THE JOURNAL OF FAMILY PRACTICE

Smoking cessation: What should you recommend?

Fifty years after a landmark report on its perils, smoking remains a major public health problem. Here's the latest on how best to help patients quit.

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The authors reported no potential conflict of interest relevant to this article.

PRACTICE RECOMMENDATIONS

› *Prescribe varenicline, bupropion, or nicotine replacement as first-line single pharmacotherapy for smoking cessation.* (A)

› *Provide counseling along with medication, as the combination has proven to be more effective than either option alone.* (A)

› *Refer patients to their state Quit Line—a toll-free tobacco cessation coaching service that has been shown to be an effective form of counseling.* (A)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

In its 2014 report, "The Health Consequences of Smoking—50 Years of Progress,"[1] the US Surgeon General concluded that, while significant improvements have been made since the publication of its landmark 1964 report, cigarette smoking remains a major public health problem. It is the leading cause of preventable death, increasing the risks of such common causes of mortality as cardiovascular disease, pulmonary disease, and malignancy. Cigarette smoking is responsible for an estimated 443,000 deaths annually.[2]

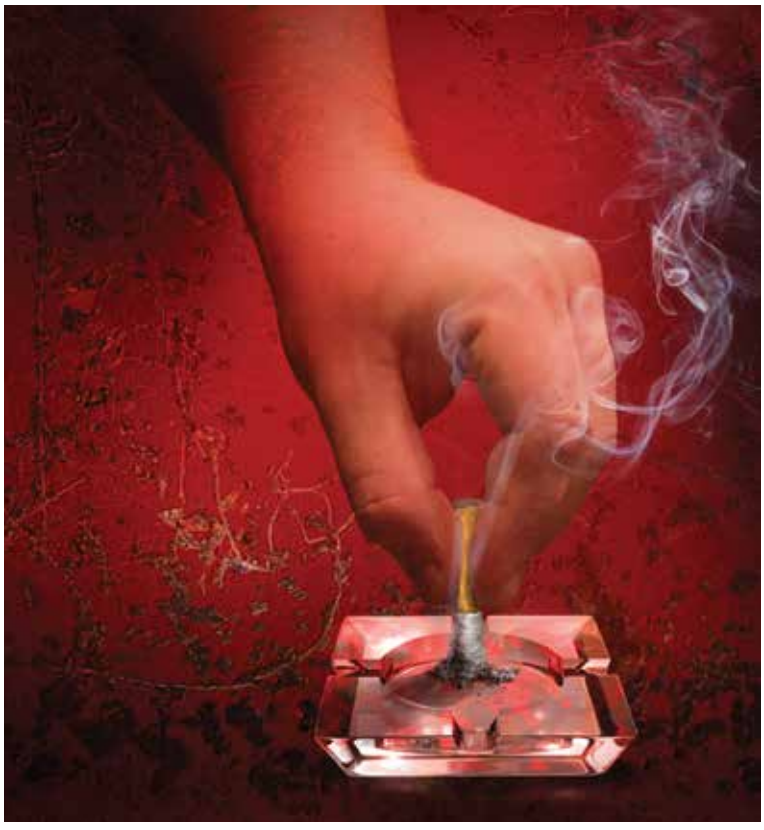
Overall, 42 million US adults and about 3 million middle and high school students smoke, despite the availability of an array of pharmacologic interventions to help them quit.[1] Half of those who continue to smoke will die from a tobacco-related cause. Stopping before the age of 50 years cuts the risk in half, and quitting before age 30 almost completely negates it.[3]

The most recent comprehensive smoking cessation guideline, sponsored by the US Public Health Service, was published in 2008.[4] The US Preventive Services Task Force (USPSTF) recommendation that "clinicians ask all adults about tobacco use and provide tobacco cessation interventions" for those who smoke was issued one year later.[5] Since then, multiple studies have assessed the merits of the various medications, forms of nicotine replacement therapy (NRT), and counseling aimed at helping smokers maintain abstinence from tobacco.

This article reviews the guideline and provides family physicians with an evidence-based update.

The guideline: Treating tobacco use and dependence

Prescribing a first-line medication (bupropion SR, varenicline, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, or nicotine patch) for every patient who seeks to quit smoking is a key component of the 2008 guideline (See **TABLE W1** at jfponline.com).[4] The only exceptions: patients for



The number of cigarettes smoked per day and how long a patient is awake before smoking that first cigarette are important factors in determining which medication to select for smoking cessation.

whom such agents are medically contraindicated and groups for which there is insufficient evidence of effectiveness, such as pregnant women and adolescents.

