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Update on Pharmacologic Options for Smoking Cessation Treatment

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ABSTRACT

Although the proportion of the adult population in the United States that smokes has decreased steadily, the rate of successful quit attempts is still low. Smokers develop nicotine dependence that resembles other addictions, and may require multiple attempts and long-term treatment to sustain abstinence. Currently available first-line agents for smoking cessation therapy include nicotine replacement therapy, which is available in several formulations, including transdermal patch, gum, nasal spray, inhaler, and lozenge; bupropion, an atypical antidepressant; and varenicline, a partial agonist of the $\alpha_4\beta_2$ nicotinic acetylcholine receptor that was recently developed and approved specifically for smoking cessation therapy. Second-line agents are nortriptyline, a tricyclic antidepressant agent, and clonidine, an antihypertensive drug. With the exception of varenicline, which has been shown to offer significant improvement in abstinence rates over bupropion, all of the available treatments appear similarly effective. However, the adverse event profiles of nortriptyline and clonidine make them more appropriate for second-line therapy, when first-line treatments have failed or are not tolerated. Rimonabant, a cannabinoid-1 receptor antagonist that was being developed for smoking cessation, received a nonapprovable letter from the FDA in 2006 and there is no further information as to whether development for this indication is continuing for this agent. Nicotine vaccines are under investigation and offer promise, especially for relapse prevention. Ultimately, selection of pharmacologic agent should be based on the patient's comorbidities and preferences, as well as on the agent's adverse event profile.

KEYWORDS: Antidepressants; Clonidine; Nicotine replacement; Smoking cessation; Varenicline

The US Surgeon General has characterized smoking cessation as "the single most important step that smokers can take to enhance the length and quality of their lives."[1] Over 70% of smokers say they want to quit[2] and approximately 40% make a quit attempt each year.[3] Unfortunately, the overwhelming majority of quit attempts are unaided, resulting in abstinence rates at 6 months of approximately 3% to 5%.[4] Why are so few unaided quit attempts successful? Smokers trying to quit have to simultaneously cope with the psychological, behavioral, and physical aspects of tobacco dependence. Psychologically, many smokers become dependent on nicotine as a mood stabilizer, and negative affect is a common reason given for relapse.[5,6] Behaviorally, through repeated pairing with tobacco use, everyday events such as seeing others smoke, drinking coffee or alcohol, driving the car, or taking a break become powerful triggers to smoke. Physically, due to nicotine's short half-life (<2 hours), strong cravings can develop within several hours of the last cigarette.[7] This is primarily due to reduced release of dopamine in the nucleus accumbens, one of the areas in the brain associated with reward. Other withdrawal symptoms may soon develop, including difficulty concentrating, irritability, frustration, anxiety, depressed mood, and increased appetite.[8] The withdrawal symptoms tend to peak within the first 7 days, but can last for weeks or months.[9] Studies have shown that the majority of smokers relapse within the first week of quitting.[4]

Statement of conflict of interest: Please see Author Disclosures section at the end of this document.

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Table 1 Odds ratios of abstinence with first- and second-line smoking cessation therapy[21,31,60]

Treatment	Odds Ratio (95% CI)*
First-line therapies	
NRT: All forms, pooled (meta-analysis of 123 studies with ≥6 mo follow-up)	1.77 (1.66–1.88)
Gum	1.66 (1.52–1.81)
Patch	1.81 (1.63–2.02)
Inhaler	2.14 (1.44–3.18)
Lozenge	2.05 (1.62–2.59)
Nasal spray	2.35 (1.63–3.38)
Bupropion (meta-analysis of 19 trials with ≥6 mo follow-up)	2.06 (1.77–2.40)
Varenicline†	Gonzales et al (2006)[45] (phase 3 trial of 1,027 smokers) 12 wk: 3.85 (2.70–5.50) 52 wk: 3.09 (1.95–4.91) Jorenby et al (2006)[46] (phase 3 trial of 1,025 smokers) 12 wk: 3.85 (2.69–5.50) 52 wk: 2.66 (1.72–4.11)
Second-line therapies	
Nortriptyline (meta-analysis of 6 trials with ≥6 mo follow-up)	2.14 (1.49–3.06)
Clonidine (meta-analysis of 6 trials with ≥12 wk follow-up)	1.89 (1.30–2.74)

CI = confidence interval; NRT = nicotine replacement therapy.
*Odds ratios are derived from *Cochrane Review* articles unless otherwise noted.
†Due to the relatively recent availability of clinical trial data for varenicline, there is currently no *Cochrane Review* or other meta-analysis of this agent.

Although unsuccessful attempts to stop smoking can be disheartening, patients who receive optimal pharmacologic treatment together with nonpharmacologic cessation counseling have greatly improved odds of attaining long-term abstinence. This article reviews the mechanisms of action, efficacy, safety, and place in the therapeutic armamentarium of pharmacologic treatments currently available or in development for smoking cessation.

