each analytical category to permit meaningful analysis.

In ideal circumstances, the Panel could evaluate each characteristic by consulting randomized controlled trials relevant to the specific categories in question. Unfortunately, with the exception of medication interventions, very few or no randomized controlled trials are designed to address the effects of specific treatment or assessment characteristics of interest. Moreover, treatment characteristics frequently are confounded with one another. For example, comparisons among clinicians often are confounded with the type of counseling and the format and intensity of the interventions. Therefore, direct, unconfounded comparisons of categories within a particular analysis type often were impossible. These characteristics nevertheless were analyzed because of their clinical importance, and because it was possible to reduce confounding by careful selection of studies and by statistical control of some confounding factors.

**Table 6.1. Topics meta-analyzed for the 2008 Guideline update**

| Characteristics analyzed | Categories of those characteristics |
|---|---|
| Quitline | • No quitline intervention<br>• Use of a proactive quitline<br>• Use of a proactive quitline in combination with medication<br>• Number of quitline sessions |
| Combining counseling and medication | • Medication alone<br>• Counseling alone<br>• Medication and counseling combined |

**Table 6.1. Topics meta-analyzed for the 2008 Guideline update (continued)**

| Characteristics analyzed | Categories of those characteristics |
|---|---|
| Medications | • Placebo medication<br>• Bupropion SR<br>• Clonidine<br>• Nicotine gum<br>• Nicotine inhaler<br>• Nicotine lozenge<br>• Nicotine nasal spray<br>• Nicotine patch<br>• Nortriptyline<br>• Varenicline<br>• Long-term medication<br>• Single medication<br>• Combination of medications<br>• High-dose nicotine patch |
| Providing tobacco treatment as a health care insurance benefit | • Not providing coverage for tobacco treatment<br>• Providing services as a covered insurance benefit |
| Systems features | • No intervention<br>• Clinician training<br>• Clinician training and reminder systems |
| Specific populations | • Adolescent smokers, pregnant smokers, smokers with psychiatric disorders, including substance use disorders and smokers with low socioeconomic status/limited formal education (see Chapter 7 for description) |

**Table 6.2. Topics meta-analyzed for the 1996 and 2000 Guidelines and included in the 2008 Guideline update (but not re-analyzed)**

| Characteristics analyzed | Categories of those characteristics |
|---|---|
| Screen for tobacco use | • No screening system in place<br>• Screening system in place |
| Advice to quit | • No advice to quit<br>• Physician advice to quit |
| Intensity of person-to-person clinical contact | • No person-to-person intervention<br>• Minimal counseling (longest session ≤ 3 minutes in duration)<br>• Low intensity counseling (longest session > 3 minutes and ≤ 10 minutes in duration)<br>• Higher intensity counseling (longest session > 10 minutes)<br>• Total amount of contact time<br>• Number of person-to-person treatment sessions |

**Table 6.2. Topics meta-analyzed for the 1996 and 2000 Guidelines and included in the 2008 Guideline update (but not re-analyzed) (continued)**

| Characteristics analyzed | Categories of those characteristics |
|---|---|
| Type of clinician | • No clinician<br>• Self-help materials only<br>• Nonphysician health care clinician (e.g., psychologist, counselor, social worker, nurse, dentist, graduate student, pharmacist, tobacco treatment specialist)<br>• Physician<br>• Number of types of clinicians |
| Formats of psychosocial intervention | • No contact<br>• Self-help/self-administered (e.g., pamphlet, audiotape, videotape, mailed information, computer program)<br>• Individual counseling/contact<br>• Group counseling/contact<br>• Proactive telephone counseling/contact<br>• Number of types of formats |
| Self-help interventions | • No self-help intervention<br>• Number of self-help interventions<br>• Self-help interventions |
| Types of counseling and behavioral therapies | • No counseling<br>• No person-to-person intervention or minimal counseling<br>• General: problemsolving/coping skills/relapse-prevention/stress-management approach<br>• Negative affect/depression intervention<br>• Weight/diet/nutrition intervention<br>• Extratreatment social support intervention<br>• Intratreatment social support intervention<br>• Contingency contracting/instrumental contingencies<br>• Rapid smoking<br>• Other aversive smoking techniques<br>• Cigarette fading/smoking reduction prequit<br>• Acupuncture |
| Over-the-counter (OTC) medication | • Placebo OTC nicotine patch therapy<br>• OTC nicotine patch therapy |

Additional topics that were important and clinically relevant—but did not lend themselves to analysis due to a lack of long-term abstinence data—nevertheless were considered by the Panel through a review of the existing literature. The strength of evidence associated with these recommended actions for clinical interventions was at the "B" or "C" level (see below), reflecting the fact that they are not based primarily on meta-analyses.

This chapter addresses the treatment and assessment characteristics outlined in Tables 6.1 and 6.2 and is divided into three sections: (1) evidence for counseling and psychosocial interventions; (2) evidence for medication interventions; and (3) evidence for systems changes. For each topic, background information, clinical recommendations, and the basis for those recommendations are provided. As described in Chapter 1, each recommendation was given a strength-of-evidence classification based on the criteria shown in Table 6.3. Finally, for many topics, recommendations for further research are provided.

**Table 6.3. Summary of strength of evidence for recommendations**

| Strength-of-evidence classification | Criteria |
|---|---|
| Strength of Evidence = A | Multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings. |
| Strength of Evidence = B | Some evidence from randomized clinical trials supported the recommendation, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the recommendation. |
| Strength of Evidence = C | Reserved for important clinical situations in which the Panel achieved consensus on the recommendation in the absence of relevant randomized controlled trials. |

# A. Counseling and Psychosocial Evidence

## *1. Screening and Assessment*

### Screen for Tobacco Use

**Recommendation: All patients should be asked if they use tobacco and should have their tobacco use status documented on a regular basis. Evidence has shown that clinic screening systems, such as expanding the vital signs to include tobacco use status or the use of other reminder systems such as chart stickers or computer prompts, significantly increase rates of clinician intervention. (Strength of Evidence = A)**

The Panel relied on the meta-analyses from the original 1996 Guideline to determine the impact of tobacco screening systems. Tobacco screening

systems were evaluated in terms of their impact on two outcomes: the rate of tobacco treatment by clinicians, and the rate of cessation by patients who smoke.

**Identifying Tobacco Users: Impact on Clinical Intervention.** Nine studies met the selection criteria and were meta-analyzed as part of the 1996 Guideline to assess the impact of screening systems on the rate of smoking cessation intervention by clinicians. The results of this meta-analysis are shown in Table 6.4. Implementing clinic systems designed to increase the assessment and documentation of tobacco use status markedly increases the rate at which clinicians intervene with their patients who smoke.

**Table 6.4. Meta-analysis (1996): Impact of having a tobacco use status identification system in place on rates of clinician intervention with their patients who smoke (n = 9 studies)[a]**

| Screening system | Number of arms | Estimated odds ratio (95% C.I.) | Estimated rate of clinician intervention (95% C.I.) |
|---|---|---|---|
| No screening system in place to identify smoking status (reference group) | 9 | 1.0 | 38.5 |
| Screening system in place to identify smoking status | 9 | 3.1 (2.2–4.2) | 65.6 (58.3–72.6) |

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

**Identifying Tobacco Users: Impact on Tobacco Cessation.** Three studies met the selection criteria and were meta-analyzed as part of the 1996 Guideline to assess the impact of identifying smokers on actual rates of smoking cessation. The results of this meta-analysis are shown in Table 6.5. These results, combined with the results from Table 6.4, show that having a clinic system in place that identifies smokers increases rates of clinician intervention but does not, by itself, produce significantly higher rates of smoking cessation.

Strategy A1 (see Chapter 3A) and Systems Strategy 1 (see Chapter 5) detail an approach for including tobacco use status as a vital sign with systematic prompts and reminders. Although the data assessing this intervention were gathered exclusively from cigarette smokers, the Panel believed

that these results are generalizable to all tobacco users. This approach is designed to produce consistent assessment and documentation of tobacco use. Evidence from controlled trials shows that this approach increases the probability that tobacco use is assessed and documented consistently.[54,232] However, documenting smoking status is not by itself sufficient to promote treatment by clinicians.[233] Systems changes beyond smoker identification strategies are likely to be needed to increase rates of cessation advice and intervention.[139,234-237]

**Table 6.5. Meta-analysis (1996): Impact of having a tobacco use status identification system in place on abstinence rates among patients who smoke (n = 3 studies)[a]**

| Screening system | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No screening system in place to identify smoking status (reference group) | 3 | 1.0 | 3.1 |
| Screening system in place to identify smoking status | 3 | 2.0 (0.8–4.8) | 6.4 (1.3–11.6) |

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

## Specialized Assessment

**Recommendation: Once a tobacco user is identified and advised to quit, the clinician should assess the patient's willingness to quit at this time. (Strength of Evidence = C)**

If the patient is willing to make a quit attempt at this time, interventions identified as effective in this Guideline should be provided. (See Chapters 3A and 4.)

