Medicine Cabinet

Medications for smoking cessation

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Summary points

- Cigarette smoking is the primary preventable cause of morbidity and mortality in the United States
- Effective medications are available to help patients quit smoking
- In the absence of contraindications, all patients attempting to quit smoking should use one or more approved medications
- The Food and Drug Administration has approved several first-line medications for smoking cessation, including nicotine gum, nicotine transdermal patches, nicotine nasal spray, the nicotine inhaler, and sustained-release bupropion hydrochloride
- Second-line medications, which are not approved for smoking cessation but have demonstrated some effectiveness, include clonidine hydrochloride and nortriptyline hydrochloride
- Drug therapy should be combined with behavioral counseling to optimize cessation rates

An estimated 46.5 million Americans smoke[1]; of these, 70% want to quit completely,[2] and each year, about 17 million adults in the United States make a serious attempt to quit.[3] In a recent analysis of more than 6,000 published articles, two clear treatment-related themes have emerged: first, the use of approved medications for cessation at least doubles the likelihood of quitting, and second, the effects of medications for cessation are substantially increased when coupled with behavioral interventions.[4,5]

In a meta-analysis of trials assessing the effects of cessation advice from medical practitioners, it was determined that brief advice is associated with an increased likelihood of quitting versus no advice (odds ratio, 1.7); in addition, more intensive advice leads to higher quit rates than with more minimal advice (odds ratio, 1.4).[6] Physicians are in an ideal position to identify tobacco users and facilitate patients' attempts to quit and should routinely ask patients about tobacco use, strongly advise tobacco users to quit, assess patients' readiness to quit, assist patients with quitting, and arrange follow-up counseling.[4]

A Clinical Practice Guideline from the US Public Health Service suggests that when feasible and not medically contraindicated, tobacco cessation interventions should include at least one Food and Drug Administration (FDA)-approved pharmaceutical aid in combination with tobacco dependence counseling.[4] Here we summarize the medications currently available in the United States for smoking cessation. Approaches for behavioral interventions are presented elsewhere[4,7] and will not be addressed.

Adam Hart-Davis/DHD Photo Gallery

Medication and behavioral counseling help patients stop smoking

FIRST-LINE AGENTS

Currently, five agents have been approved by the FDA for smoking cessation: four nicotine replacement preparations (nicotine gum, transdermal nicotine patches, nicotine nasal spray, and nicotine inhaler) and sustained-release bupropion hydrochloride. Key prescribing information for these first-line medications for smoking cessation[4] are presented in table 1 on our web site (www.ewjm.com); important patient education points are shown in table 2.

Nicotine replacement therapy

Smoking-cessation success rates improve significantly with the use of nicotine replacement therapy (NRT), approximately doubling the likelihood of quitting compared with placebo.[4,8] Nicotine replacement therapy promotes quitting by reducing nicotine withdrawal symptoms, which allows patients to focus on the behavioral and psychological aspects of smoking. In addition, because the onset of action of NRT is not as rapid as that of nicotine obtained through smoking, patients become less accustomed to the nearly immediate reinforcing effects of inhaled tobacco.

Precautions

Nicotine replacement therapy should be used with caution in patients with underlying serious arrhythmias, those with serious or worsening angina pectoris, and those with