CURRENTLY AVAILABLE PHARMACOTHERAPY FOR SMOKING CESSATION

First-line Therapies

First-line therapeutic agents are approved by the US Food and Drug Administration (FDA) for smoking cessation therapy and are proved to reliably increase smoking abstinence rates without causing excessive adverse events. A summary of their efficacy in clinical trials, expressed as odds ratios (ORs) of abstinence compared with control, is given in **Table 1**. **Table 2** provides information for product selection and administration.

Nicotine Replacement Therapy. The most recent Department of Health and Human Services (DHHS) guidelines for treatment of nicotine dependence recommend nicotine replacement therapy (NRT) for first-line treatment, except in the presence of contraindications.[10] Currently, there are 6 NRT formulations: transdermal patch, nasal spray, gum, lozenge, vapor inhaler, and sublingual tablet (not available in the United States).[11] Recommended dosages for the specific formulations are given in Table 2.

The multiple formulations of NRT offer smokers a choice in the route of administration, which may have a positive influence on adherence to treatment. The transdermal patch system offers a continuous release of nicotine over 16 or 24 hours, whereas the other formulations (gum, lozenge, inhaler, and nasal spray) are short-acting NRT (SANRT), so the dose can be self-titrated. The choice of agent is primarily driven by patient preference, word-of-mouth, advertising, price, route of administration, and perceived adverse effects. Allowing smokers to sample the various delivery systems before initiation of therapy is a way to encourage the use of SANRT, allowing patients to find the formulation that works best for them. As part of a multicomponent smoking cessation program for entertainment industry workers in Los Angeles, smokers tested 1 piece of nicotine gum, 1 nicotine lozenge, and 1 inhaler cartridge for about 5–10 minutes each at the first visit.[12] As a result, >90% of participants chose to use 1 of the products as part of their medication plan. Studies by Schneider and colleagues[13,14] have also shown that half-day testing of SANRT results in strong individual preferences that could potentially translate to improved utilization and quit rates.

Mechanism of Action. The principal mechanism of action of NRT is to partially replace the nicotine formally obtained from tobacco, which aids smoking cessation by reducing the severity of withdrawal symptoms and cravings[15] and also reduces the reinforcing effects of nicotine delivered via tobacco while providing an alternative source of some reinforcing and cognitive effects.[16] Differences in formulations may have an impact on the efficacy for some of these effects. For example, the more rapid delivery of nicotine obtained with the nasal spray appears to provide faster relief of withdrawal symptoms. Furthermore, the inhaler formu-

Table 2 Medications for smoking cessation*

Medication	Comments	Most Common Adverse Events	Contraindications/Precautions	Dosage
Nicotine patch	FDA-approved for smoking cessation Continuous-release (long-acting) formulation Available OTC Can be worn for 24 hr or for only 16 hr to avoid insomnia	Mild skin irritation at placement site	Pregnancy category D; avoid in pregnant women due to continuous delivery formulation Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	>10 cigarettes/day: 21 mg/24 hr for 6–8 wk; decrease to 14 mg/24 hr for 2–4 wk; then to 7 mg/24 hr for 2–4 wk ≤10 cigarettes/day: 14 mg/24 hr for 6 wk; then decrease to 7 mg/24 hr for 2–4 wk
Nicotine gum	FDA-approved for smoking cessation SANRT formulation allows for flexible dosing Available OTC Heavy smokers achieve greater benefit with 4-mg gum than 2-mg gum (see *Dosage*) Shown to reduce or delay weight gain	Jaw pain, mouth soreness, dyspepsia, hiccoughs	Pregnancy category C; the risk–benefit ratio may be favorable in pregnant smokers if efforts to quit without medication have failed and if the patient is continuing to smoke more than 10–15 cigarettes/day Avoid in patients with temporomandibular joint disease Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	≥25 cigarettes/day: use 4 mg nicotine gum; <25 cigarettes/day: use 2 mg nicotine gum on the following schedule: day 1 of abstinence through week 6: 1 piece every 1–2 hr; weeks 7–9: 1 piece every 2–4 hr; weeks 10–12: 1 piece every 4–8 hr It is suggested to use ≥9 pieces/day for the first 6 wk (max: 20–30 pieces/day)
Nicotine inhaler	FDA-approved for smoking cessation SANRT formulation allows for flexible dosing By prescription only Hand-to-mouth use mimics action of smoking, providing a coping mechanism for conditioned smoking cues	Mouth and throat irritation, cough	Pregnancy category D Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	6–16 10-mg cartridges/day for 12 wk; taper dosage over next 6–12 wk Each cartridge delivers 4 mg of nicotine
Nicotine lozenge	FDA-approved for smoking cessation SANRT formulation allows for flexible dosing Available OTC	Mouth and throat irritation, hiccoughs	Pregnancy category D Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	Patients who smoke their first cigarette within 30 min of awakening should use 4-mg lozenges; others should use the 2-mg dose 1 lozenge every 1 to 2 h for weeks 1 to 6; 1 lozenge every 2 to 4 h for weeks 7 to 9; 1 lozenge every 4 to 8 h for weeks 10 to 12
Nicotine nasal spray	FDA-approved for smoking cessation SANRT formulation allows for flexible dosing By prescription only Fastest delivery system for NRT, which is useful for rapid relief of withdrawal symptoms (especially in heavy smokers)	Runny nose, throat and nasal irritation, cough Side effects usually resolve after 3 days	Pregnancy category D Use with caution in acute cardiovascular conditions, such as recent AMI; however, risk–benefit ratio may be favorable in those patients who continue to smoke	1 or 2 0.5-mg doses in each nostril hourly for 3–6 mo; taper doses over 4–6 wk