If the patient is unwilling to quit at this time, an intervention designed to increase future quit attempts should be provided. (See Chapter 3B.)

**Recommendation: Tobacco dependence treatment is effective and should be delivered even if specialized assessments are not used or available. (Strength of Evidence = A)**

Every individual entering a health care setting should receive an assessment that determines his or her tobacco use status and interest in quitting. The patient should be asked, "Are you willing to make a quit attempt at this time?" Such an assessment (willing or unwilling) is a necessary first step in treatment. In addition, every patient should be assessed for physical or medical conditions that may affect the use of planned treatments (e.g., medication).

The clinician also may want to perform specialized assessments of individual and environmental attributes that provide information for tailoring treatment and that predict quitting success. Specialized assessments refer to the use of formal instruments (e.g., questionnaires, clinical interviews, or physiologic indices such as carbon monoxide, serum nicotine/cotinine levels, and/or pulmonary function) that may be associated with cessation outcome (in addition, the reader may find other assessments relevant to medication use and specific populations when selecting treatment). Some of the variables targeted by specialized assessments that predict quitting success are listed in Table 6.6.

Several considerations should be kept in mind regarding the use of specialized assessments. First, there is little consistent evidence that a smoker's status on a specialized assessment is useful for treatment matching. The one exception is that persons who are highly nicotine dependent may benefit more from higher nicotine gum or lozenge doses (see Medication Evidence; Section B of Chapter 6). More importantly, the Panel found that, regardless of their standing on specialized assessments, all smokers have the potential to benefit from tobacco dependence treatments. Therefore, delivery of tobacco dependence treatments should not depend on the use of specialized assessments. Finally, tailored interventions based on specialized assessments do not consistently produce higher long-term quit rates than do nontailored interventions of equal intensity. Some promising studies exist, however, that suggest that individualizing self-help materials may be beneficial (see Individually Tailored and Stepped-Care Interventions, page 92).[238-245] In addition, the Panel recognizes that some effective interventions, such as general problemsolving (see Types of Counseling and Behavioral Therapies, on page 96), entail treatment tailoring based on a systematic assessment that occurs as an integral part of treatment.

**Table 6.6. Variables associated with higher or lower abstinence rates**

| Variables associated with higher abstinence rates | |
|---|---|
| **Variable** | **Examples** |
| High motivation | Tobacco user reports a strong motivation to quit. |
| Ready to change | Tobacco user is ready to quit within a 1-month period. |
| Moderate to high self-efficacy | Tobacco user is confident in his or her ability to quit. |
| Supportive social network | A smoke-free workplace and home; friends who do not smoke in the quitter's presence. |
| **Variables associated with lower abstinence rates** | |
| **Variable** | **Examples** |
| High nicotine dependence | Tobacco user smokes heavily ( ≥ 20 cigarettes/day), and/or has first cigarette of the day within 30 minutes after waking in the morning. |
| Psychiatric comorbidity and substance use | Tobacco user currently has elevated depressive symptoms, active alcohol abuse, or schizophrenia. |
| High stress level | Stressful life circumstances and/or recent or anticipated major life changes (e.g., divorce, job change). |
| Exposure to other smokers | Other smokers in the household. |

The existing evidence suggests that treatment can be effective despite the presence of risk factors for relapse (e.g., high nicotine dependence, other smokers in the home), but abstinence rates in smokers with these characteristics tend to be lower than rates in those without these characteristics.[246-248]

## Future Research

The following topics regarding specialized assessment require additional research:

- Whether treatment adjustment based on specialized assessments can improve long-term abstinence rates

- Whether working to change the social network can improve abstinence rates (e.g., intervening with other smokers in the household to change their smoking patterns, teaching quitting support, or encouraging a smokefree home)

- Disparities in screening and assessment in specific populations

# 2. Treatment Structure and Intensity

## Advice To Quit Smoking

**Recommendation: All *physicians* should strongly advise every patient who smokes to quit because evidence shows that physician advice to quit smoking increases abstinence rates. (Strength of Evidence = A)**

For these recommendations, the 2008 Guideline Panel relied on meta-analyses performed for the 1996 Guideline. Seven studies were included in the 1996 meta-analysis of the effectiveness of physician advice to quit smoking. In the studies used in this analysis, the modal length of clinician intervention was 3 minutes or less. Two studies in this analysis used interventions lasting about 5 minutes. Results of the meta-analysis on physician advice are shown in Table 6.7. This analysis shows that brief physician advice significantly increases long-term smoking abstinence rates. These results were also supported by a more recent, independent meta-analysis.[56]

Advice by physicians was examined in the Table 6.7 meta-analysis from the 1996 Guideline; there were too few studies to examine advice delivered by any other type of clinician, although one study found that advice to quit from health care providers in general did significantly increase quit rates.[249] The analysis for total amount of contact time (see Table 6.9) indicates that minimal counseling (advice) delivered by a variety of clinician types increases long-term abstinence rates. Also, studies have shown that dentists and dental hygienists can be effective in assessing and advising smokeless/spit tobacco users to quit[250] (see Chapter 7). Given the large number of smokers who visit a clinician each year, the potential public health impact of universal advice to quit is substantial.[56]

**Table 6.7. Meta-analysis (1996): Effectiveness of and estimated abstinence rates for advice to quit by a physician (n = 7 studies)[a]**

| Advice | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No advice to quit (reference group) | 9 | 1.0 | 7.9 |
| Physician advice to quit | 10 | 1.3 (1.1–1.6) | 10.2 (8.5–12.0) |

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

## Future Research

The following topics regarding advice to quit require additional research:

- Effectiveness of advice to quit smoking given by clinicians other than physicians (e.g., nurses, nurse practitioners, pharmacists, dentists, dental hygienists, tobacco treatment specialists, physician's assistants)
- Cumulative effectiveness of combined advice from physicians and other types of clinicians

## Intensity of Clinical Interventions

**Recommendation: Minimal interventions lasting less than 3 minutes increase overall tobacco abstinence rates. Every tobacco user should be offered at least a minimal intervention, whether or not he or she is referred to an intensive intervention. (Strength of Evidence = A)**

**Recommendation: There is a strong dose-response relation between the session length of person-to-person contact and successful treatment outcomes. Intensive interventions are more effective than less intensive interventions and should be used whenever possible. (Strength of Evidence = A)**

**Recommendation: Person-to-person treatment delivered for four or more sessions appears especially effective in increasing abstinence rates. Therefore, if feasible, clinicians should strive to meet four or more times with individuals quitting tobacco use. (Strength of Evidence = A)**

These recommendations are supported by three separate meta-analyses conducted for the 2000 Guideline: one involving session length, one involving total amount of contact time, and one involving the number of sessions.

**Table 6.8. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for various intensity levels of session length (n = 43 studies)[a]**

| Level of contact | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No contact | 30 | 1.0 | 10.9 |
| Minimal counseling (< 3 minutes) | 19 | 1.3 (1.01–1.6) | 13.4 (10.9–16.1) |
| Low-intensity counseling (3-10 minutes) | 16 | 1.6 (1.2–2.0) | 16.0 (12.8–19.2) |
| Higher intensity counseling (> 10 minutes) | 55 | 2.3 (2.0–2.7) | 22.1 (19.4–24.7) |

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

**Session Length.** Forty-three studies met selection criteria for comparison across various session lengths. Whenever possible, session length was categorized based on the maximum amount of time the clinician spent with a smoker addressing tobacco dependence in a single contact. Minimal counseling interventions were defined as 3 minutes or less, low-intensity counseling was defined as greater than 3 minutes to 10 minutes, and higher intensity counseling interventions were defined as greater than 10 minutes. Interventions could involve multiple patient-clinician contacts, with the session length determined for coding purposes as the length of time of the longest session. These levels of person-to-person contact were compared with a no-contact reference group involving study conditions in which subjects received no person-to-person contact (e.g., self-help-only conditions). There is a dose-response relation between session length and abstinence rates. As Table 6.8 shows, all three session lengths (minimal counseling, low-intensity counseling, and higher intensity counseling) significantly increased abstinence rates over those produced by no-contact conditions. However, there was a clear trend for abstinence rates to increase across these session lengths, with higher intensity counseling producing the highest rates.

**Total Amount of Contact Time.** Thirty-five studies met the selection criteria for the analysis assessing the impact of total contact time. The amount of contact time was calculated from the text as the total time accumulated (the number of sessions multiplied by the session length). When the exact time was not known for minimal and low-intensity interventions, they were assigned median lengths of 2 and 6.5 minutes, respectively. The total amount of contact time was then categorized as no-contact, 1–3 minutes, 4–30 minutes, 31–90 minutes, 91–300 minutes, and greater than 300 minutes. As Table 6.9 shows, any contact time significantly increased abstinence rates over those produced by no contact. However, there was a clear trend for abstinence rates to increase across contact time, up to the 90-minute mark. There was no evidence that more than 90 minutes of total contact time substantially increases abstinence rates.