Table 2 *Patient education for nicotine-replacement therapy products*

Agent	Issues to address with patients
Nicotine gum	Use on regularly scheduled basis (eg, initially every 1–2 hr while awake) and as needed to control cravings Proper chewing technique Chew each piece slowly Stop chewing when peppery, minty, or citrus taste or tingling sensation becomes apparent (~15–30 chews) Park between cheek and gum (to allow absorption of nicotine across buccal mucosa) Resume chewing when taste or tingle fades Repeat chew-park steps until most of nicotine is gone (taste or tingle does not return; generally 30 min) Park in different areas of mouth (to prevent mucosal irritation) No food or acidic beverages—juice, coffee, wine, soft drinks—15 min before and during use (may decrease absorption of nicotine)
Nicotine patch	Apply the patch to a clean, dry, hairless area of skin on the upper body or the upper outer part of the arm Do not apply patch to skin that is inflamed, burned, or irritated; this may alter nicotine absorption When applying the patch, press firmly on the skin with the palm of the hand for 10 sec to create an adequate seal Wash hands immediately after patch application; nicotine on hands can get into eyes or nose and cause stinging or redness Water—bathing, swimming, showering, or exercising—will not harm the nicotine patch if applied correctly Shortly after the nicotine patch is applied, mild itching, burning, or tingling may occur; this should resolve within 1 hr 16-hr patches should be removed at bedtime After the patch is removed, the skin may appear red for the next 24 hr If a rash develops or if the skin under the patch becomes swollen or remains irritated for >4 days, discontinue use of the patch Rotate patch application sites daily; wait at least 1 wk before applying a patch to the same site to minimize the potential for skin reactions
Nicotine nasal spray	1 dose = 2 sprays (1 in *each* nostril) For best results, initially use at least 8 doses daily Before using spray, blow nose if it is not clear Tilt head back slightly; insert tip of bottle into nostril as far as comfortable Breathe through mouth and spray once in each nostril Do *not* sniff, swallow, or inhale through the nose during administration; this increases the irritating effects of the spray If nose runs, gently sniff to keep spray in nose Wait at least 2–3 min before blowing nose Avoid contact with skin, eyes, and mouth; nicotine can be absorbed across these sites A hot peppery sensation in the back of the throat or nose, sneezing, coughing, watery eyes, or a runny nose may occur Regular use of the nasal spray during the first week will help adapt to the irritating effects of the spray Do not exceed 5 sprays per hr or 40 sprays a day Gradually decrease use over 3–6 mo
Nicotine inhaler	Initially use at least 6 cartridges a day, and increase as needed to a maximum of 16 cartridges per day Inhale vapor into back of throat or puff in short breaths; do *not* inhale into the lungs (like a cigarette), but "puff" as if lighting a pipe; deep pulmonary inhalation can result in symptoms of nicotine excess—nausea, vomiting, lightheadedness Do not eat or drink acidic beverages—juice, coffee, wine, or soft drinks—15 minutes before and while using the inhaler (may decrease absorption of nicotine) Best results are achieved with frequent continuous puffing for 20 min Nicotine in cartridge is depleted after 20 min of active puffing Titrate therapy to control nicotine cravings; eg, use the inhaler for a few minutes; put it down, and use later for a total of 20 min of active puffing per cartridge Open cartridge retains potency for 24 hr; once opened, each cartridge whether fully used or not should be replaced after 24 hr Mild irritation of the mouth or throat or cough may occur when first using the inhaler Regular use during the first week will help adapt to the irritating effects of the inhaler The inhaler may not be as effective in very cold temperatures (eg, the delivery of nicotine vapor is compromised in temperatures <15°C [<59°F])

a recent (<2 weeks) myocardial infarction.[4] This is because nicotine may cause adverse cardiovascular effects by increasing the myocardial workload through increased heart rate and blood pressure. Nicotine also may constrict coronary arteries, leading to cardiac ischemia.[9] However, the risks of NRT in patients with cardiovascular disease are small relative to the risks of continued smoking.[10,11]

The FDA has classified nicotine as a "pregnancy category D," meaning there is evidence of risk to the human fetus. Accordingly, none of the NRT formulations have received FDA approval for use in pregnancy. Although NRT may pose a risk to a developing fetus, it is arguably less than the risks of continued smoking.[12] However, because it is assumed that NRT can cause fetal harm when administered during pregnancy, NRT should be reserved for women unable to quit using nonpharmacologic methods. If NRT is warranted, it is prudent to prescribe doses at the low end of the effective dose range and consider the use of formulations that yield intermittent rather than continuous drug exposure, eg, the gum, nasal spray, or inhaler.[4]

Nicotine polacrilex gum

Nicotine polacrilex gum, which is available without a prescription, is a resin complex of nicotine and polacrilin in a

sugar-free chewing gum base. Buffering agents (sodium carbonate, sodium bicarbonate) increase salivary pH, thereby enhancing absorption of nicotine across the buccal mucosa.

Patients should use the gum on a fixed schedule rather than as needed to control cravings. Nicotine gum is more viscous than ordinary chewing gum, and its use is contraindicated in patients with temporomandibular joint disease. Furthermore, this product tends to adhere to dental work and may not be suitable for patients with braces, dentures, bridges, or significant dental restorations.

The use of nicotine gum improves cessation rates by about 50% compared with control interventions.[4] This agent may be an appropriate option for patients who desire oral stimulation during cessation, identify boredom as a trigger for smoking, or are concerned about weight gain after quitting.[4]

Transdermal nicotine patch

The transdermal nicotine patch, available both with and without prescription, uses a concentration-dependent, continuous low-level delivery of nicotine across the skin. Currently, four formulations are available. Dosing is based on the number of cigarettes smoked per day (table 1).