Table 2 Continued

Medication	Comments	Most Common Adverse Events	Contraindications/Precautions	Dosage
Bupropion-SR	FDA-approved for smoking cessation May be used in combination with NRT Works equally well in women and men Effective for smokers with history of depression Suppresses weight gain associated with cessation Can be safely used in patients with cardiovascular disease	Insomnia, dry mouth, headache, tremors, nausea, anxiety	Pregnancy category C Avoid in patients with seizure disorder or at risk for seizures Avoid in patients taking MAOIs	Begin 1–2 wk before quit date with 150 mg qd for 3 days, then increase to 150 mg bid for 7–12 wk
Varenicline	FDA-approved for smoking cessation Works equally well in men and women Well tolerated Unique mechanism of action that decreases withdrawal and craving and also prevents reinforcing effects of nicotine during relapse	Nausea, insomnia, abnormal dreaming, headache	Pregnancy category C No clinically significant drug interactions or contraindications	Begin 1 wk before quit date. Target dose is 1 mg bid following a 1-wk titration: 0.5 mg qd on days 1–3 and 0.5 mg bid on days 4–7 Initial treatment duration of 12 wk. For those not smoking at week 12, an additional 12 wk is recommended for relapse prevention
Nortriptyline	Efficacy similar to bupropion or NRT, but safety profile prevents classification as first-line treatment	Sedation, dry mouth, constipation	Pregnancy category D Avoid in patients with cardiovascular disorders, such as AMI, or those at risk for arrhythmia Avoid in patients taking MAOIs Nortriptyline can be lethal in an overdose	Begin 10–28 days before quit date with 25 mg qd; gradually increase to 75–100 mg qd for 12 wk Taper dosage before discontinuing
Clonidine	Available for oral use or as a transdermal patch	Dry mouth, dizziness, sedation, constipation, postural hypotension	Pregnancy category C Abrupt discontinuation can cause rebound hypertension	Begin shortly before (3 days) or on the quit date Oral dosage: 0.15–0.75 mg qd; or transdermal dosage: 0.1–0.3 mg qd for 3–10 weeks Taper dosage before discontinuing

AMI = acute myocardial infarction; bid = twice daily; FDA = food and drug administration; MAOI = monoamine oxidase inhibitor; OTC = over the counter; qd = once daily; SANRT = short-acting nicotine replacement therapy; SR = sustained release.

*Table is not all-inclusive. Please see more comprehensive prescribing information for each agent.

lation provides an alternative coping mechanism for the behavioral aspects of smoking by mimicking the hand-to-mouth motion. However, as discussed below, no particular NRT has been proved to be more effective than any other. Table 2 presents some important differences among the formulations.

Clinical Efficacy. NRT does not completely eliminate all symptoms of withdrawal because the available delivery systems do not reproduce the rapid and high levels of nicotine achieved through inhalation of cigarette smoke.[17,18,19] **Figure 1**[20] illustrates nicotine plasma concentrations obtained from smoking a cigarette compared with those of oral snuff or NRT. Despite these differences, a *Cochrane Review* article recently found that all forms of NRT approximately double the chance of long-term abstinence from smoking (Table 1).[21] Similarly, a study enrolling 504 patients found that all forms of NRT tested (gum, patch, nasal spray, and inhaler) produced similar quit rates and were equally effective at reducing the frequency, duration, and severity of urges to smoke.[22] There is some controversy as to whether NRT is less effective for women than men, particularly at 1-year follow-up[23]; however, the available data are insufficient to conclusively support or disprove this finding.

Safety and Tolerability. Overall, NRT has a benign adverse event profile, with a relatively low rate of discontinuation due to adverse events.[21,22] Adverse events are generally formulation-specific, depending on the delivery system used (Table 2).[11] Despite the vasoconstrictor effects of nicotine, studies have failed to demonstrate an increased risk with the use of NRT in patients with cardiovascular disease.[24,25] Thus, the benefit of NRT appears to outweigh the risk for cardiovascular patients who continue to smoke. FDA pregnancy categories are given in Table 2.