**Table 6.9. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for total amount of contact time (n = 35 studies)[a]**

| Total amount of contact time | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No minutes | 16 | 1.0 | 11.0 |
| 1–3 minutes | 12 | 1.4 (1.1–1.8) | 14.4 (11.3–17.5) |
| 4–30 minutes | 20 | 1.9 (1.5–2.3) | 18.8 (15.6–22.0) |
| 31–90 minutes | 16 | 3.0 (2.3–3.8) | 26.5 (21.5–31.4) |
| 91–300 minutes | 16 | 3.2 (2.3–4.6) | 28.4 (21.3–35.5) |
| > 300 minutes | 15 | 2.8 (2.0–3.9) | 25.5 (19.2–31.7) |

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

**Number of Sessions.** Forty-six studies involving at least some person-to-person contact met selection criteria for the analysis addressing the impact of number of treatment sessions. Zero or one session was used as the reference group. As shown in Table 6.10, multiple treatment sessions increase smoking abstinence rates over those produced by zero or one session. The evidence suggests a dose-response relation between number of sessions and treatment effectiveness.

It is important to note that although the use of more intensive interventions (i.e., longer sessions, more sessions) may produce enhanced abstinence rates, these interventions may have limited reach (affect fewer smokers) and may not be feasible in some primary care settings. For instance,

not all smokers are interested in participating in an intensive intervention, and not all smokers may have access to or be able to afford services that can provide intensive interventions. Finally, the clinician can link the patient to additional treatment options, such as quitlines or other intensive cessation treatment programs, to provide additional person-to-person treatment.

## Future Research

The following topics regarding intensity of person-to-person contact require additional research:

- Effects of treatment duration, timing, and spacing of sessions (i.e., the number of days or weeks over which treatment is spread). For instance, does front loading sessions (having the majority of the sessions during the first few weeks of a quit attempt) or spacing sessions throughout the quit attempt yield better long-term abstinence rates?
- Methods to increase the appeal and utilization of intensive treatments
- Effectiveness of intensive inpatient treatment programs

**Table 6.10. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for number of person-to-person treatment sessions (n = 46 studies)[a]**

| Number of sessions | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| 0–1 session | 43 | 1.0 | 12.4 |
| 2–3 sessions | 17 | 1.4 (1.1–1.7) | 16.3 (13.7–19.0) |
| 4–8 sessions | 23 | 1.9 (1.6–2.2) | 20.9 (18.1–23.6) |
| > 8 sessions | 51 | 2.3 (2.1–3.0) | 24.7 (21.0–28.4) |

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

## Type of Clinician

**Recommendation: Treatment delivered by a variety of clinician types increases abstinence rates. Therefore, all clinicians should provide smoking cessation interventions. (Strength of Evidence = A)**

**Recommendation: Treatments delivered by multiple types of clinicians are more effective than interventions delivered by a single type of clinician. Therefore, the delivery of interventions by more than one type of clinician is encouraged. (Strength of Evidence = C)**

**Clinician Types.** Twenty-nine studies met selection criteria for the 2000 meta-analysis examining the effectiveness of various types of clinicians providing tobacco use treatment. These analyses compared the effectiveness of interventions delivered by different types of clinicians with interventions in which there were no clinicians (e.g., when there was no intervention or the intervention consisted of self-help materials only). Tobacco use treatments delivered by any single type of health care provider, such as a physician or other clinician (e.g., nurse, psychologist, dentist, or counselor), or by multiple clinicians, increase abstinence rates relative to interventions in which there is no clinician (e.g., self-help interventions). None of the studies in these analyses involved medication, but they did involve psychosocial intervention, principally counseling. Results are shown in Table 6.11. Results suggest that physicians and other clinicians are similarly effective in delivering tobacco cessation counseling. New research reviewed since the 2000 Guideline suggests that trained peer counselors also may be effective.[251-253]

**Number of Clinician Types.** Thirty-seven studies met selection criteria for the 2000 analysis examining the effectiveness of multiple clinicians used in smoking cessation interventions. "Multiple clinicians" refers to the number of different *types* of clinicians (if a nurse and a physician each delivered parts of an intervention, two types of clinicians would be involved). Tobacco use treatments delivered by two or more types of clinicians increase abstinence rates relative to those produced by interventions in which there is no clinician (Table 6.12). However, the number of clinician types is confounded with treatment intensity. For instance, if an individual meets with a physician for a medication consultation and then talks to a health educator about the quit plan, that is two clinicians and two sessions. The number of contacts may be more important than the number of clinicians providing treatment.

**Table 6.11. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for interventions delivered by different types of clinicians (n = 29 studies)[a]**

| Type of clinician | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No clinician | 16 | 1.0 | 10.2 |
| Self-help | 47 | 1.1 (0.9–1.3) | 10.9 (9.1–12.7) |
| Nonphysician clinician | 39 | 1.7 (1.3–2.1) | 15.8 (12.8–18.8) |
| Physician clinician | 11 | 2.2 (1.5–3.2) | 19.9 (13.7–26.2) |

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

**Table 6.12. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for interventions delivered by various numbers of clinician types (n = 37 studies)[a]**

| Number of clinician types | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No clinician | 30 | 1.0 | 10.8 |
| One clinician type | 50 | 1.8 (1.5–2.2) | 18.3 (15.4–21.1) |
| Two clinician types | 16 | 2.5 (1.9–3.4) | 23.6 (18.4–28.7) |
| Three or more clinician types | 7 | 2.4 (2.1–2.9) | 23.0 (20.0–25.9) |

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

## Future Research

The following topics regarding type of clinician require additional research:

- Effectiveness of specific types of clinicians (e.g., quitline counselors, trained peer counselors, nurses, physician assistants, pharmacists, social workers)
- Relative effectiveness of various numbers and types of clinicians, with the intensity of the intervention held constant

## Formats of Psychosocial Treatments

**Recommendation: Proactive telephone counseling, group counseling, and individual counseling formats are effective and should be used in smoking cessation interventions. (Strength of Evidence = A)**

**Recommendation: Smoking cessation interventions that are delivered in multiple formats increase abstinence rates and should be encouraged. (Strength of Evidence = A)**

**Recommendation: Tailored materials, both print and Web-based, appear to be effective in helping people quit. Therefore, clinicians may choose to provide tailored self-help materials to their patients who want to quit. (Strength of Evidence = B)**

**Format Types.** Overall format type (delivery mode) recommendations rest on the 2000 Guideline meta-analysis, although new focused analyses of proactive quitlines were conducted for the 2008 update. Fifty-eight studies met selection criteria and were included in the 2000 meta-analysis comparing different types of formats (see Table 6.13). Tobacco use treatment delivered by means of proactive telephone counseling/contact (quitlines, call-back counseling), individual counseling, and group counseling/contact all increase abstinence rates relative to no intervention.

**Self-Help.** The 2000 format meta-analysis also evaluated the effectiveness of self-help interventions (e.g., pamphlets/booklets/mailings/manuals, videotapes, audiotapes, referrals to 12-step programs, reactive telephone hotlines/helplines [see Glossary], computer programs/Internet, and lists of community programs). Interventions delivered by means of widely varied self-help materials (whether as stand-alone treatments or as adjuvants) appear to increase abstinence rates relative to no intervention in this particular analysis. However, the effect of self-help was weak and typically not significant across analyses conducted for the 2000 Guideline (see Tables 6.13 and 6.15).

**Number of Formats.** Fifty-four studies met selection criteria and were included in the 2000 meta-analysis comparing the number of format types used for tobacco use treatment. The self-help treatments included in this analysis occurred either by themselves or in addition to other treatments. Tobacco use treatment that used three or four format types was especially effective. Results of this analysis are shown in Table 6.14.

**Self-Help: Focused Analyses.** Because the format meta-analysis revealed self-help to be of marginal effectiveness, another analysis was undertaken in 2000 to provide additional, focused information on self-help. Studies were accepted for the 2000 analysis if the presence of self-help materi-

als constituted the sole difference in treatment arms. In the main format analysis, some treatment arms differed on factors other than self-help *per se* (e.g., intensity of counseling). The treatments that accompanied self-help material in the focused analysis ranged from no advice or counseling to intensive counseling. The results of this analysis were comparable to those in the larger format analysis (i.e., self-help was of marginal effectiveness).

For the 2000 Guideline analysis, 21 studies met selection criteria to evaluate the effectiveness of providing multiple types of self-help interventions (e.g., pamphlets, videotapes, audiotapes, and reactive hotlines/helplines). The results provide little evidence that the provision of multiple types of self-help, when offered without any person-to-person intervention, significantly enhances treatment outcomes (see Table 6.15).

Two final 2000 meta-analyses addressed the impact of self-help brochures *per se*. In one analysis, brochures were used as the only intervention. In the other analysis, self-help brochures were used in addition to counseling. In neither analysis did self-help significantly boost abstinence rates.