The use of any of these medications as a single agent nearly doubles the likelihood of success compared with placebo, with an average cessation rate of 25% (**TABLE 1**).[4] Combination therapy (pairing a nicotine patch and an additional agent) was found to be even more effective, with some combinations attaining success rates as high as 65%.[4]

Second-line therapies, including clonidine and nortriptyline, were also cited as effective, with an average cessation rate of 24%.[4] Although the meta-analyses that these averages were based on did not include head-to-head comparisons, subsequent studies that also showed efficacy did include such comparisons.

Counseling is an essential component

In one of the meta-analyses on which the guideline was based, the combination of counseling and medication proved to be more effective than either intervention alone. Individual, group, and telephone counseling were all effective (odds ratio [OR]=1.7 [1.4-2.0], 1.3 [1.1-1.6], and 1.2 [1.1-1.4], respectively), provided they included practical help that emphasized problem solving and skills training, as well as social support. The benefits of a team-based approach were evident from the finding that counseling provided by more than one type of clinician had higher effect sizes (OR=2.5 [1.9-3.4] when 2 different clinical disciplines were involved and 2.4 [2.1-2.9] for 3 or more disciplines).[4]

The guideline also found state-sponsored quit lines, accessible at no charge via 800-QUIT-NOW, are an effective option. (For more information about this and other resources, see **TABLE W2** at jfponline.com.)

For patients who aren't ready to stop smoking, the guideline recommends motivational interviewing[4]—a direct, patient-centered technique used to explore and work through ambivalence. Further information about this method is available at motivationalinterviewing.org/.

In counseling patients considering a quit attempt, it is important to present all options. A smoking history is needed, too, because factors such as the number of cigarettes smoked per day, how long a patient is typically awake before smoking the first cigarette of the day, and level of dependence are important factors in determining medication and dosage. Consider the advantages and disadvantages of the various medications (**TABLE 2**)[4,6,7] or methods used for prior quit attempts and reasons for relapse, if appropriate; and patient preference.

CONTINUED

INSTANT POLL

Which of the following would you be most likely to recommend to a patient who wants to quit smoking?

- ☐ *Varenicline*
- ☐ *Bupropion*
- ☐ *Nicotine replacement therapy*
- ☐ *Electronic cigarettes*

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TABLE 1

US Public Health Service smoking cessation guideline: An evidence summary[4]

Medication* (dose)	No. of groups analyzed	Estimated OR (95% CI)	Estimated abstinence rate % (95% CI)†
Placebo	80	1	13.8
Monotherapy			
Varenicline: (2 mg/d)	5	3.1 (2.5-3.8)	33.2 (28.9-37.8)
(1 mg/d)	3	2.1 (1.5-3)	25.4 (19.6-32.2)
Nicotine nasal spray	4	2.3 (1.7-3)	26.7 (21.5-32.7)
Nicotine patch >2.5 mg (standard and long-term)	4	2.3 (1.7-3)	26.5 (21.3-32.5)
(6-14 wk)	32	1.9 (1.7-2.2)	23.4 (21.3-25.8)
(>14 wk)	10	1.9 (1.7-2.3)	23.7 (21-26.6)
Nicotine gum: (>14 wk)	6	2.2 (1.5-3.2)	26.1 (19.7-33.6)
(6-14 wk)	15	1.5 (1.2-1.7)	19 (16.5-21.9)
Nicotine inhaler	6	2.1 (1.5-2.9)	24.8 (19.1-31.6)
Clonidine	3	2.1 (1.2-3.7)	25 (15.7-37.3)
Bupropion SR	26	2.0 (1.8-2.2)	24.2 (22.2-26.4)
Nortriptyline	5	1.8 (1.3-2.6)	22.5 (16.8-29.4)
Combination therapies			
Patch (>14 wk) + 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 + 2nd generation antidepressants (paroxetine, venlafaxine)	3	2 (1.2-3.4)	24.3 (16.1-35)

CI, confidence interval; NRT, nicotine replacement therapy; OR, odds ratio.

* Selective serotonin reuptake inhibitors and naltrexone were not shown to be effective.

† Estimated abstinence rate is an average across trials and includes both self-reports and biochemically confirmed findings. Relative efficacy is compared with placebo and estimated abstinence rates reported at 6 months post quit.