Most smokers perceive NRT, regardless of formulation, as being substantially less satisfying than smoking cigarettes, in part because of the slower delivery of nicotine and in part because NRT only partially addresses the reinforcing effects of smoking that are not associated with nicotine.[11,16] Thus, NRT has been shown to have low liability for abuse and low dependence potential.[26] Additionally, there is no evidence of withdrawal discomfort when patients discontinue NRT use.[26]

Bupropion. Bupropion, the first non-nicotine agent to demonstrate efficacy in the treatment of tobacco dependence, was initially approved by the FDA as an atypical antidepressant; later, in 1997, it was approved in the United States for smoking cessation.[16] It is recommended as a first-line therapy by the DHHS guidelines for nicotine dependence.[10] Bupropion is formulated as a 150-mg sustained-release (SR) tablet to be taken twice daily.[27]

Mechanism of Action. The mechanism of action of bupropion for smoking cessation is not completely understood, but this agent is an inhibitor of dopamine and norepinephrine reuptake and also appears to be a weak antagonist at nicotinic receptors.[28] Its dopaminergic and noradrenergic properties, which largely account for its antidepressant effect, may contribute to the utility of bupropion as an aid to smoking cessation,[29] although its antidepressant action has been shown to account for $<$20% of this effect.[30]

Clinical Efficacy. A *Cochrane Review* article focusing on 19 trials with bupropion found that it doubles the chances of quitting smoking compared with placebo (Table 1).[31] Also, it has been shown to decrease nicotine withdrawal symptoms and cravings.[32] Pooled analyses of studies with bupropion generally show quit rates similar to NRT.[21,31]

Unlike NRT, bupropion appears to be as effective in women as in men for long-term abstinence and relapse prevention.[33] Also, as has been shown for nicotine gum,[34,35] bupropion can significantly delay or decrease the weight gain associated with quitting smoking,[36] which can be an important barrier to quitting, particularly in women. Bupropion has also been found equally effective in smokers with and without a history of depression.[31] Although the DHHS guidelines recommend that bupropion-SR (or nortriptyline, if bupropion is contraindicated) be considered first for patients with comorbid depression, they state overall that there is insufficient evidence for a general preference between bupropion and NRT.[10]

Safety and Tolerability. The most common adverse events with bupropion when used for smoking cessation are insomnia, which occurs in 30% to 40% of patients, and dry mouth, which occurs in 10% of patients.[31] In a comparative trial, the incidence of nausea was similar with bupropion, NRT, and the combination of both, and approximately doubles that observed with placebo.[27] Rates of discontinuation from clinical trials due to adverse events generally range from 7% to 12%.[31]

A risk of seizures has been observed with bupropion treatment. Two large studies, 1 of which was specifically for smoking cessation, reported seizure incidences of approximately 1 per 1,000.[37,38] Because of this risk, bupropion is contraindicated for patients with seizure disorders, bulimia, anorexia, and those undergoing alcohol or sedative withdrawal.[27]

Allergic reactions, including pruritus, hives, angioedema, and dyspnea, have been reported at a rate of 1 to 3 per 1,000 in clinical trials. There also have been case reports of delayed hypersensitivity symptoms.[31] Therefore, bupropion is contraindicated for patients with histories of allergic responses to bupropion or any of its ingredients. Bupropion is also contraindicated in conjunction with monoamine oxidase inhibitors.[27] The prescribing information for bupropion carries a "black-box" warning based on observations that antidepressants have increased the risk for suicidal ideation and behavior in children and adolescents with certain psychiatric disorders.[27] Bupropion is safe for use in patients with cardiovascular disease.[39]

Varenicline. Varenicline is the most recently FDA-approved agent for smoking cessation and has been included in the DHHS guidelines for the treatment of tobacco dependence.[10] It is formulated as 0.5-mg and 1-mg tablets. The recommended dosage is 1 mg twice daily following a 1-week titration: 0.5 mg once daily on days 1 to 3 and 0.5 mg twice daily on days 4 to 7.[40]

Mechanism of Action. Varenicline is a partial agonist specific for the neuronal nicotinic acetylcholine receptor subtype $\alpha_4\beta_2$,[41,42] which plays a central role in nicotine addiction.[43,44] As a partial agonist, varenicline stimulates receptor-mediated activity, but at a lower level than nicotine. Varenicline stimulates dopamine turnover in the nucleus accumbens to between 32% and 45% of the level elicited by nicotine injections.[41,42] The result is a moderate and sustained increase in dopamine levels, which provides relief from nicotine craving and withdrawal symptoms that are caused by low levels of dopamine during cessation attempts. The partial agonist action of varenicline also makes it useful for patients who have a lapse after their quit day; its competitive binding to the $\alpha_4\beta_2$ nicotinic acetylcholine receptor subtype inhibits dopaminergic activation

