CONCISE REVIEW FOR CLINICIANS

Treating Tobacco Dependence in Light of the 2008 US Department of Health and Human Services Clinical Practice Guideline

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On completion of this article, you should be able to (1) apply current clinical practice guidelines to the treatment of tobacco use and dependence in the office practice, (2) name the recommended first-line pharmacotherapies for tobacco cessation treatment, and (3) identify commonly encountered adverse effects of first-line pharmacotherapies for the treatment of tobacco dependence.

Cigarette smoking is the most important preventable cause of morbidity, mortality, and excess health care costs in the United States. From 2000 through 2004, cigarette smoking caused an estimated annual average of 443,595 deaths and cost $193 billion per year in smoking-attributable productivity losses and smoking-related health care expenditures. Preventing smoking and providing effective treatment to help smokers quit will remain a public health priority for the foreseeable future. In support of this goal, the US Department of Health and Human Services recently published the clinical practice guideline entitled Treating Tobacco Use and Dependence: 2008 Update. The new guideline updates the previous guidelines published in 1996 and 2000 and presents many new research findings to provide a broader evidence base for effective intervention. This article briefly reviews the major updates and recommendations from the new guideline and highlights its practical clinical applications.


KEY ADVANCES IN THE 2008 CLINICAL PRACTICE GUIDELINE

Counseling
The new practice guideline presents compelling evidence that counseling (both in person and by telephone) is effective for smokers motivated to become tobacco abstinent. Even minimal counseling by a physician lasting 3 minutes or less results in an increase in the odds for prolonged abstinence compared with no intervention (odds ratio [OR], 1.3; 95% confidence interval [CI], 1.0-1.6). A dose-response relationship exists between time spent in counseling for smoking cessation and abstinence rates, with higher-intensity counseling (>10 minutes) resulting in a near doubling of abstinence rates compared with minimal (<3 minutes) counseling (ie, estimated abstinence rates of 22.1% [OR, 2.3; 95% CI, 2.0-2.7] for high-intensity and 13.4% [OR, 1.3; 95% CI, 1.0-1.6] for minimal counseling).

INSURANCE COVERAGE FOR TOBACCO USE AND DEPENDENCE TREATMENT

Insurance coverage for tobacco use and dependence treatment increases the number of smokers seeking treatment and improves tobacco abstinence rates. Tobacco cessation treatments are cost-effective and have been shown to reduce health care costs for defined populations over time. Clinicians can help ensure the availability of such treatments by advocating for systems changes that promote treatment services for tobacco dependence in the hospitals and clinics where they provide care and by advocating that health insurers and managed care organizations provide coverage for guideline-approved counseling and pharmacological treatments.

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EXPANDED MEDICATION OPTIONS
Since the previous guidelines were published, the number of effective medications for tobacco dependence treatment has increased, the dosing options have expanded, and new combinations of medications have proven effective. The most important changes include an increase in the number of first-line medications (to 7), development of effective combinations of first-line medications, and extended treatment length with nicotine replacement therapy (NRT).

A PRACTICAL GUIDE TO TREATMENT FROM THE 2008 CLINICAL PRACTICE GUIDELINE

HOW DO I BEST COUNSEL A PATIENT TO STOP SMOKING IN 3 MINUTES?
To counsel a patient to quit smoking in a limited amount of time, practitioners should create a system that ensures an assessment of tobacco use (both current and past) at every office visit. A practical way to accomplish this is the assessment of tobacco use as “the new vital sign” obtained and recorded by the office staff who record other routine vital signs. Once identified, all smokers should receive clear, concise, and simple advice to quit. Beyond providing such advice, clinicians should assess the willingness of every smoker to quit (“Are you willing to make a quit attempt now?”). Smokers who are willing to stop smoking need assistance in developing a plan for quitting that includes a quit date, practical counseling help, and effective medications. Practical counseling should teach problem-solving and review coping skills that the patient can readily learn to use. Problem-solving strategies may be as simple as advising removal of all tobacco products from home and work before quitting and planning for high-risk situations. To help their patients successfully maintain abstinence, clinicians should facilitate the development of coping strategies (eg, deep breathing for relaxation or changing a routine in which smoking is often involved).

A brief (3-minute) counseling session should focus on 2 key questions. First, the clinician should ask the patient: “Are you willing (motivated) to make a quit attempt now?” If the patient is not willing to make a quit attempt, then the clinician should offer to help at another time when the patient is more motivated to quit. If the patient instead answers the motivation question affirmatively, the clinician should set a quit date and move on to question 2: “What worked or did not work when you tried to quit before?” The clinician should try to encourage ideas that were previously successful. If the patient has no ideas, the clinician should offer practical advice about strategies that generally work (eg, avoidance of high-risk situations or changing a routine in which smoking usually occurs).