Quitting smoking by age 50 cuts the risk of a smoking-related death in half, and quitting by age 30 almost completely negates it.

Evidence update: What's best?

Since 2009, many clinical trials have examined the best way to help smokers quit. Here's a closer look at the latest evidence.

NRT boosts long-term cessation

A 2012 Cochrane review examined 150 trials and found that every type of NRT—gum, lozenge, patch, inhaler, and nasal spray—was associated with long-term cessation (relative risk [RR]=1.60; 95% CI, 1.53-1.68).[8] This effect was essentially unchanged regardless of the duration, setting, or intensity of supportive therapy offered, and no single type of NRT was more effective than any other. However, combining a short-acting form like a lozenge with a long-acting patch was found to be more effective than either one alone (RR=1.34; 95% CI, 1.18-1.51).

Starting the NRT before the patient quit did not improve cessation rates over traditional start times (RR=1.18; 95% CI 0.98-1.41). Neither was there an added benefit to using

TABLE 2

Medications for smoking cessation: Dosing, advantages, and adverse effects[4,6,7]

Medication	Dosing	Advantages	Adverse effects
Nicotine patch	7 mg, 14 mg, or 21 mg patch daily for ≤8 wk* Start with 21 mg patch if >10 cigarettes/d; 14 mg patch if 6-10 cigarettes/d	First-line agent; inexpensive; long-acting, effective in combination with short-acting agents PRN; high adherence rates; available OTC	Local skin irritation, insomnia
Nicotine gum	2-4 mg gum, PRN up to 24 pieces/d ≤12 wk Use 4 mg dose if first cigarette <30 min after waking Gum should be chewed until a tingling or peppery taste is noticed, then "parked" between the cheek and gums; repeat once tingling or taste is lost	First-line agent, effective in combination with patch; high adherence rates; available OTC	Mouth soreness, dyspepsia
Nicotine lozenge	2-4 mg lozenge, PRN up to 20 lozenges/d ≤12 wk; use 4 mg dose if first cigarette <30 min after waking Should not be chewed; can be "parked" between cheek and gums	First-line agent, effective in combination with patch; available OTC	Nausea, heartburn
Nicotine inhaler	10 mg cartridges PRN up to 16/d ≤6 mo	First-line agent; similar feel to real cigarette	Local irritation of mouth and throat
Nicotine nasal spray	0.5 mg per spray PRN up to 40 doses/d ≤6 mo	First-line agent	Nasal irritation
Varenicline	1 mg bid for 12 weeks Start 1 week before quit date with 0.5 mg/d for 3 days, then 0.5 mg bid for 4 d, then increase to full dose	First-line agent; effective for cessation even for those not yet ready to commit to quitting	Nausea, insomnia, abnormal dreams, possible neuropsychiatric symptoms
Bupropion SR	150 mg bid for 12 wk Start 1 wk before quit date with 150 mg once daily for 3 d, then increase to full dose	First-line agent; inexpensive; can treat comorbid depression	Insomnia, dry mouth, seizures, possible neuropsychiatric symptoms
Nortriptyline (off-label)	75-100 mg/d for 12-14 wk	Inexpensive; can treat comorbid depression	Drowsiness, dry mouth, potential QT prolongation
Clonidine (off-label)	0.1-0.3 mg/d transdermal; 0.15-0.45 mg/d oral for up to 12 wk	Inexpensive; can treat comorbid hypertension	Drowsiness and postural hypotension

OTC, over-the-counter; PRN, as needed.

* Use initial dose patch for 6 weeks, then titrate to next lower dose patch every 2 weeks, then stop.

NRT beyond the recommended 24-week prescription period,[9] although doing so was found to be safe. Another 2012 Cochrane review looked specifically at the use of pharmacologic smoking cessation interventions during pregnancy and concluded that there

was still not sufficient data to document efficacy for this patient population.[10]

Adherence. In deciding on which type of NRT to prescribe, it is important to consider not only patient preference and previous efforts, but also the latest evidence. A study comparing various NRT formulations found patient adherence to be highest with the patch, followed by nicotine gum, which had a higher compliance rate than either the nicotine inhaler or nasal spray.[11]

Varenicline is still a first-line agent

Since the 2008 guideline recommended this partial nicotinic receptor agonist/antagonist as a first-line pharmacologic agent, additional meta-analyses have confirmed its long-term efficacy in smokers who are ready to quit.[12,13] A 2012 Cochrane review found varenicline to increase long-term cessation compared with placebo (RR=2.27; 95% CI, 2.02-2.55).[13] It also showed varenicline to be more effective than bupropion SR (RR=1.52; 95% CI, 1.22-1.88), but about as effective as NRT (RR=1.13; 95% CI, 0.94-1.35).