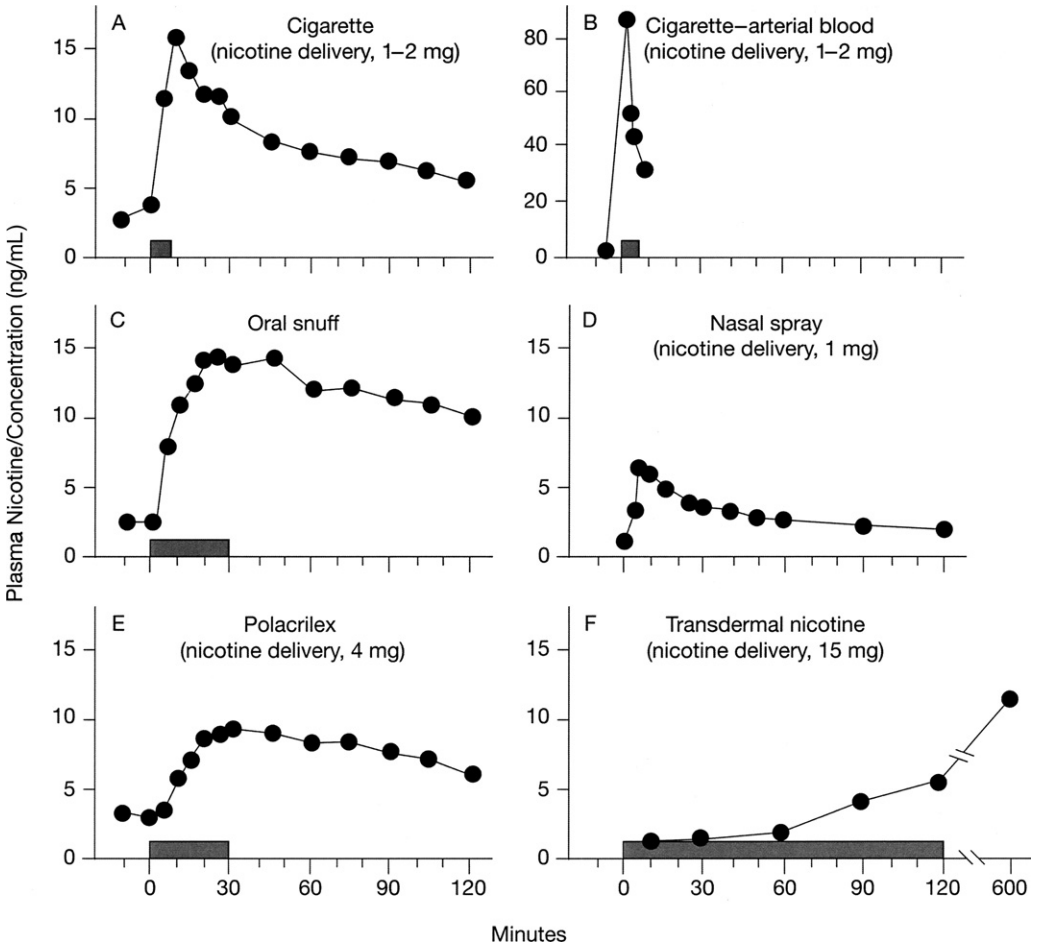

Figure 1 Rise in plasma nicotine concentrations after smoking a cigarette and after using different nicotine replacement therapy products. Values are for venous blood, except where indicated. The shaded bar represents the period of nicotine delivery. (Reprinted with permission from *N Engl J Med.*[20])

experienced upon smoking, thus preventing a pharmacologic reward during relapse.[41,42]

Clinical Efficacy. In 2 identically-designed randomized, double-blind, multicenter trials, which were placebo-controlled and active-controlled with bupropion-SR 150 mg twice daily, investigators demonstrated that in relatively healthy smokers the odds of quitting with varenicline 1 mg twice daily are almost quadrupled compared with placebo and almost doubled compared with bupropion after 12 weeks of treatment.[45,46] After 1 year, varenicline, bupropion, and placebo abstinence rates were about 22%, 15%, and 9%, respectively, so the odds of quitting with varenicline were approximately 2.5 times that of placebo, and approximately 1.7 times better than with bupropion (Table 1 and **Figure 2**).[45,46] Similar, results were obtained in 2 trials in Asian smokers.[47,48] When evaluated for long-term maintenance treatment in patients who quit smoking during 12-week open-label treatment with varenicline, this agent was shown to offer significant advantages over placebo after 6 months of treatment (OR, 2.48; 95% confidence interval [CI], 1.95–3.16) and at 1-year follow-up (OR, 1.34; 95% CI, 1.06 to 1.69).[49] Varenicline also significantly reduces craving and withdrawal symptoms compared with placebo.[45–49] Clinical trial information for varenicline only became available in mid-2006; the efficacy and safety results of the phase 2 and 3 clinical trials for this agent are reviewed in more detail by Hays and colleagues[50] in this supplement.

Safety and Tolerability. Varenicline is generally well tolerated, with the most common adverse events being nausea, insomnia, and headache.[45,46] Although approximately 30% of the subjects in the phase 3 clinical trials reported nausea as an adverse event, it was generally mild to moderate, with <3% of subjects discontinuing treatment owing to nausea.[45,46] It is recommended that patients take each dose after food and with a full glass of water to reduce the incidence or severity of nausea.[40] The overall incidence of adverse events leading to discontinuation is similar to that observed with placebo (in one phase 3 trial,[45] 8.6% for varenicline and 9.0% for placebo; in another phase 3 trial,[46] 4.1% for varenicline and 3.8% for placebo). The ceiling effect seen with partial agonists (i.e., increasing the dose beyond a

certain point does not increase the effect) suggests a low potential for abuse with varenicline.[51]

Second-line Therapies

Second-line therapies are agents that do not have FDA approval for smoking cessation but have demonstrated efficacy in this therapeutic area (Table 1) and are recommended by current guidelines for patients unresponsive to or unable to tolerate first-line agents.[10] The choice of a second-line agent should be based on the individual patient's clinical characteristics and careful consideration of the agent's adverse event profile (Table 2).