More extensive office-based counseling (lasting ≥10 minutes) may be used to develop detailed plans for quitting and relapse prevention. In motivational interviewing, a patient-centered approach that is often used for more extensive counseling interventions, the clinician elicits from patients their motivations for quitting and helps them identify the personal resources they possess for an attempt to quit.

Follow-up should be arranged to provide continued support for abstinence and to alter treatment plans, if necessary. These recommendations follow the 5 As strategy (Ask about tobacco use at every visit; Advise the smoker to quit in a clear, strong, and personalized manner; Assess willingness to make a quit attempt; Assist the quit attempt with counseling and pharmacotherapy; and Arrange follow-up to support the patient) that has been a part of the guideline since 1996 (known then as the 4 As). The Figure illustrates a brief strategy for treating nicotine-dependent patients.

HOW DO I BEST TREAT PATIENTS WHO HAVE NOT QUIT SMOKING DESPITE PREVIOUS PHARMACOTHERAPY?
Currently, 7 medications have a labeled indication for tobacco dependence treatment (varenicline; bupropion sustained-release [SR]; and NRT patch, gum, lozenge, inhaler, and nasal spray [Table]). For patients willing to make a quit attempt, pharmacotherapy should be discussed and, unless contraindicated, recommended. The selection of a pharmacotherapeutic aid to smoking cessation should be guided by the patient’s medical history, the presence of contraindications, the preferences of the patient and clinician, and the cost of therapy. The current guideline provides greater evidence than previous guidelines that combining counseling with effective medications is superior to either treatment approach alone.

The best options in case of relapse to smoking or simply failure to achieve abstinence with appropriate medication are to try a first-line medication not previously used, to use combination therapy, or to recommend a longer course of treatment.

Try a First-line Medication Not Previously Used.
Varenicline is the newest first-line medication introduced in the 2008 guideline and is a “partial agonist” at the α4β2 neuronal nicotinic acetylcholine receptor (nAChR). As a partial agonist, varenicline partially stimulates the nAChR, causing a sustained, moderate level of dopamine release in the brain’s reward center, which is thought to reduce withdrawal symptoms. It also acts as an antagonist at the α4β2 nAChR, which may inhibit the rewarding effects of nicotine and reduce satisfaction during lapses to smoking. The recommended target dose of varenicline is 1 mg twice daily and can be achieved by titrating from 0.5 mg once
daily for 3 days, to 0.5 mg twice daily for 4 days, to the target dose. A recent study investigated a flexible dosing strategy that allowed the patient to self-regulate the varenicline dose between 0.5 mg/d (minimum dose allowed) and 1 mg twice daily (maximum dose allowed). Most patients in this study took an average dose of about 1.3 mg/d and achieved abstinence rates of greater than 40% at 12 weeks. Because most of the adverse effects of varenicline therapy are dose-dependent, lower doses may eliminate many adverse effects, while retaining most of the efficacy for smoking cessation. Bupropion SR or NRT products not previously tried may also be an appropriate alternative for smokers who have been unable to stop smoking with other pharmacotherapies.

Use Combination Therapy. Combinations of NRT (a nicotine patch plus nicotine gum or nicotine nasal spray) may be more effective for some smokers than NRT monotherapy. The guideline recommends combination NRT for patients who are unable to quit using 1 of the recommended treatments as monotherapy. Combined treatment with bupropion SR and a nicotine patch is recommended for patients who are unable to quit using either as a single-agent treatment.

Recommend a Longer Course of Treatment. Although relatively brief therapy (8-12 weeks) with NRT may be adequate, occasional patients may benefit from treatment for longer periods. In particular, the data on comparative medication effectiveness in the guideline suggest that prolonged treatment with a nicotine patch (>14 weeks) is superior to standard duration of treatment. An attempt to wean every patient from NRT is appropriate, but in some cases indefinite NRT treatment is necessary to prevent relapse to smoking. Some experienced tobacco treatment experts have suggested that prolonged or indefinite therapy with an approved smoking cessation medication (eg, NRT) may be required to prevent relapse in certain smokers.