Among the various types of nicotine replacement therapy, the patch has the highest adherence rate.

Newer data suggest that varenicline may also be effective for those who are willing to *cut down* on smoking but not yet ready to give up cigarettes completely. Used for 24 weeks by those who were initially resistant to quitting, researchers found varenicline nearly tripled the cessation rate at 52 weeks compared with placebo (RR=2.7; 95% CI, 2.1-3.5).[14]

Latest evidence on safety. Additional concerns about the safety of varenicline have been raised, however, since the 2008 guideline was published. In 2009, the US Food and Drug Administration (FDA) required that black box warnings be added to the labels of both varenicline and bupropion SR based on post-marketing safety reports showing the risk of neuropsychiatric symptoms, including suicidality.[15] In 2011, a large case control study by the FDA Adverse Event Reporting System also showed an increased risk of suicidality in patients taking these drugs.[16]

Follow-up studies, however, including a large prospective cohort study and a large meta-analysis, failed to show an increased association with neuropsychiatric adverse effects.[17,18] A smaller randomized controlled trial (RCT) showed that in smokers diagnosed with schizophrenia and bipolar disorder, maintenance therapy with varenicline was effective in preventing smoking relapse for up to 52 weeks. Abstinence rates were 60% for those in the varenicline group vs 19% for those in the placebo group (OR=6.2; 95% CI, 2.2-19.2). Although no increased risk of adverse psychiatric events was found in this study, it was not powered to detect them.[19] Also of note: a meta-analysis of 14 RCTs showed an increased rate of cardiovascular events associated with varenicline.[20] There are concerns about methodologic flaws in this meta-analysis, however, and 2 subsequent meta-analyses failed to find a cardiovascular risk.[21,22]

The higher quality studies that have been published since the original concerns about varenicline's safety are reassuring, but it is still essential to carefully weigh the risks and benefits of varenicline. Review cardiac and psychiatric history and conduct a suicidality assessment before prescribing it as a smoking cessation aid, and provide close follow-up.

A closer look at antidepressants

Bupropion SR, an atypical antidepressant, was also listed as a first-line treatment in the 2008 guideline. A 2014 Cochrane review of 90 studies confirmed the evidence for this recommendation.[6] Monotherapy with this agent was found to significantly increase rates of long-term cessation (RR=1.62; 95% CI, 1.49-1.76). No increased risk of serious adverse events was identified compared with placebo. As already noted, associations with neuropsychiatric symptoms were found, but this risk must be considered with any antidepressant.

Bupropion's efficacy was not significantly different from that of NRT, but moderate evidence suggests that it is less effective than varenicline, (RR=0.68; 95% CI, 0.56-0.83). Other classes of antidepressants, including selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors, were found to be ineffective for smoking cessation.[6]

Nortriptyline, a tricyclic antidepressant, was not significantly different from bupropion SR (RR, 1.30; 95% CI, 0.93-1.82) in efficacy for smoking cessation, but it lacks

FDA approval for this purpose and is not considered a first-line agent.[6]

Second-line agents

Clonidine is an alpha-2 adrenergic receptor agonist that was originally used to treat hypertension but found to be effective for smoking cessation in a meta-analysis performed for the 2008 guideline.[4] Like nortriptyline, however, clonidine is not FDA-approved for this purpose and is not considered a first-line agent.[5] A 2013 Cochrane meta-analysis further showed that clonidine is effective for smoking cessation vs placebo (RR=1.63; 95% CI, 1.22-2.18),[7] but suggested that its significant dose-related adverse effects, including postural hypotension and sedation, could limit its usefulness.

Combination therapies are highly effective

Evidence for various combinations of smoking cessation pharmacotherapy continues to mount.[23-26] Perhaps the most compelling evidence comes from a comparative effectiveness trial that randomized 1346 patients in 12 primary care clinics to nicotine patches, nicotine lozenges, bupropion SR, a combination of patch plus lozenge, and bupropion SR plus lozenge. The 6-month abstinence rate was 30% for the bupropion SR plus lozenge combination, the most effective option. The combination was superior to either patch or bupropion SR monotherapy (OR, 0.56 and 0.54, respectively).[23] Based on data from the 2008 guideline, similar combinations (eg, nicotine patch plus nicotine gum or bupropion SR plus the patch) are likely to be equally effective. The 2008 guideline also supports a nicotine patch and nicotine inhaler combination.