The 16- and 24-hour patches demonstrate similar efficacy; however, patients with patch-related sleep disturbances (abnormal or vivid dreams, insomnia) might better tolerate the 16-hour patch, and patients with strong morning cravings might have more success with a 24-hour patch. Patients who have substantial withdrawal symptoms or cravings should consider a higher dose. Patients who have adverse effects—dizziness, perspiration, nausea, vomiting, diarrhea, headache, abdominal pain—should use the next lower dose. Reactions to patch adhesives are common (up to 50%) and can be treated with 1% hydrocortisone cream or oral antihistamines. Because the adhesives vary among products, patients who have a skin reaction may consider switching brands. Patients with dermatologic conditions (eg, psoriasis, eczema, atopic dermatitis) are more likely to have skin irritation and should consider other NRT formulations.

Cessation rates in patients using the nicotine patch are generally 1.9 times higher than those observed in patients using placebo.[4] Because of its once-a-day dosing, transdermal formulations may be ideal when compliance is a concern.

Nicotine nasal spray

Nicotine nasal spray is an aqueous solution of nicotine for nasal administration. Each actuation delivers a 0.5-mg bolus of nicotine that is absorbed rapidly (<10 minutes) across the nasal mucosa.

Initially, most patients will have nose and throat irritation (peppery sensation), watery eyes, sneezing, or coughing. However, with regular use, tolerance generally develops, and after the first week, most patients have minimal difficulty tolerating the spray. The spray is not recommended for patients with chronic nasal disorders (rhinitis, polyps, and sinusitis) or patients with severe reactive airway disease because of the spray's irritant effects. Drug absorption may be reduced in patients with rhinitis or the common cold.

Cessation rates associated with the nicotine nasal spray range from 1.8 to 4.1 times higher than in controls.[4] Because of its rapid onset of action, the spray is a possible option for patients who prefer a medication to rapidly manage withdrawal symptoms.

Nicotine inhaler

The nicotine inhalation system consists of a plastic mouthpiece and unit-dose cartridges that deliver 4 mg of inhaled nicotine (with a light menthol taste) from a porous plug. Following inhalation, nicotine is vaporized and absorbed across the oropharyngeal mucosa.

The nicotine inhaler is not operated like the oral inhalers used to treat pulmonary conditions. Patients should not inhale the drug deeply into their lungs because this increases the delivery of nicotine and the incidence of adverse effects. Patients may initially have mild local irritation of the mouth or throat, cough, or rhinitis; these adverse effects decrease with repeated use.

Studies suggest that patients who use the nicotine inhaler are 1.7 to 3.6 times more likely to remain abstinent than patients using a placebo inhaler.[4] Those who seek a substitute for cigarettes may find this formulation appealing because the hand-to-mouth ritual associated with the use of this product is similar to that with smoking.

Sustained-release bupropion

In 1997, sustained-release bupropion was approved as the first non-nicotine medication for smoking cessation. The mechanism of action for this agent, originally marketed as an antidepressant, is thought to be due to its capacity to block neural reuptake of the neurotransmitters dopamine and norepinephrine, reducing cravings for nicotine and symptoms of withdrawal.[4]

Patients should initiate bupropion therapy 1 to 2 weeks before their quit date, starting with 150 mg once a day for 2 days, then increasing to 150 mg twice a day. The medication is started before the quit date because steady-state therapeutic levels are reached after about 7 days of therapy.

Adverse effects associated with bupropion therapy include insomnia (30%-40%) and dry mouth (11%); these

usually lessen with continued use. Taking the second dose in the early evening but no sooner than 8 hours after the first dose may minimize insomnia. Less common side effects include tremors (3.4%) and rash (2.4%). Because seizures have been reported in about 1 out of every 1,000 patients, bupropion is contraindicated in patients with a history of seizures or factors known to increase the risk of seizures, including a current or previous diagnosis of bulimia or anorexia nervosa, central nervous system tumors, and concurrent use of medications known to lower the seizure threshold. Because seizures are dose-related, patients should space doses at least 8 hours apart, and the total daily dose should not exceed 300 mg. Studies of healthy smokers suggest that bupropion may be safely used in combination with NRT. Bupropion is classified as pregnancy category B; it has not been studied in pregnant women, and thus, its use should be considered only when nonpharmacologic methods are ineffective.