Nortriptyline. Nortriptyline is a tricyclic antidepressant that is available in capsule or liquid form.[52,53] In smoking cessation studies, nortriptyline has been administered at dosages of 75 to 100 mg/day or titrated to serum levels used for depression.[31]

Mechanism of Action. Several plausible theories for the mechanism of action of nortriptyline in nicotine dependence have been suggested, including that the mutual symptom exacerbation of smoking cessation and depression leads to high relapse rates that could potentially be prevented by antidepressant use, that nortriptyline's noradrenergic effects replace those of nicotine, and that nortriptyline is a nicotine receptor antagonist; however, there are no preclinical or clinical studies available to support any of these potential mechanisms.[52]

Clinical Efficacy. A *Cochrane Review* meta-analysis of 6 randomized clinical trials indicated that nortriptyline treatment doubles the odds of smoking cessation, with an OR for abstinence of 2.14 (95% CI, 1.49 to 3.06) (Table 1).[52] Thus, nortriptyline appears to be as effective as NRT or bupropion. However, nortriptyline has been evaluated in a much smaller number of smokers than either bupropion or NRT.[52]

Safety and Tolerability. The incidence of adverse events has varied in the few clinical trials of nortriptyline in smoking cessation therapy, ranging between 38% and 78% in the 6 trials included in the *Cochrane Review*.[52] Approximately 4% to 12% of those treated with nortriptyline discontinued therapy owing to adverse events, a range similar to that for NRT and bupropion.[52] The most common adverse events associated with use of nortriptyline for smoking cessation include anticholinergic effects such as dry mouth, constipation, and sedation.[31] Whereas these adverse events occur frequently in patients being treated for depression, they have been less common at the doses used for smoking cessation. Although tricyclic antidepressants carry a risk for weight gain, a particular problem for smokers trying to quit, trials with nortriptyline for smoking cessation have not demonstrated this to be a problem.[53] Other considerations with nortriptyline include the potential for cardiovascular effects, such as arrhythmia, hypertension, orthostatic hypotension, and tachycardia; potentially dangerous interactions with several other drugs, including monoamine oxidase inhibitors, norepinephrine, and epinephrine; and a potential for lethal overdose.[52,54] Nortriptyline is contraindicated for patients recovering from recent myocardial infarction.[53] Further, patients taking nortriptyline should not discontinue therapy abruptly, as withdrawal symptoms such as nausea, headache, and malaise may result.[53]

The prescribing information for nortriptyline carries a black-box warning similar to that for bupropion regarding an increased risk of suicidal ideation and behavior among children and adolescents taking antidepressants.[53] Moreover, the safety of nortriptyline has not been evaluated in special populations, such as pregnant women, patients with cardiovascular disease, or individuals who continue to smoke.[52] Because of the limited number and range of patients in whom nortriptyline has been evaluated for smoking cessation, the complete safety profile in these patients is unclear.[53]

In summary, the antidepressant effect of nortriptyline is the most common rationale for its use.[52] However, as with bupropion, the benefit of nortriptyline in smoking cessation appears to be independent of its antidepressant effect.[55] Whereas the efficacy of nortriptyline in treating nicotine dependence appears roughly equivalent to NRT and bupropion,[52] in the absence of more extensive testing, nortriptyline's safety profile has to date prevented its reclassification as a first-line agent for smoking cessation.[52]

Clonidine. Clonidine is approved by the FDA only for the treatment of hypertension but has demonstrated efficacy as an aid to smoking cessation.[10] It is available in tablets for oral administration and as a transdermal patch.[56,57]

Mechanisms of Action. Clonidine is an α_2-adrenergic agonist that acts on the central nervous system (CNS) to decrease sympathetic outflow.[56,57,58] Consistent with its α_2-adrenergic agonist activity, clonidine's central effects include sedation and anxiolysis, while its systemic effects include hypotension, bradycardia, and decreased sweating.[59] It is believed that clonidine's efficacy for smoking cessation is based on its ability to counteract CNS features of nicotine withdrawal, including craving and anxiety.[59]

Clinical Efficacy. Clonidine was found to be an effective aid for smoking cessation in a *Cochrane Review* article focusing on 6 clinical trials using either the oral tablet at dosages of 0.15 to 0.45 mg/day or the transdermal patch at dosages of 0.1 to 0.3 mg/day.[60] Pooled results from these 6 trials demonstrated an approximate doubling of the rate of abstinence after ≥12 weeks of follow-up compared with placebo (OR, 1.89; 95% CI, 1.30 to 2.74) (Table 1).[60]

Safety and Tolerability. The *Cochrane Review* noted a high incidence of dose-dependent adverse events with clonidine,