Another study found varenicline combined with the patch to be highly effective, with a 65% abstinence rate at 24 weeks vs 47% for varenicline alone (number needed to treat [NNT]=6; 95% CI, 4-11).[24]

In heavy smokers—defined as those who smoke ≥20 cigarettes daily—a varenicline and bupropion SR combination was more effective than varenicline alone (NNT= 9; 95% CI, 4.6-71.6), but the combination can lead to increased anxiety and depression.[25] A smaller study found *triple* therapy using nicotine patch plus inhaler plus bupropion SR to be more effective than the nicotine patch alone (35% abstinence vs 19% abstinence at 26 weeks; NNT=6).[26] Consider using these combinations in patients who have high nicotine dependency levels or have been unable to quit using a single first-line agent.

What role do e-cigarettes play?

The use of electronic cigarettes or "vapes"—battery-operated devices that deliver nicotine to the user through vapor—has increased significantly since their US introduction in 2007. A recent study found that "ever use" of e-cigarettes increased from 1.8% in 2010 to 13% in 2013; current use increased from 0.3% to 6.8% in the same time frame.[27] "Vaping," as inhaling on an e-cigarette is sometimes known, causes a sensor to detect airflow and initiate the heating element to vaporize the liquid solution within the cartridge, which contains propylene glycol, flavoring, and nicotine.

There is limited evidence of the efficacy of e-cigarettes for smoking cessation, but there is support for their role in reducing the quantity of conventional cigarettes smoked. A 2014 Cochrane review of 2 RCTs evaluating e-cigarette efficacy for smoking cessation or reduction found evidence of increased abstinence at 6 months in users of e-cigarettes containing nicotine compared with placebo e-cigarettes (9% vs 4%; RR=2.29; 95% CI, 1.05-4.96). Additionally, e-cigarette use was associated with >50% decrease in cigarette smoking vs placebo (36% vs 27%; RR=1.31; 95% CI, 1.02-1.68) or patch (61% vs 44%; RR=1.41; 95% CI, 1.20-1.67).[28]

A survey published after the review also showed a correlation between cigarette reduction (but not cessation) after one year of e-cigarette use.[29] A subsequent RCT conducted in a controlled laboratory setting found that e-cigarettes were highly effective in reducing cessation-related cravings.[30] And at 8-month follow-up, 44% of those using e-cigarettes were found to have at least a 50% reduction in the use of conventional cigarettes—and complete cessation in some cases.

Concerns about health effects

E-cigarettes have generally been thought to

Higher quality studies published since initial safety concerns for varenicline were raised are reassuring, but it's still essential to weigh the drug's risks and benefits for each patient.

be safer than conventional cigarettes, given that they mainly deliver nicotine and propylene glycol instead of the more toxic chemicals—eg, benzene, carbon monoxide, and formaldehyde—released by conventional cigarettes.[31] Carcinogens have also been found in e-cigarettes, but at significantly lower levels.[31] However, a systematic review found wide variation in the toxin content of e-cigarettes.[32] In addition, recent reports have detailed incidents in which e-cigarette devices were alleged to have exploded, causing severe bodily harm.[33]

Adverse effects of e-cigarettes include minor irritation of the throat, mouth, and lungs. Among cigarette-naive patients, lightheadedness, throat irritation, dizziness, and cough were most commonly reported. No serious adverse events have been reported, but the lack of long-term safety data is a source of concern.[32]

Additionally, minimal regulatory oversight of the e-cigarette industry exists. Currently, the FDA only has authority to regulate e-cigarettes that are marketed for therapeutic purposes, although the agency is seeking to extend its oversight to all e-cigarettes.

The bottom line: More data on safety and regulatory oversight are needed before recommendations on the use of e-cigarettes as a smoking cessation tool can be made.

A systematic review found a wide variation in the toxin content of e-cigarettes.