Cessation rates in patients who use sustained-release bupropion are generally 2.1 times higher than those observed in patients receiving placebo.[4] The advantages of bupropion include an oral formulation with twice-a-day dosing, no risk of nicotine toxicity if the patient continues to smoke, can be used in combination with NRT, and may be beneficial for use in patients with coexisting depression.

SECOND-LINE AGENTS

Although not FDA-approved specifically for smoking cessation, the prescription medications clonidine hydrochloride and nortriptyline hydrochloride are recommended as second-line agents.[4] Clonidine is a centrally acting α_2-agonist antihypertensive agent that about doubles cessation rates. Initial recommended doses include 0.1 mg orally twice a day or the 0.1-mg/day patch applied weekly. Effective doses have ranged from 0.15 to 0.75 mg daily (orally) and 0.1 to 0.2 mg daily (transdermally) for 3 to 10 weeks. The likelihood of quitting is about tripled with the use of nortriptyline, a tricyclic antidepressant agent, compared with that of placebo. The recommended initial dose is 25 mg at bedtime, gradually increasing to a target dose of 75 to 100 mg daily for 12 weeks. Lack of an FDA-approved indication for smoking cessation, as well as undesirable side effect profiles, currently prohibit these agents from achieving first-line classification.[4]

COMBINATION THERAPY AND HIGH-DOSE NRT

Although most clinical trials have examined the use of a single agent, some investigators have reported improved cessation rates when agents are used in combination. There is evidence that the concurrent use of two forms of NRT, whereby one form provides steady levels of nicotine in the body and the second form is used as needed to control cravings, suppresses nicotine withdrawal symptoms and increases the ability to quit compared with monotherapy.[13-16] The use of dual NRT, however, is recommended only for patients who are unable to quit using monotherapy, because of the inherent increased risk of nicotine overdose.[4] The use of bupropion in combination with the nicotine patch was associated with a cessation rate that was 5.2% points higher than the rate with sustained-release bupropion alone (35.5% with the former, 30.3% with the latter), but this increase was not significant.[17] Trials evaluating higher doses of NRT have yielded conflicting results. Some suggest that higher doses of NRT may be more effective in heavy smokers,[18,19] and others have demonstrated slight but not significant improvements in cessation rates.[20,21] Thus, despite the small number of trials that have examined combination and high-dose NRT therapy, the results appear promising and may be particularly applicable to refractory patients who have been unable to quit using single-agent therapy or conventional-dose NRT.

CONCLUSION

Tobacco use is the primary preventable cause of morbidity and mortality in the United States, with an estimated 430,000 deaths caused by smoking each year.[22,23] Because tobacco-related disease is preventable, efforts to promote cessation in patients who smoke should be a routine preventive health care measure. When not contraindicated, all patients attempting to quit smoking should use a first-line medication to increase their likelihood of successful cessation. Currently, insufficient data are available to rank-order the effectiveness of the different cessation agents.[4] Selection of an agent should be individually tailored for each patient. Important factors to consider include patient preference, medication compliance issues, previous experience with cessation agents, and patient characteristics, eg, contraindications, history of depression, and level of smoking. Finally, pharmacologic therapy should be accompanied by appropriate behavioral counseling to enhance long-term cessation rates.

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The Doctor's Wife

Years later she came to me
for a menagerie of shots
and some advice on water
in New Guinea. It didn't take
a minute to notice the tic
that sprung up since the last
bout of whatever her illness was
and the devastated nails.
Her church was sending her
for three months, maybe six,
to a site on the north coast
where thousands of refugees
had fled to escape a war
on the next island, a conflict
that hadn't made the news
so far. They needed a nurse
more than a preacher, but she
volunteered for both. I wished
we had more time to talk
that morning. Her waxen aura
was singular, like speaking
to a statue by candelight —
it's hard to explain. The church
was sending a team with her,
plus some outdated medicines
from the clinic. She withdrew
her eyes from my desk at last
and whispered, *He always wished*
to do God's work in the missions,
didn't he? I had never met
the man. He placed the bullet
in his head before I came
to town. I knew the handwriting
that he used to cure the sick, though,
and the once-vivid stories
of his compassion. *He's looking*
over your should in this,
I said. *Remember that.*

Jack Coulehan

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