Use an Increased Dose of NRT. Higher-dose nicotine patch therapy (typically, 25 mg/d or more) may provide a small incremental benefit vs standard-dose nicotine patch therapy, with an estimated relative risk of 1.15 (95% CI, 1.01-1.30). The 2008 practice guideline analysis showed...
a benefit for higher-dose nicotine patch therapy compared with placebo (OR, 2.3; 95% CI, 1.7-3.0) but did not show a benefit for this treatment vs a standard-dose nicotine patch (OR, 1.2; 95% CI, 0.9-1.6). If this approach is used, the initial nicotine patch dose can be approximated by roughly matching the patch dose (in milligrams) to the number of cigarettes smoked per day.

**What Adverse Effects Are Expected From First-Line Medications?**

**Nicotine Replacement Therapy.** The adverse effects of the various NRT formulations differ. Local skin reactions at the patch application site, nausea, vomiting, sweating, alteration in mood status, and sleep disturbances are among the more common adverse effects seen with the nicotine patch (the most widely used NRT). Common adverse effects associated with nicotine gum include jaw fatigue and soreness, hiccupping, burping, and nausea. Adverse effects associated with the nicotine inhaler and nasal spray are attributed to local irritation at the site of administration (ie, mouth or nose). Hiccups, a burning sensation in the mouth, a sore throat, coughing, dry lips, and mouth ulcers have been reported with nicotine sublingual tablets. Although concern has been expressed about the safety of NRT in smokers with cardiac disease, a meta-analysis of safety data from clinical studies with the transdermal patch and a recent review of NRT safety in patients with cardiovascular disease found no evidence of an increased risk of cardiac events associated with NRT treatment. The risk that dependence will develop in patients who are using NRT products for smoking cessation is low.

**Bupropion SR.** The only adverse effects that occurred more commonly with bupropion vs placebo in early smoking cessation trials were dry mouth and insomnia. Both of these adverse effects appear to be dose-related, and neither is a common cause for drug discontinuation. The most common adverse effects associated with drug discontinuation in clinical trials with bupropion have been tremor, rash, headache, and urticaria, with typical dropout rates attributed to adverse effects ranging from 7% to 12%. However, in one study conducted in a clinical practice setting, medication discontinuations attributed to adverse effects were reported in 25.9% of patients receiving 150 mg/d of bupropion SR and in 31.1% of those receiving 300 mg/d of bupropion SR. When used as a treatment for depression and as an aid to smoking cessation, bupropion SR has been associated with a small increased incidence of seizures (rate of 1/1000), particularly among those whose medical history suggests increased risk (eg, any prior seizure; structural brain lesion from previous stroke, tumor, etc).

### Table: Abstinence Rates at 6 Months After Smoking Cessation for Various Medications and Medication Combinations vs Placebo or Standard-Dose Nicotine Patch Therapy (N=83 Studies)\(^a\)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Treatment arms</th>
<th>Estimated abstinence rate % (95% CI)</th>
<th>Estimated OR vs placebo (95% CI)</th>
<th>Estimated OR vs nicotine patch therapy (^b) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varenicline (2 mg/d)</td>
<td>5</td>
<td>33.2 (28.9-37.8)</td>
<td>3.1 (2.5-3.8)</td>
<td>1.6 (1.3-2.0)</td>
</tr>
<tr>
<td>Nicotine nasal spray</td>
<td>4</td>
<td>26.7 (21.5-32.7)</td>
<td>2.3 (1.7-3.0)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>High-dose nicotine patch (&gt;25 mg) (includes both standard and long-term treatment)</td>
<td>4</td>
<td>26.5 (21.3-32.5)</td>
<td>2.3 (1.7-3.0)</td>
<td>1.2 (0.9-1.6)</td>
</tr>
<tr>
<td>Long-term nicotine gum (&gt;14 wk)</td>
<td>6</td>
<td>26.1 (19.7-33.6)</td>
<td>2.2 (1.5-3.2)</td>
<td>1.2 (0.8-1.7)</td>
</tr>
<tr>
<td>Varenicline (1 mg/d)</td>
<td>3</td>
<td>25.4 (19.6-32.2)</td>
<td>2.1 (1.5-3.0)</td>
<td>1.1 (0.8-1.6)</td>
</tr>
<tr>
<td>Nicotine inhaler</td>
<td>6</td>
<td>24.8 (19.1-31.6)</td>
<td>2.1 (1.5-2.9)</td>
<td>1.1 (0.8-1.5)</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>26</td>
<td>24.2 (22.2-26.4)</td>
<td>2.0 (1.8-2.2)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>Nicotine patch (6-14 wk)</td>
<td>32</td>
<td>23.4 (21.3-25.8)</td>
<td>1.9 (1.7-2.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>Long-term nicotine patch (&gt;14 wk)</td>
<td>10</td>
<td>23.7 (21.0-26.6)</td>
<td>1.9 (1.7-2.3)</td>
<td>1.0 (0.9-1.2)</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>5</td>
<td>22.5 (16.8-29.4)</td>
<td>1.8 (1.3-2.6)</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Nicotine gum (6-14 wk)</td>
<td>15</td>
<td>19.0 (16.5-21.9)</td>
<td>1.5 (1.2-1.7)</td>
<td>0.8 (0.6-1.0)</td>
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<tr>
<td><strong>Combination therapies</strong></td>
<td></td>
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<tr>
<td>Patch (long-term; &gt;14 wk)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>+ NRT (gum or spray)</td>
<td></td>
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</tr>
<tr>
<td>ad libitum</td>
<td>3</td>
<td>36.5 (28.6-45.3)</td>
<td>3.6 (2.5-5.2)</td>
<td>1.9 (1.3-2.7)</td>
</tr>
<tr>
<td>Patch + bupropion SR</td>
<td>3</td>
<td>28.9 (23.5-35.1)</td>
<td>2.5 (1.9-3.4)</td>
<td>1.3 (1.0-1.8)</td>
</tr>
<tr>
<td>Patch + nortriptyline</td>
<td>2</td>
<td>27.3 (17.2-40.4)</td>
<td>2.3 (1.3-4.2)</td>
<td>0.9 (0.6-1.4)</td>
</tr>
<tr>
<td>Patch + inhaler</td>
<td>2</td>
<td>25.8 (17.4-36.5)</td>
<td>2.2 (1.3-3.6)</td>
<td>1.1 (0.7-1.9)</td>
</tr>
</tbody>
</table>