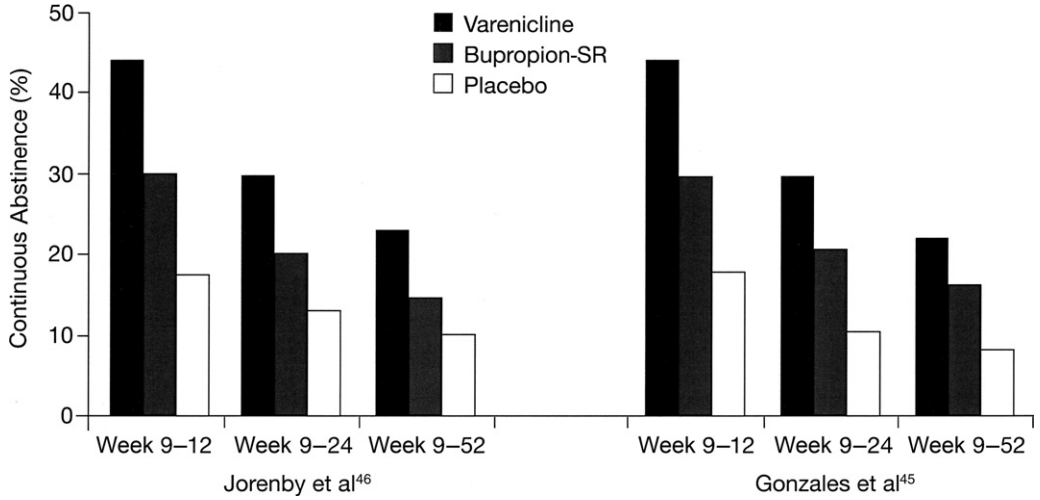

Figure 2 Carbon monoxide-confirmed continuous abstinence rates with varenicline or bupropion-SR versus placebo. In the study by Jorenby et al,[46] $P < 0.001$ for all comparisons except bupropion-SR versus placebo at weeks 9 to 12 ($P = 0.001$); varenicline versus bupropion-SR ($P = 0.003$) and bupropion-SR versus placebo ($P = 0.01$) at weeks 9 to 24; varenicline versus bupropion-SR ($P = 0.004$) and bupropion-SR versus placebo ($P = 0.08$) at weeks 9 to 52. In the study by Gonzales et al,[45] $P < 0.001$ for all comparisons except varenicline versus bupropion-SR at weeks 9 to 24 ($P = 0.007$), varenicline versus bupropion-SR at weeks 9 to 52 ($P = 0.057$), and bupropion-SR versus placebo at weeks 9 to 52 ($P = 0.001$). (Adapted from *JAMA*.[45,46])

including significant sedation and postural hypotension.[60] Other dose-related adverse events with clonidine include dry mouth and constipation. Patients using the transdermal patch may develop local allergic reactions to the patch; these patients may benefit from a switch to oral clonidine, but they may be susceptible to allergic reactions with the oral formulation as well.[56,57]

Clonidine may increase the effects of CNS-depressive drugs such as barbiturates and alcohol. Caution should also be used when coadministering clonidine with β-blockers, calcium channel blockers, and digitalis. Patients who stop clonidine use abruptly may experience symptoms such as agitation, headache, and tremor, as well as rebound hypertension.[56,57]

Combination Therapy

Combination treatment is often used in patients who have failed to achieve abstinence with monotherapy, and clinical trials have suggested improved efficacy with this approach. Combination therapy often involves adding an SANRT (nicotine gum, lozenge, inhaler, or nasal spray) to longer-acting agents, including the nicotine patch[21] or bupropion.[61] A meta-analysis of trials using both an SANRT along with the nicotine patch showed a modest but significant improvement in the odds of abstinence with combination treatment (OR, 1.42; 95% CI, 1.14 to 1.76).[21] It has been demonstrated that abstinence rates significantly increase with the number of agents used and the duration of treatment. In 1 study, patients were encouraged to use combinations of ≥1 long-acting medications (patch/bupropion) with ≥1 SANRT. Results demonstrated that a higher number of medications used (from 1 to ≥4) predicted higher abstinence rates at 4 weeks, although these differences did not remain significant at 6 months (**Figure 3**).[62] It is uncertain at this time whether or not the combination of NRT with varenicline would be expected to improve outcomes, because the proposed mechanism of action of varenicline as a high affinity partial agonist would tend prevent the binding and pharmacologic action of nicotine from the NRT. Although the efficacy of combined use of varenicline with either NRT or bupropion has not been studied, pharmacokinetic studies of combined use of the nicotine patch with varenicline have demonstrated a greater number of patients discontinuing treatment because of adverse events such as nausea, headache, and vomiting.[40]

FUTURE PHARMACOLOGIC AGENTS FOR SMOKING CESSATION

Rimonabant

Rimonabant, a cannabinoid-1 (CB_1) receptor antagonist, has been investigated for treatment of obesity[63] and for smoking cessation.[64] Early in 2006, the FDA issued a nonapprovable letter for the smoking cessation indication, thus further studies may be required before the FDA will reconsider approval of rimonabant for smoking cessation.[65] However, because rimonabant has the potential to limit postcessation weight gain, which is on average 13.0 pounds (5.85 kg) after 12 months of abstinence,[66] it may be useful in patients for whom weight gain is a significant barrier to cessation.[67]

In July 2007, the manufacturer withdrew the New Drug Application (NDA) to the FDA for obesity, because of to FDA concerns regarding the safety profile of rimonabant.[68] Furthermore, after the European Medicines Agency

(EMEA) reevaluated safety data for rimonabant as an obesity therapy in June 2007, the manufacturer updated the product labeling to include contraindications for patients with ongoing major depressive illness and/or ongoing antidepressive treatment and issued a letter to physicians in the European countries where the product was marketed advising them of the labeling change.[69] There is no further information available from the manufacturer at this time on the possible resubmission to the FDA of an NDA for rimonabant for either obesity or smoking cessation.