**Table 6.13. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for various types of formats (n = 58 studies)[a]**

| Format Number | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No format | 20 | 1.0 | 10.8 |
| Self-help | 93 | 1.2 (1.02–1.3) | 12.3 (10.9–13.6) |
| Proactive telephone counseling | 26 | 1.2 (1.1–1.4) | 13.1 (11.4–14.8) |
| Group counseling | 52 | 1.3 (1.1–1.6) | 13.9 (11.6–16.1) |
| Individual counseling | 67 | 1.7 (1.4–2.0) | 16.8 (14.7–19.1) |

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

**Table 6.14. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for number of formats (n = 54 studies)[a]**

| Number of formats[b] | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No format | 20 | 1.0 | 10.8 |
| One format | 51 | 1.5 (1.2–1.8) | 15.1 (12.8–17.4) |
| Two formats | 55 | 1.9 (1.6–2.2) | 18.5 (15.8–21.1) |
| Three or four formats | 19 | 2.5 (2.1–3.0) | 23.2 (19.9–26.6) |

[a] Go to *www.surgeongeneral.gov/tobacco/gdlnrefs.htm* for the articles used in this meta-analysis.
[b] Formats included self-help, proactive telephone counseling, group, or individual counseling.

**Table 6.15. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for number of types of self-help (n = 21 studies)[a]**

| Factor | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No self-help | 17 | 1.0 | 14.3 |
| One type of self-help | 27 | 1.0 (0.9–1.1) | 14.4 (12.9–15.9) |
| Two or more types | 10 | 1.1 (0.9–1.5) | 15.7 (12.3–19.2) |

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

**Quitlines.** Both the substantial growth in quitline research and the implementation of a national network of tobacco quitlines (available through 1-800-QUIT-NOW) led the 2008 Guideline Panel to identify quitline effectiveness as a topic deserving focused meta-analyses. Nine studies met selection criteria and were analyzed for the 2008 Guideline update comparing the effectiveness of a quitline intervention versus minimal or no contact or self-help materials. This differs from the 2000 meta-analysis (Table 6.13) in that the current analysis focused on study arms that used quitline intervention alone rather than telephone counseling that may have occurred with other types of interventions. For the purpose of this analysis, quitlines are defined as telephone counseling in which at least some of the contacts are initiated by the quitline counselor to deliver tobacco use interventions, including call-back counseling. Quitlines significantly increase abstinence rates compared to minimal or no counseling interventions (Table 6.16).[254] In a second 2008 meta-analysis of quitlines, six studies were analyzed comparing the effect of adding quitline counseling to medication versus medication alone. The addition of quitline counseling to medication significantly improves abstinence rates

compared to medication alone (see Table 6.17). These analyses suggest a robust effect of quitline counseling and are consistent with a recent independent analysis[254] and with the recently released Centers for Disease Control and Prevention's *Guide to Community Preventive Services*.[92]

**Table 6.16. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for quitline counseling compared to minimal interventions, self-help, or no counseling (n = 9 studies)[a]**

| Intervention | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Minimal or no counseling or self-help | 11 | 1.0 | 8.5 |
| Quitline counseling | 11 | 1.6 (1.4–1.8) | 12.7 (11.3–14.2) |

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

**Table 6.17. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for quitline counseling and medication compared to medication alone (n = 6 studies)[a]**

| Intervention | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Medication alone | 6 | 1.0 | 23.2 |
| Medication and quitline counseling | 6 | 1.3 (1.1–1.6) | 28.1 (24.5–32.0) |

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

**Individually Tailored and Stepped-Care Interventions.** Recent research has focused on the use of individually tailored materials. Tailored materials are those that are designed to address smoker-specific variables, such as support sources, recency of quitting, and concerns about quitting. Tailored materials can either be print materials, such as letters mailed to patients, or Web-based materials such as interactive Web sites.[238,242] Some applications of tailoring have been shown to be effective and to have broad reach.[241,245,255,256] The Panel also considered the use of stepped-care interventions (see Glossary) and concluded that there is not enough evidence to recommend a stepped-care approach as a basis for tailoring.[257,258] However, these approaches warrant future research.

**Computerized Interventions.** E-health or Internet interventions have the potential to be accessed by a large percentage of the smoking population, permit extensive tailoring of content to the tobacco user's needs or characteristics, and, due to low personnel costs, are likely to be inexpensive to deliver. Such interventions may be used as stand-alone or adjuvant treatments. These programs typically collect information from the tobacco user and then use algorithms to tailor feedback or recommendations. They also typically permit the user to select from various features, including extensive information on quitting, tobacco dependence, and related topics. Current applications permit multiple iterations of feedback, development and monitoring of a quit plan, and proactive e-mail prompts to users.[259,260] Optimal features of Web site resources have not yet been identified; some sites may be confusing and may not exploit the tailoring potential of this medium.[261] Clearly, more research is needed to identify their optimal structures, features, and contents.[262-265]

E-health tobacco interventions generally have yielded positive results. In a recent review of the use of these interventions with adult tobacco users, Walters et al. found that 7 of 15 studies with adults reported significantly improved outcomes over control conditions.[259] Hall et al. combined computerized individualized feedback designed to motivate smokers using principles of the Stages of Change model with six 30-minute sessions of counseling and the nicotine patch. This was compared with untailored self-help material. Significant improvement due to the more intensive treatment was found at 18-month followup.[266] Strecher et al. compared a multifaceted Web-based intervention (tailored cessation guide based on cognitive-behavioral principles, a medication adherence intervention, tailored e-mails, and a behavioral support person) in concert with the nicotine patch. This was contrasted with the patch alone. Favorable outcomes were obtained at 3 months postquit.[241] Similar positive effects also have been reported for a population study using computer-generated reports based on the Stages of Change model[267] and a Web site study offered in a worksite program.[268] A study with adolescents[269] reported positive results due to access to a complex intervention that comprised an interactive computer intervention, clinician advice, brief motivational interviewing, and telephonic booster sessions. The control condition was information about eating more fruits and vegetables. Null results with computerized or computer-tailored interventions also have been obtained (see, e.g., Velicer et al.[270] and Aveyard et al.[271]). Moreover, in many of the studies yielding positive results, the Web-based intervention is just one

element of a complex intervention, or is considerably more intense than the comparison intervention. Given the potential reach and low costs of such interventions, however, they remain a highly promising delivery system for tobacco dependence.

## Future Research

The following topics regarding formats require additional research:

- Which combinations of formats are most effective
- Relative effectiveness of different types of self-help interventions, including computer-based interventions
- Effectiveness of tailoring
- Effectiveness of fax-to-quit programs and other programs designed to increase quitline use
- Effective features of Web-based interventions
- Effect of computer-delivered interventions as a format versus the effect of the content of the intervention
- Optimal methods to decrease barriers and increase the appeal and use of effective counseling treatments

## Followup Assessment and Procedures

**Recommendation: All patients who receive a tobacco dependence intervention should be assessed for abstinence at the completion of treatment and during subsequent contacts. (1) Abstinent patients should have their quitting success acknowledged, and the clinician should offer to assist the patient with problems associated with quitting (see Chapter 3C, For the Patient Who Has Recently Quit). (2) Patients who have relapsed should be assessed to determine whether they are willing to make another quit attempt. (Strength of Evidence = C)**

If the patient is willing to make another quit attempt, provide or arrange additional treatment (see Chapter 3A, For the Patient Willing To Quit).

If the patient is not willing to try to quit, provide or arrange an intervention designed to increase future quit attempts (see Chapter 3B, For the Patient Unwilling To Quit).

All patients should be assessed with respect to their smoking status during followup clinical contacts. In particular, assessments within the first week after quitting should be encouraged.[272,273] Abstinent patients should receive reinforcement for their decision to quit, be congratulated on their success at quitting, and be encouraged to remain abstinent (see Chapter 3C, Strategy C1). The existing evidence does not show that these steps will prevent relapse, but continued involvement on the part of the clinician may increase the likelihood that the patient will consult the clinician in later quit attempts should they be needed. Clinicians also should inquire about and offer to help the patient with potential problems related to quitting (see Chapter 3C, Strategy C2), such as significant weight gain or residual withdrawal symptoms.

Patients who have relapsed should again be assessed for their willingness to quit. Patients who currently are motivated to make another quit attempt should be encouraged to use a tobacco dependence intervention (see Chapter 3A, For the Patient Willing To Quit). Clinicians may wish to increase the intensity of psychosocial treatment at this time or refer the patient to a tobacco dependence specialist/program for a more intensive treatment if the patient is willing. In addition, medication should be offered again to the patient, if appropriate. If the previous quit attempt included medication, the clinician should review whether the patient used the medication in an effective manner and determine whether the medication was helpful. Based on this assessment, the clinician should recommend retreatment with the same medication, another medication, or a combination of medications (see Tables 6.26–6.28). Patients who have relapsed and are unwilling to quit at the current time should receive a brief intervention designed to increase future quit attempts (see Chapter 3B).