Looking ahead

Several novel pharmacotherapies have been evaluated for smoking cessation in recent years. Among them is a nicotine vaccine that several drug companies have been pursuing. In theory, such a vaccine would create an immunologic reaction to nicotine in a smoker, thereby preventing the substance from reaching the brain and providing rewarding stimuli. A 2008 Cochrane review of 4 trials assessing the efficacy of nicotine vaccines for tobacco cessation found that none showed efficacy.[34]

Naltrexone, an opioid antagonist, has shown efficacy in helping those with opioid or alcohol dependence achieve abstinence from these substances, raising the possibility that it might aid in smoking cessation, as well. A 2013 Cochrane review of 8 trials found that this was not the case: Compared with placebo, naltrexone was not beneficial when used alone (RR=1.00; 95% CI, 0.66-1.51) or as an adjunct to NRT compared with NRT alone (RR=0.95; 95% CI, 0.70-1.30).[35]

Cytisine, an extract from plants in the Faboideae family, has been used in Eastern Europe for decades for smoking cessation. It appears to work as a nicotine receptor partial agonist similar to varenicline. The extract does not have FDA approval, but the National Institutes of Health's Center for Complementary and Integrative Health is sponsoring early-stage safety trials that could lead to its approval in the United States.[36]

A 2012 Cochrane review identified 2 recent RCTs evaluating cytisine and found it to be effective in increasing smoking cessation rates vs placebo (RR=3.98; 95% CI, 2.01-7.87).[13] JFP

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ACKNOWLEDGEMENT
The authors thank Matt Orr, PhD, and Kathryn E. Bornemann for their help with this manuscript.

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TABLE W1

The 2008 US Public Health Service guideline: 10 key recommendations[4]

1. Tobacco dependence is a chronic disease that often requires repeated intervention and multiple attempts to quit. Effective treatments can significantly increase rates of long-term abstinence.
2. It is essential that clinicians consistently identify and document tobacco use and attempt to treat every patient who smokes.
3. Tobacco dependence treatments are effective across a broad range of populations; clinicians should encourage every patient willing to make a quit attempt to use the recommended counseling and medications.
4. Brief tobacco dependence treatment is effective and should be offered to every patient who smokes.
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Key components include practical counseling (problem solving/skills training) and social support.
6. Clinicians should encourage all patients attempting to quit to use any of the medications found to be effective (the only exceptions are medical contraindication or insufficient evidence of effectiveness). Seven first-line medications and some combination therapies reliably increase long-term smoking abstinence rates.
7. Counseling or medication is effective when used alone but the combination is more effective.
8. Telephone (Quit Line) counseling is effective and should be provided to every patient who smokes.
9. Use motivational interviewing techniques to encourage a tobacco user who is unwilling to try to quit to do so.
10. Tobacco dependence treatments are clinically effective and highly cost effective.*

* Insurers and purchasers should ensure that all health plans include the counseling and medication identified as effective in this guideline as covered benefits.

TABLE W2

Smoking cessation resources

Resource (Sponsor[s])	Description
Web-based	
www.ffsonline.org (Freedom from Smoking Online [ALA])	Detailed online modules/workbooks to support smoking cessation, from thinking about quitting to making a plan to staying smoke-free. Patients must create a free account
www.smokefree.gov (CDC, NCI, and NIH)	Links to live helplines and an online step-by-step guide to quitting. Access is free, with no need to establish an account
www.stopsmokingcenter.net (Evolution Health Systems Inc)	Opportunity for patients to create a free account/online support program and track progress; features include downloadable handbook and online support groups
www.quitadvisormd.com (NIDA)	Patient portal designed by one of the authors (SMS) to help smokers better understand the process of quitting and to provide additional resources to help them
www.quitconnect.org (University of South Carolina and North American Quitline Consortium; CDC)	A community designed to give smokers single-source access to national cessation resources and support and allow providers at state quit lines, health departments, etc, to give QuitConnect members evidence-based tools and test innovative cessation approaches
Text-based	
SmokefreeTXT (NCI)	6- to 8-wk mobile text messaging service created to provide 24/7 encouragement, advice, and tips to help smokers quit and remain abstinent; sign up by phone (Text QUIT to 47848) or online at smokefree.gov/smokefreetxt
Apps	
QuitGuide (NCI)	Free app tracks cravings, moods, slips, and progress to help patients understand smoking patterns and build the skills needed to successfully stay smoke-free
QuitStart (NCI)	Free app to help patients track cravings and moods, monitor progress toward smoke-free milestones, identify triggers, and more; designed for teens but can be used by all ages
Telephone-based	
Quit Lines (North American Quitline Consortium)	Free telephone counseling service, proven to be effective, accessible via 800-QUIT-NOW

ALA, American Lung Association; CDC, Centers for Disease Control and Prevention; NCI, National Cancer Institute; NIDA, National Institute on Drug Abuse; NIH, National Institutes of Health.