\(^a\) CI = confidence interval; NRT = nicotine replacement therapy; OR = odds ratio; SR = sustained-release.

\(^b\) Treatments are compared with monotherapy with nicotine patch (14-25 mg/d) lasting 14 weeks or less.

Adapted from Treating Tobacco Use and Dependence: 2008 Update.
operation, or trauma; alcohol abuse; concomitant drug therapy that may lower seizure threshold). The most common adverse effect attributed to the administration of 1 mg of varenicline twice daily is nausea, occurring in approximately one-third of treated patients. However, most of the nausea reported in these trials was mild or moderate, and treatment discontinuation due to nausea occurred in only approximately 3% of patients. Other common adverse effects reported with varenicline are headache, insomnia, and abnormal dreams. Insomnia also tended to be mild and was less common than in bupropion-treated patients. Postmarketing reports have indicated treatment-emergent incidence of agitation, depressed mood, changes in behavior, and suicidal ideation in patients taking varenicline, which has resulted in the US Food and Drug Administration releasing a notice to all prescribers warning of these possible adverse effects. Although smoking cessation alone has been associated with increased anxiety, anger, changes in behavior, depressed mood, and increased depression, if any of these symptoms occur in a patient taking varenicline, varenicline treatment should be discontinued immediately and the patient should be assessed.

WHERE ELSE CAN MY PATIENTS TURN FOR HELP?

Telephone counseling appears to be as effective as face-to-face counseling for smoking cessation. Most states and many insurance carriers and employers have a telephone counseling service available at low or no cost. Some of the services may even provide medications at low or no cost. Telephone counseling removes many of the barriers to smoking cessation services, such as cost, need to travel, and time away from work and family duties, that are posed by an office visit. Certified tobacco treatment specialists are now available in many areas. Referral to a tobacco treatment specialist is appropriate for patients who have had little or no success with previous office interventions.

WHAT OTHER INFORMATION HAS BECOME AVAILABLE SINCE THE PUBLICATION OF THE 2008 CLINICAL PRACTICE GUIDELINE?

HOSPITALIZED SMOKERS

A hospital admission is a prime opportunity to provide help for smoking cessation. A meta-analysis of smoking cessation interventions provided to hospitalized smokers observed a benefit for counseling interventions that began in the hospital and provided additional supportive contacts for more than 1 month after discharge. Adding NRT to the intervention may increase long-term abstinence rates even further. Counseling intervention and NRT should be provided to every hospitalized smoker who is motivated to attempt to quit smoking. Hospitalizations provide an excellent opportunity to begin treatment.