## Future Research

The following topics regarding followup assessment and treatments require additional research:

- Optimal timing and types of relapse prevention interventions
- Effectiveness of various formats for relapse prevention treatments (e.g., effectiveness of telephone contacts in reducing the likelihood of relapse after a minimal intervention)

# *3. Treatment Elements*

## Types of Counseling and Behavioral Therapies

**Recommendation: Two types of counseling and behavioral therapies result in higher abstinence rates: (1) providing smokers with practical counseling (problemsolving skills/skills training), and (2) providing support and encouragement as part of treatment. These types of counseling elements should be included in smoking cessation interventions. (Strength of Evidence = B)**

Sixty-four studies met selection criteria for meta-analyses in 2000 to examine the effectiveness of interventions using various types of counseling and behavioral therapies. The results, shown in Table 6.18, reveal that four specific types of counseling and behavioral therapy categories yield statistically significant increases in abstinence rates relative to no-contact (i.e., untreated control conditions). These categories are: (1) providing practical counseling such as problemsolving/skills training/stress management; (2) providing support during a smoker's direct contact with a clinician (intratreatment social support); (3) intervening to increase social support in the smoker's environment (extratreatment social support); and (4) using aversive smoking procedures (rapid smoking, rapid puffing, other smoking exposure). A separate analysis was conducted eliminating studies that included the use of U.S. Food and Drug Administration (FDA)-approved medications. The results of this analysis were substantially similar to the main analysis.

**Table 6.18. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for various types of counseling and behavioral therapies (n = 64 studies)[a]**

| Type of counseling and behavioral therapy | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No counseling/behavioral therapy | 35 | 1.0 | 11.2 |
| Relaxation/breathing | 31 | 1.0 (0.7–1.3) | 10.8 (7.9–13.8) |
| Contingency contracting | 22 | 1.0 (0.7–1.4) | 11.2 (7.8–14.6) |
| Weight/diet | 19 | 1.0 (0.8–1.3) | 11.2 (8.5–14.0) |
| Cigarette fading | 25 | 1.1 (0.8–1.5) | 11.8 (8.4–15.3) |
| Negative affect | 8 | 1.2 (0.8–1.9) | 13.6 (8.7–18.5) |
| Intratreatment social support | 50 | 1.3 (1.1–1.6) | 14.4 (12.3–16.5) |
| Extratreatment social support | 19 | 1.5 (1.1–2.1) | 16.2 (11.8–20.6) |
| Practical counseling (general problemsolving/skills training) | 104 | 1.5 (1.3–1.8) | 16.2 (14.0–18.5) |
| Other aversive smoking | 19 | 1.7 (1.04–2.8) | 17.7 (11.2–24.9) |
| Rapid smoking | 19 | 2.0 (1.1–3.5) | 19.9 (11.2–29.0) |

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

The 2008 Guideline Panel decided not to recommend extratreatment social support in the current Guideline update. This change was based on recent literature on extratreatment social support that does not show a strong effect for helping smokers identify and utilize support outside of the treatment relationship.[274-276] Aversive smoking was recommended in the 2000 Guideline. However, new studies that have been conducted since the 2000 Guideline, including a Cochrane Review, cast doubt on the effectiveness of aversive smoking.[277] Because of this and the side effects of this treatment, the Guideline Panel decided not to recommend the use of aversive smoking therapy in the 2008 update.

The strength of evidence for the 2008 Guideline update recommendations regarding practical counseling and intratreatment social support did not warrant an "A" rating for several reasons. First, the evidence reviewed indicated that tobacco use treatments rarely used a particular type of counsel-

ing or behavioral therapy in isolation. Second, various types of counseling and behavioral therapies tended to be correlated with other treatment characteristics. For instance, some types of counseling and behavioral therapies were more likely to be delivered using a greater number of sessions across longer time periods. Third, all of these types of counseling and behavioral therapies were compared with no-contact/control conditions. Therefore, the control conditions in this meta-analysis did not control for nonspecific or placebo effects of treatment. This further restricted the ability to attribute effectiveness to particular types of counseling and behavioral therapies *per se*. Fourth, the studies used in this analysis often tailored the types of counseling and behavioral therapies to the needs of specific populations being studied, thereby affecting the generalizability of the study results. Fifth, there was considerable heterogeneity within each type of counseling and behavioral therapy.

Tables 6.19 and 6.20 outline elements of practical counseling (problemsolving/skills training) and intratreatment social support, respectively. These tables are designed to help clinicians using these counseling and behavioral therapies. It must be noted, however, that these treatment labels are nonspecific and include heterogeneous treatment elements. The effectiveness of encouragement and support as part of treatment is consistent with the literature regarding the importance of providing a caring, empathic, and understanding context in making other health behavior changes.[278-280]

**Table 6.19. Common elements of practical counseling (problemsolving/skills training)**

| Practical counseling (problemsolving/ skills training) treatment component | Examples |
|---|---|
| Recognize danger situations – Identify events, internal states, or activities that increase the risk of smoking or relapse. | • Negative affect and stress<br>• Being around other tobacco users<br>• Drinking alcohol<br>• Experiencing urges<br>• Smoking cues and availability of cigarettes |
| Develop coping skills – Identify and practice coping or problemsolving skills. Typically, these skills are intended to cope with danger situations. | • Learning to anticipate and avoid temptation and trigger situations<br>• Learning cognitive strategies that will reduce negative moods<br>• Accomplishing lifestyle changes that reduce stress, improve quality of life, and reduce exposure to smoking cues<br>• Learning cognitive and behavioral activities to cope with smoking urges (e.g., distracting attention; changing routines) |

**Table 6.19. Common elements of practical counseling (problemsolving/skills training) (continued)**

| Practical counseling (problemsolving/ skills training) treatment component | Examples |
|---|---|
| Provide basic information – Provide basic information about smoking and successful quitting. | • The fact that any smoking (even a single puff) increases the likelihood of a full relapse<br>• Withdrawal symptoms typically peak within 1–2 weeks after quitting but may persist for months. These symptoms include negative mood, urges to smoke, and difficulty concentrating.<br>• The addictive nature of smoking |

**Table 6.20. Common elements of intratreatment supportive interventions**

| Supportive treatment component | Examples |
|---|---|
| Encourage the patient in the quit attempt. | • Note that effective tobacco dependence treatments are now available.<br>• Note that one-half of all people who have ever smoked have now quit.<br>• Communicate belief in patient's ability to quit. |
| Communicate caring and concern. | • Ask how patient feels about quitting.<br>• Directly express concern and willingness to help as often as needed.<br>• Ask about the patient's fears and ambivalence regarding quitting. |
| Encourage the patient to talk about the quitting process. | Ask about:<br>• Reasons the patient wants to quit.<br>• Concerns or worries about quitting.<br>• Success the patient has achieved.<br>• Difficulties encountered while quitting. |

**Acupuncture.** A separate meta-analysis was conducted in 2000 to evaluate the effectiveness of acupuncture. Evidence, as shown in Table 6.21, did not support the effectiveness of acupuncture as a tobacco use treatment. The acupuncture meta-analysis comparing "active" acupuncture with "control" acupuncture (see Glossary) revealed no difference in effectiveness between the two types of procedures. These results suggest that any effect of acupuncture might be produced by other factors such as positive expectations about the procedure. These results are consistent with the more recent Cochrane analysis.[281] Moreover, the Guideline Panel did not identify scientific literature to support the effectiveness of the more recent electrostimulation or laser acupuncture treatments for tobacco use.

**Hypnosis.** The 1996 Guideline did not conduct a separate meta-analysis on hypnosis because few studies met inclusion criteria, and those that did used very heterogeneous hypnotic procedures. There was no common or standard intervention technique to analyze. Literature screening for the 2000 Guideline revealed no new published studies on the treatment of tobacco dependence by hypnosis that met the inclusion criteria; therefore, this topic was not reexamined. Moreover, an independent review of nine hypnotherapy trials by the Cochrane Group found insufficient evidence to support hypnosis as a treatment for smoking cessation.[282] In contrast to the Cochrane Review and other reviews, a small recent study reported preliminary positive results with hypnotherapy.[283]

**Other Interventions.** The number of studies was insufficient to accurately appraise the effectiveness of other types of counseling and behavioral therapies, such as physiological feedback, restricted environmental stimulation therapy,[284] and the use of incentives.[285]

**Table 6.21. Meta-analysis (2000): Effectiveness of and estimated abstinence rates for acupuncture (n = 5 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Placebo | 7 | 1.0 | 8.3 |
| Acupuncture | 8 | 1.1 (0.7–1.6) | 8.9 (5.5–12.3) |

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

## Future Research

The following topics regarding types of counseling and behavioral therapies require additional research:

- Effectiveness of motivational interventions, cigarette fading, and physiological feedback of smoking effects
- Mechanisms through which counseling interventions exert their effects
- Effectiveness of specific counseling interventions among various patient populations (e.g., those with cancers; chronic obstructive pulmonary disease [COPD]; psychiatric disorders, including substance use disorders; and atherosclerosis)

- Effectiveness of smokefree policies, particularly smokefree homes and worksites, on increasing interest in, and the effectiveness of, tobacco dependence treatment[286]

- Effectiveness of family systems interventions as a means to increase support

## Combining Counseling and Medication

**Recommendation: The combination of counseling and medication is more effective for smoking cessation than either medication or counseling alone. Therefore, whenever feasible and appropriate, both counseling and medication should be provided to patients trying to quit smoking. (Strength of Evidence = A)**

**Recommendation: There is a strong relation between the number of sessions of counseling, when it is combined with medication, and the likelihood of successful smoking cessation. Therefore, to the extent possible, clinicians should provide multiple counseling sessions, in addition to medication, to their patients who are trying to quit smoking. (Strength of Evidence = A)**

Evidence in this Guideline update supports the independent effectiveness of both counseling interventions and medication interventions. In the 2008 Guideline update, the Panel evaluated whether combining counseling and medication improved cessation rates relative to using either of these treatments alone.

**Providing Counseling in Addition to Medication.** Eighteen studies met selection criteria to evaluate the effectiveness of providing counseling in addition to medication versus medication alone. The results of this 2008 meta-analysis indicate that providing counseling in addition to medication significantly enhances treatment outcomes (see Table 6.22). These same 18 studies also were analyzed to examine the relation of counseling intensity when it was used in combination with a medication. Results revealed that two or more sessions significantly enhance treatment outcomes, and more than eight sessions produced the highest abstinence rates (see Table 6.23). The counseling provided in these studies was delivered either in person or via telephone.

**Table 6.22. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for the combination of counseling and medication vs. medication alone (n = 18 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Medication alone | 8 | 1.0 | 21.7 |
| Medication and counseling | 39 | 1.4 (1.2–1.6) | 27.6 (25.0–30.3) |

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

**Table 6.23. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for the number of sessions of counseling in combination with medication vs. medication alone (n = 18 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| 0–1 session plus medication | 13 | 1.0 | 21.8 |
| 2–3 sessions plus medication | 6 | 1.4 (1.1–1.8) | 28.0 (23.0–33.6) |
| 4–8 sessions plus medication | 19 | 1.3 (1.1–1.5) | 26.9 (24.3–29.7) |
| More than 8 sessions plus medication | 9 | 1.7 (1.3–2.2) | 32.5 (27.3–38.3) |

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

**Providing Medication in Addition to Counseling.** The effect of adding medication to counseling also was examined. Nine studies met inclusion criteria and provided 24 arms to compare medication and counseling with counseling alone. The results of this 2008 meta-analysis indicate that providing medication in addition to counseling significantly enhances treatment outcomes (see Table 6.24).

**Table 6.24. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for the combination of counseling and medication vs. counseling alone (n = 9 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Counseling alone | 11 | 1.0 | 14.6 |
| Medication and counseling | 13 | 1.7 (1.3–2.1) | 22.1 (18.1–26.8) |

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

Medication and/or counseling are effective and should be provided as stand-alone interventions when it is not feasible to do both or the patient is not interested in both. By combining medication and counseling, however, the clinician can significantly improve abstinence rates. The clinician providing the medication does not need to be the clinician providing the counseling. It may be that a physician, dentist, physician assistant, or nurse practitioner could prescribe medicine, and counseling could be provided by a health educator, dental hygienist, tobacco treatment specialist, pharmacist, or quitline. Adherence to treatment, both medication and counseling, is important for optimal outcomes. Even though there is compelling evidence that both counseling and medications increase smoking cessation success, the clinician should encourage the patient to make a quit attempt even if she or he declines such treatment.

## Future Research

The following topics regarding the combination of counseling and medication require additional research:

- Optimal timing and length of counseling and medication interventions (e.g., timing and spacing of postquit counseling sessions)
- Effectiveness and acceptability/appeal of different counseling formats and techniques (e.g., computer-based counseling, quitline counseling, motivational interviewing)
- Strategies to address misconceptions about effective counseling and medication treatments
- Relative cost-effectiveness of various treatment combinations

## For Smokers Not Willing To Make a Quit Attempt At This Time

**Recommendation: Motivational intervention techniques appear to be effective in increasing a patient's likelihood of making a future quit attempt. Therefore, clinicians should use motivational techniques to encourage smokers who are not currently willing to quit to consider making a quit attempt in the future. (Strength of Evidence = B)**

Evidence suggests that a variety of motivational interventions can increase the motivation for behavior change. These interventions have varied contents and labels (e.g., individualized motivational intervention, motivational consulting, and motivational interviewing; see e.g., Chan et al.,[170] Butler et al.,[171] and Brown et al.[173]). The motivational intervention that has perhaps the greatest level of support and content specificity is motivational interviewing.

Motivational interviewing (MI) is a specific counseling strategy that is intended to increase a person's motivation for behavior change.[168] MI comprises a variety of strategies that are designed to help individuals resolve ambivalence about such change.[175] The technique has been used successfully to help individuals attempt and achieve many types of behavior change, including reduced drinking and illicit drug use, and reduction of HIV risk behaviors.[175,287,288]

Several studies have shown that MI techniques appear to be effective in motivating smokers to make quit attempts. A randomized controlled trial of an MI-based intervention among 137 smokers with cancer found that MI significantly increased quit attempts compared to an advice condition.[289] Another study found that a single session of MI, versus either brief psychoeducational counseling or advice, significantly increased the proportion of patients with schizophrenia who contacted a tobacco dependence treatment provider and attended an initial treatment session.[174] A third study showed that two 45-minute individual counseling sessions based on MI principles yielded higher levels of intention to quit smoking among adolescents than did a brief advice condition.[173] No differences in quitting attempts or quitting success were seen in that study, however. Studies that used motivational approaches that shared features of MI (but that were not

MI) yielded a mixed pattern of results, with some studies showing significant increases in quit attempts (see, e.g., Butler et al.[171]); others showed only trends in that direction.[170] Finally, one study that targeted unmotivated smokers showed that counseling based on the "5 R's" (see Chapter 3, Strategy B2) significantly increased the odds of making a quit attempt that lasted at least 24 hours.[169]

The available evidence shows that the reviewed motivational interventions such as MI increase quit attempts when used with individuals not already interested in quitting. The evidence does not show that such interventions are reliably effective as cessation treatments,[173,175,290] nor is there consistent evidence that MI-induced quit attempts translate into higher long-term abstinence rates. Evidence also shows that such interventions are more effective in smokers with little pre-existing motivation to quit.[171,173] Finally, some evidence suggests that extensive training is needed before competence is achieved in the MI technique.[175,291]

## Physiological Monitoring/Biological Marker Feedback To Motivate Smokers To Quit

Investigators have sought to determine whether feedback regarding either smoking effects or disease risk motivates quit attempts. Modest evidence indicates that such feedback motivates quit attempts.[292] One small study found that multifaceted feedback involving CO level, vital capacity measurement, and discussion of pulmonary symptoms led to more quit attempts among smokers identified during routine medical screening.[293] In a second study, feedback regarding CO level and genetic susceptibility to cancer was associated with a greater likelihood of quit attempts 1 year later.[294] Although these results are encouraging, there is too little information to evaluate definitively the effects of physiological feedback.[284] In addition, there is insufficient information as to how this feedback affects those at different levels of readiness to quit. It also is unclear whether feedback that a person is *not* at high risk would encourage continued smoking. Finally, data are mixed regarding the effectiveness of feedback as a cessation versus motivational intervention. That is, data are mixed as to whether or not feedback increases abstinence rates.[284,295,296]

### 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, selegeline), 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<br>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) + *ad lib* 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 review[297] 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 year[306] 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 anitarrhythmics, 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 review[298] 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 review[158] 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 Hochberg[319] 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 colleagues[321] 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 analysis[323] 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/gdlnrefs.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 reviews[299] (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 trials[338-340] 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 methodolgical 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

# C. Systems Evidence

## *Clinician Training and Reminder Systems*

**Recommendation: All clinicians and clinicians-in-training should be trained in effective strategies to assist tobacco users willing to make a quit attempt and to motivate those unwilling to quit. Training appears to be more effective when coupled with systems changes. (Strength of Evidence = B)**

Meta-analyses were conducted to analyze the effects of clinician training and other systems changes. It was necessary to include studies in these analyses in which higher level units (clinicians or clinical sites) served as units of randomization. This strategy was adopted because relatively few studies in this area of research randomized individual patients to treatment or intervention conditions. Studies randomized at higher level units were considered for the analyses only if the study's analytic plan accounted for the dependency of data nested under such units or if the outcome, such as providing advice to quit, was analyzed at the same level as the randomization (e.g., clinician or clinic level). In fact, however, the few studies that analyzed data at the level of the clinician or clinic shared no common outcomes and could not be used in the meta-analysis.

Table 6.31 depicts meta-analytic results for studies that examined the effects of training on abstinence outcomes. Only two studies, somewhat heterogenous, were available for this analysis. Thus, although the meta-analysis showed a significant effect of training, the Panel elected to assign this recommendation a "B" strength of evidence.