PREGNANCY AND SMOKING CESSATION

The guideline recommends smoking cessation counseling for all pregnant smokers; pregnant smokers who are unable to quit with counseling alone should be treated with medications (starting with short-acting NRT). However, a recent study found that only 29.3% of pregnant smokers recalled any discussion of medications to aid in smoking cessation during pregnancy, and only 29.4% recalled such a discussion at a postpartum visit. Of the women in the study, 10% used medication(s) during pregnancy and 14.3% used 1 or more medications for smoking cessation postpartum. These findings show that physicians and pregnant smokers are reluctant to discuss and use smoking cessation pharmacotherapy even though it is recommended by the guideline.

COMPARATIVE EFFICACY OF SMOKING CESSATION PHARMACOTHERAPIES

The findings of an updated meta-analysis of smoking cessation pharmacotherapy by Canadian investigators were similar to those reflected in the clinical practice guideline. The new meta-analysis used a more conservative definition of abstinence than did the US guideline, requiring biochemical confirmation for a study to be included in the analysis. All 7 first-line therapies were found to be superior to placebo, and the highest point estimate of the 7 first-line therapies was observed for varenicline (OR, 2.55; 95% CI, 1.99-3.24).

CONCLUSION

The new clinical practice guideline presents more compelling evidence for the efficacy and cost-effectiveness of treatment for tobacco use and dependence. For clinicians, the current guideline offers 4 key conclusions. First, tobacco dependence is a chronic remitting and relapsing condition. Repeated attempts to quit should be encouraged for all smokers at every opportunity. Second, counseling (as brief as 3 minutes) is an effective treatment for tobacco dependence. The effectiveness of counseling increases with the length of the counseling session and with the addition of an appropriate medication. Third, a larger number of effective medications and medication combinations are currently available and should be used for all smokers who are motivated to quit. Fourth, of all the first-line medications provided as monotherapy, varenicline appears to have the greatest efficacy after 3 to 6 months. Clinicians should take every opportunity to encourage smoking cessation and provide effective treatment. If they do so consistently,
they will help ensure substantial declines in smoking-related morbidity and mortality and improved quality of life for their patients.

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REFERENCES


CME Questions About Treating Tobacco Use and Dependence

1. Which one of the following statements is true regarding counseling for tobacco use and dependence?
a. Counseling lasting 3 minutes or less has no benefit for treatment of nicotine dependence.
b. Face-to-face counseling is demonstrably more effective than telephone counseling.
c. A positive dose-response association exists between counseling and smoking abstinence outcomes.
d. Specific counseling techniques such as motivational interviewing are more effective than practical counseling.
e. Counseling is ineffective unless combined with pharmacotherapy.

2. Which one of the following statements about the key advances described in Treating Tobacco Use and Dependence: 2008 Update is true?
a. Tobacco cessation treatments are cost-effective and have been shown to reduce health care costs.
b. Telephonic counseling is ineffective for treating tobacco use and dependence.
c. Combinations of first-line pharmacotherapies are contraindicated for most tobacco users.
d. Most antidepressants have been found effective for smoking cessation.
e. Extended treatment length with nicotine replacement therapy (NRT) is no more effective than briefer durations of treatment.
3. A 45-year-old man is motivated to quit smoking his usual 20 cigarettes per day and asks for your help. His previous attempts to quit smoking by using nicotine gum (2 mg) ad libitum have been unsuccessful. Which one of the following treatments is most appropriate according to the new guideline recommendations?
   a. Nicotine lozenge, 2 mg ad libitum
   b. Nicotine gum, 4 mg ad libitum
   c. Varenicline, 1 mg twice daily for 12 weeks
   d. Nortriptyline, 25 to 50 mg/d
   e. Duloxetine, 30 mg twice daily

4. Which one of the following statements about NRT is true?
   a. All of the recommended NRTs are equally effective when provided as monotherapy
   b. Alone or in combination, NRT is more effective than varenicline for smoking cessation
   c. Monotherapy with nicotine gum for 6 to 14 weeks has the lowest point estimate for effectiveness compared with all other first- and second-line pharmacotherapies for smoking cessation
   d. Bupropion plus nicotine patch is superior to bupropion alone
   e. Long-term (>14 weeks) nicotine patch therapy is superior to shorter-term nicotine patch treatment

5. Which one of the following correctly pairs the most common adverse effect reported with the respective smoking cessation pharmacotherapy?
   a. Nicotine patch and nausea
   b. Bupropion and seizure
   c. Varenicline and depression
   d. Nicotine nasal spray and epistaxis
   e. Varenicline and nausea

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