**Table 6.31. Meta-analysis (2008): Effectiveness of and estimated abstinence rates for clinician training (n = 2 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| No intervention | 2 | 1.0 | 6.4 |
| Clinician training | 2 | 2.0 (1.2–3.4) | 12.0 (7.6–18.6) |

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

Clinician training and other systems changes are intended to increase rates of tobacco use assessment and intervention. Therefore, additional meta-analyses were conducted to ascertain the effects of systems changes on

outcomes such as clinician assessment of smoking status ("Ask"), provision of treatment ("Assist"), and arranging for treatment followup ("Arrange"). Thus, these meta-analyses focused on systems change impact on specific clinician behaviors. In the analyzed studies, clinician behavior was assessed via patient report or chart review (not via clinician report). Analyses of such clinician behaviors are of public health significance because of evidence that the provision of treatment has been shown to lead to higher tobacco cessation rates.

As noted in Table 6.32, training clinicians increases the percentage of smokers who receive treatment, such as a discussion of benefits/obstacles to quitting or strategies to prevent relapse, medication, and provision of support. Further, combining clinician training with a charting system, such as chart reminder stickers or treatment algorithms attached to the chart, increases rates of tobacco use assessment (Table 6.33), setting a quit date (Table 6.34), providing materials (Table 6.35), and arranging for followup (Table 6.36). Thus, clinician training, especially when coupled with other systems changes such as reminder systems, increases the rates at which clinicians engage in tobacco interventions that reliably boost tobacco cessation. The *Guide to Community Preventive Services*[92] found insufficient evidence to recommend provider education systems as stand-alone interventions, separate from other system changes, but does recommend provider education when part of other system changes such as reminder systems.

**Table 6.32. Meta-analysis (2008): Effectiveness of clinician training on rates of providing treatment ("Assist") (n = 2 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated rate (95% C.I.) |
|---|---|---|---|
| No intervention | 2 | 1.0 | 36.2 |
| Clinician training | 2 | 3.2 (2.0–5.2) | 64.7 (53.1–74.8) |

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

**Table 6.33. Meta-analysis (2008): Effectiveness of clinician training combined with charting on asking about smoking status ("Ask") (n = 3 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated rate (95% C.I.) |
|---|---|---|---|
| No intervention | 3 | 1.0 | 58.8 |
| Training and charting | 3 | 2.1 (1.9–2.4) | 75.2 (72.7–77.6) |

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

**Table 6.34. Meta-analysis (2008): Effectiveness of training combined with charting on setting a quit date ("Assist") (n = 2 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated rate (95% C.I.) |
|---|---|---|---|
| No intervention | 2 | 1.0 | 11.4 |
| Training and charting | 2 | 5.5 (4.1–7.4) | 41.4 (34.4–48.8) |

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

**Table 6.35. Meta-analysis (2008): Effectiveness of training combined with charting on providing materials ("Assist") (n = 2 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated rate (95% C.I.) |
|---|---|---|---|
| No intervention | 2 | 1.0 | 8.7 |
| Training and charting | 2 | 4.2 (3.4–5.3) | 28.6 (24.3–33.4) |

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

**Table 6.36. Meta-analysis (2008): Effectiveness of training combined with charting on arranging for followup ("Arrange") (n = 2 studies)[a]**

| Intervention | Number of arms | Odds Ratio (95% C.I.) | Estimated rate (95% C.I.) |
|---|---|---|---|
| No intervention | 2 | 1.0 | 6.7 |
| Training and charting | 2 | 2.7 (1.9–3.9) | 16.3 (11.8– 22.1) |

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

These meta-analyses support the finding that clinician training increases the delivery of effective tobacco use treatments. Training elements provided in these interventions included didactic presentation of material, group discussions, and role playing. These studies also examined a range of clinician training, from formal training during residency to onsite clinician training within the community.

Training should be directed at both clinicians-in-training as well as practicing clinicians. Training should be reinforced throughout the clinicians' education and practice.[363-368] Such training has been shown to be cost-effective.[369] For clinicians-in-training, most clinical disciplines currently neither

provide training nor require competency in tobacco use interventions,[370] although this is improving slowly.[371,372] One survey of U.S. medical schools found that most medical schools (69%) did not require clinical training in tobacco dependence treatment.[373] The National Cancer Institute's Prevention and Cessation Education in Medical Schools (PACE) reported that, in 2004, about 36 percent of medical school courses offered about 10 hours of tobacco-related teaching over 4 years,[374] and PACE has developed competencies for graduating medical students.[375]

Similarly, the American Dental Education Association has guidelines recommending tobacco use cessation clinical activities (TUCCA) education for dental and dental hygiene students and, in 1998, 51 percent of dental schools reported clinical training in this area.[376] Tobacco-related curricula may be taught as part of a preventive medicine or substance abuse course or as a class by itself. Similar recommendations would be relevant to virtually all other clinical disciplines. Training in tobacco use interventions should not only transmit essential treatment skills (see Chapter 3), but also should inculcate the belief that tobacco dependence treatment is a standard of good clinical practice.[130,208,250]

Several factors would promote the training of clinicians in tobacco intervention activities:[370]

- Inclusion of education and training in tobacco dependence treatments in the required curricula of all clinical disciplines
- Evaluation of effective tobacco dependence treatment knowledge and skills in licensing and certification exams for all clinical disciplines
- Adoption by medical specialty societies of a uniform standard of competence in tobacco dependence treatment for all members

Finally, clinicians who currently use any tobacco product should participate in treatment programs to stop their own tobacco use permanently. Clinicians are important role models for their patients, and those who use tobacco probably are less likely to counsel their patients to quit.[377] Therefore, it is heartening that many types of clinicians have dramatically decreased their own tobacco use during the past 40 years,[378] although this has not been universal.

## Future Research

The following topics regarding clinician training require additional research:

- Effectiveness of training programs for other health disciplines, such as nursing, psychology, dentistry (including hygienists), social work, and pharmacy
- Effective elements in successful training programs (e.g., continuing medical education, interactive components)
- Combined effect of multiple systems changes, such as clinician training, reminder systems, clinician feedback, incentive payments, and recruitment of opinion leaders

# *Cost-Effectiveness of Tobacco Dependence Interventions*

**Recommendation: The tobacco dependence treatments shown to be effective in this Guideline (both counseling and medication) are highly cost-effective relative to other reimbursed treatments and should be provided to all smokers. (Strength of Evidence = A)**

**Recommendation: Sufficient resources should be allocated for systems support to ensure the delivery of efficacious tobacco use treatments. (Strength of Evidence = C)**

Smoking exacts a substantial financial burden on the United States. A recent report of the Centers for Disease Control and Prevention estimated that tobacco dependence costs the Nation more than $96 billion per year in direct medical expenses and $97 billion in lost productivity.[28] Given these substantial costs, research has focused on the economic impact and cost-effectiveness of tobacco cessation interventions.

Tobacco use treatments, ranging from brief clinician advice to specialist-delivered intensive programs, including medication, have been shown not only to be clinically effective, but also to be extremely cost-effective relative to other commonly used disease prevention interventions and

medical treatments. Cost-effectiveness analyses have shown that tobacco dependence treatment compares favorably with routinely reimbursed medical interventions such as the treatment of hypertension and hypercholesterolemia, as well as preventive screening interventions such as periodic mammography or Papanicolaou smears.[222,224,379-382] For example, the cost per life-year saved of tobacco dependence treatment has been estimated at $3,539,[194] which compares favorably to hypertension screening for men ages 45 to 54 ($5,200) and annual cervical screening for women ages 34 to 39 ($4,100).[383] Treating tobacco dependence also is important economically in that it can prevent the development of a variety of costly chronic diseases, including heart disease, cancer, and pulmonary disease. In fact, tobacco dependence treatment has been referred to as the "gold standard" of health care cost-effectiveness.[225]

Cost-effectiveness can be measured in a variety of ways, including cost per quality-adjusted-life-year saved (QALY), cost per quit, health care costs and utilization pre- and postquit, and return on investment (ROI) for coverage of tobacco dependence treatment.

## Cost per Quality-Adjusted-Life-Year Saved and Cost per Quit

Numerous analyses have estimated the cost per QALY saved resulting from use of effective tobacco dependence interventions.[187,222,380,384-389] In general, evidence-based tobacco use interventions compare favorably with other prevention and chronic disease interventions such as treatment of hypertension and mammography screening when using this criterion. Specific analyses have estimated the costs of tobacco use treatment to range from a few hundred to a few thousand dollars per QALY saved.[228,385] Separate analyses have computed the estimated costs of treatment in terms of the cost per quit. Compared to other interventions, the cost of tobacco use treatments has been modest, ranging from a few hundred to a few thousand dollars per quit.[194,212,384,390-393]

Managed Care Organizations (MCOs) often assess the per member per month (PMPM) cost of a benefit, and the PMPM cost for tobacco use treatment has been assessed in a variety of settings. In general, the PMPM cost for tobacco use treatments has been low relative to other covered benefits, ranging from about $0.20 to about $0.80 PMPM.[210,228,391,394]

## Health Care Costs and Utilization Pre- and Postquit

A substantial body of research has investigated the effect of tobacco use treatment on health care costs.[395-399] A synthesis of these findings suggests that: (1) among individuals who quit tobacco use, health care costs typically increase during the year in which smokers quit then decline progressively, falling below those of continuing smokers for 1 to 10 years after quitting; (2) in general, smokers' health care costs begin to rise in the time period immediately prior to quit attempts; and (3) higher health care utilization predicts smoking cessation among smokers with and without chronic diseases. These findings suggest that quitting smoking often occurs in response to serious and expensive health problems. Such research also suggests that increases in health care costs, including hospitalizations, during the year of quitting may be a cause rather than a consequence of successful smoking cessation.

## Return on Investment for Coverage of Tobacco Dependence Treatment

The ROI tool is used frequently to estimate the amount of time it takes for an expenditure to earn back some or all of its initial investment. The economic arguments supporting the decision to provide insurance coverage for tobacco use treatments would be enhanced if the costs of such coverage are modest compared to economic benefits resulting from successful cessation (reductions in health care expenditures, increased productivity, and/or other costs).

Studies have documented that tobacco dependence treatments provide a timely return on investment when considered by the employer. Such analyses have concluded that providing coverage for tobacco use treatment for employees often produces substantial net financial savings through increased health care savings, increased productivity, reduced absenteeism, and reduced life insurance payouts.[229,400-402]

Financial savings are more difficult to attain for a health plan given factors such as member turnover, the difficulty of attributing reduced health care expenditures to tobacco dependence, and the absence of economic benefits resulting from productivity gains. Although most analyses have

not demonstrated cost savings, insurance coverage of evidence-based tobacco dependence treatments are highly cost-effective relative to other frequently paid-for health care services. One recent effort to simulate the financial implications of covering tobacco use treatments by MCOs found that at 5 years, coverage of tobacco use treatment cost an MCO a modest $0.61 PMPM, with quitters gaining an average of 7.1 years of life and a direct coverage cost of about $3,500 for each life-year saved.[228] The authors concluded that coverage of such cost-effective tobacco use treatment programs by MCOs should be strongly encouraged. Another study examined the trend in health care costs for former smokers over 7 years postquitting compared to continuing smokers.[395] The authors found that, by the seventh year, former smokers' cumulative costs (including increased cost in the year they quit) were lower than those of continuing smokers. A more recent analysis concluded that at 10 years, the ROI of providing a comprehensive tobacco use treatment benefit, considering only health care costs, ranged from 75 percent to 92 percent, indicating that health care savings alone have repaid more than three-fourths of the investment.[229] Other analyses have shown that multiple tobacco use treatment components, including telephone counseling and various medications,[227,403,404] yield a favorable ROI. The American Health Insurance Plans (AHIP) has provided a Web link for health plans to compute their ROI for the provision of tobacco use treatment: *www.businesscaseroi.org/roi/default.aspx*.

Tobacco cessation treatment is particularly cost-effective in certain populations, such as hospitalized patients and pregnant women. For hospitalized patients, successful tobacco abstinence not only reduces general medical costs in the short term, but also reduces the number of future hospitalizations.[9,355,405] Tobacco dependence interventions for pregnant women are especially cost-effective because they result in fewer low birth-weight babies and perinatal deaths; fewer physical, cognitive, and behavioral problems during infancy and childhood; and yield important health benefits for the mother.[406,407] One study found that interventions with U.S. pregnant smokers could net savings up to $8 million in direct neonatal inpatient costs given the cost of an intervention ($24–$34) versus the costs saved ($881) for each woman who quits smoking during pregnancy.[408] Another study showed that, for each low-income pregnant smoker who quit, Medicaid saved $1,274.[409] A simulation study found that a 1 percent decrease in smoking prevalence among U.S. pregnant women would save $21 million (1995 dollars) in direct medical costs in the first year.[406,410,411]

## Tobacco Dependence Treatment as a Part of Assessing Health Care Quality

**Recommendation: Provision of Guideline-based interventions to treat tobacco use and dependence should remain in standard ratings and measures of overall health care quality (e.g., NCQA HEDIS). These standard measures should also include measures of outcomes (e.g., use of cessation treatment, short- and long-term abstinence rates) that result from providing tobacco dependence interventions. (Strength of Evidence = C)**

The provision of tobacco dependence treatment should be increased by: (1) attention to health organization "report cards" (e.g., HEDIS, The Joint Commission, Physician Consortium for Performance Improvement, National Quality Forum, Ambulatory Quality Alliance),[89,412-414] which support smoker identification and treatment; (2) accreditation criteria used by The Joint Commission and other accrediting bodies that include the presence of effective tobacco assessment and intervention policies; and (3) increasing the use of tobacco-related measures in pay-for-performance initiatives.

## Future Research

The following topics regarding cost-effectiveness and health systems require additional research:

- Cost-effectiveness of the various tobacco dependence treatments, both short- and long-term
- Optimal ways to remove systemic barriers that prevent clinicians from effectively delivering tobacco dependence treatments
- Systemic interventions to encourage provider and patient utilization of effective tobacco dependence treatments
- Relative costs and economic impacts of different formats of effective treatments (e.g., proactive telephone counseling, face-to-face contact, medication)

- Impact of using tobacco intervention performance measures on clinician intervention and patient outcomes, including the use of such measures in "pay for performance" programs

## Providing Treatment for Tobacco Use and Dependence as a Covered Benefit

**Recommendation: Providing tobacco dependence treatments (both medication and counseling) as a paid or covered benefit by health insurance plans has been shown to increase the proportion of smokers who use cessation treatment, attempt to quit, and successfully quit. Therefore, treatments shown to be effective in the Guideline should be included as covered services in public and private health benefit plans. (Strength of Evidence = A)**

Multiple studies have assessed the impact of including tobacco dependence treatment as a covered health insurance benefit for smokers. Most studies have documented that such health insurance coverage increases both treatment utilization rates and the rates of cessation,[210,212,391,415] although some research is not consistent with these findings.[416] A recent Cochrane analysis (2005) concluded that health care financing systems that offered full payment for tobacco use treatment increased self-reported prolonged abstinence rates at relatively low costs when compared with a partial benefit or no benefit. Moreover, the presence of prepaid or discounted prescription drug benefits increases patients' receipt of medication and smoking abstinence rates.[231,348,417] These studies emphasize that removing all cost barriers yields the highest rates of treatment utilization.

Three studies met criteria to be included in a 2008 Guideline update meta-analysis of the effects of providing tobacco use treatments as a covered health insurance benefit. Three different outcomes were examined: rates of treatment provision, quit attempts, and quit rates. As can be seen in Tables 6.37 through 6.39, compared to not having tobacco use treatment as a covered benefit, individuals with the benefit were more likely to receive treatment, make a quit attempt, and abstain from smoking.

**Table 6.37. Meta-analysis (2008): Estimated rates of intervention for individuals who received tobacco use interventions as a covered health insurance benefit (n = 3 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated intervention rate (95% C.I.) |
|---|---|---|---|
| Individuals with no covered health insurance benefit | 3 | 1.0 | 8.9 |
| Individuals with the benefit | 3 | 2.3 (1.8–2.9) | 18.2 (14.8–22.3) |

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

**Table 6.38. Meta-analysis (2008): Estimated rates of quit attempts for individuals who received tobacco use interventions as a covered health insurance benefit (n = 3 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated quit attempt rate (95% C.I.) |
|---|---|---|---|
| Individuals with no covered benefit | 3 | 1.0 | 30.5 |
| Individuals with the benefit | 3 | 1.3 (1.01–1.5) | 36.2 (32.3–40.2) |

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

**Table 6.39. Meta-analysis (2008): Estimated abstinence rates for individuals who received tobacco use interventions as a covered benefit (n = 3 studies)[a]**

| Treatment | Number of arms | Estimated odds ratio (95% C.I.) | Estimated abstinence rate (95% C.I.) |
|---|---|---|---|
| Individuals with no covered benefit | 3 | 1.0 | 6.7 |
| Individuals with the benefit | 3 | 1.6 (1.2–2.2) | 10.5 (8.1–13.5) |

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

It may be in the best interests of insurance companies, MCOs, purchasers, and governmental bodies within a specific geographic area to work collaboratively to ensure that tobacco dependence interventions are a covered benefit and that enrollees are aware of these benefits. This would allow the financial benefits of the successful use of these services to be realized by all of the health plans within a community.

## Future Research

- Impact of promotion or communication of tobacco dependence treatment benefits on utilization and resulting population health and economic effects
- Cost-effectiveness of specific elements of tobacco dependence treatment
- Appropriate level of payment needed to optimize clinician delivery of tobacco dependence treatment