Mechanism of Action. Rimonabant is an antagonist at the central mammalian CB_1 receptor. Animal studies suggest this receptor may play a role in the reinforcing effects of drugs of abuse such as nicotine.[64] Functionally, chronic nicotine treatment appears to hyperactivate the cerebral endocannabinoid system and endocannabinoid levels in limbic regions and the CB_1 receptor plays a key role in this interaction.[64] Thus, it has been proposed that CB_1 antagonists may have value in smoking cessation therapy.[70,71]

Preclinical Efficacy. In preclinical trials, rimonabant has been shown to reduce nicotine self-administration and dopamine turnover in the nucleus accumbens,[70] and to attenuate reinstatement of nicotine-seeking behavior in the presence of conditioned stimuli.[71]

Clinical Efficacy. In the Studies with Rimonabant and Tobacco Use–United States (STRATUS-US) trial[72] of 787 smokers, 27.6% of patients treated with rimonabant 20 mg/day for 10 weeks achieved carbon monoxide–confirmed abstinence during the last 4 weeks of treatment, compared with 16.1% of patients treated with placebo (OR, 2.2; $P = 0.004$). In addition, there was a 77% reduction in postcessation weight gain with rimonabant compared with placebo among patients who were nonobese at baseline (body mass index <30).

Safety and Tolerability. Detailed safety information for rimonabant from smoking cessation trials have not yet been published, but reports from the STRATUS-US trial show that with rimonabant 20 mg/day, 6.9% of patients discontinued treatment due to adverse events, compared with 3.8% of placebo-treated patients.[72] An obesity trial (Rimonabant In Obesity [RIO]-Europe) showed that the most common adverse events reported with rimonabant 20 mg/day were gastrointestinal disorders (i.e., nausea, diarrhea), gastroenteritis, influenza, nasopharyngitis, headache, dizziness, arthralgia, and back pain.[63] In that trial, the rate of discontinuation from treatment due to adverse events was 15.4% in patients treated with rimonabant 20 mg/day, compared with 9.2% in placebo-treated patients.[63] The most common side effects leading to study discontinuation were psychiatric disorders, including depression, anxiety, psychomotor agitation, and sleep disorders.[73]

Nicotine Vaccines. Nicotine vaccines represent a new approach to the treatment of nicotine dependence and are currently under investigation. Because nicotine is a small molecule and an incomplete antigen, it is linked to a carrier protein order to stimulate the necessary immune response. The 3 vaccines currently under development differ in the carrier protein used and in how the molecules are joined.[16,67]

Mechanisms of Action. Nicotine vaccination elicits the production of antibodies that bind to nicotine, making the resulting compound too large to cross the blood-brain barrier and therefore inhibiting the psychoactive effects associated with smoking.[74] Preclinical studies in rats show that nicotine vaccines reduce the distribution of nicotine to the brain by 64%.[75]

Preclinical Efficacy. In studies using rats, the vaccine was observed to reduce penetration of nicotine into the brain and inhibit dopamine overflow in the nucleus accumbens[75,76]; it also attenuated the typical locomotor and cardiovascular responses to nicotine and the reinforcing properties of nicotine.[75,77] Additionally, vaccinated rats did not resume nicotine-seeking behavior after extinction of the response and rechallenge.[78]

Clinical Efficacy. The 3 vaccines in development have been evaluated in phase 1 and 2 trials. Two of them use cholera toxin B as a carrier. The vaccine candidate CYT002-NicQb yielded 12-month continuous abstinence rates of 21% to 42% depending on the level of response (versus 21% with placebo; $P = 0.044$). The TA-NIC vaccine demonstrated 12-month abstinence rates of 19% to 38% with 250-μg and 1,000-μg doses (versus 8% with placebo) in clinical trials.[67,79,80] The third vaccine is based on *Pseudomonas aeruginosa* exotoxin A. The 200-μg dose yields a 38% quit rate (versus 9% with placebo).[74] This vaccine recently received a Fast-Track designation from the FDA.[67,81] Achieving high antibody levels is essential for efficacy with these vaccines; however, subjects require multiple injections, usually over 4 to 6 weeks, before achieving sufficient antibody titers.[67,74] Furthermore, there can be great interindividual variability in the immunogenicity of the vaccine, which could present a challenge for routine use in clinical practice.[74] Although it has been suggested that vaccinated individuals may increase compensatory smoking to overcome the effects of the vaccine, this has not been demonstrated in clinical trials.[74] In effect, the slow buildup of titers over a 4- to 6-week period is analogous to nicotine fading or weaning. Long-term use might be particularly effective to prevent relapse.[67]

Safety and Tolerability. The safety of individual vaccines will depend largely on the carrier protein used.[11,67] In general, the vaccines have been reported to be safe and well tolerated. The observed side effects are similar to those of

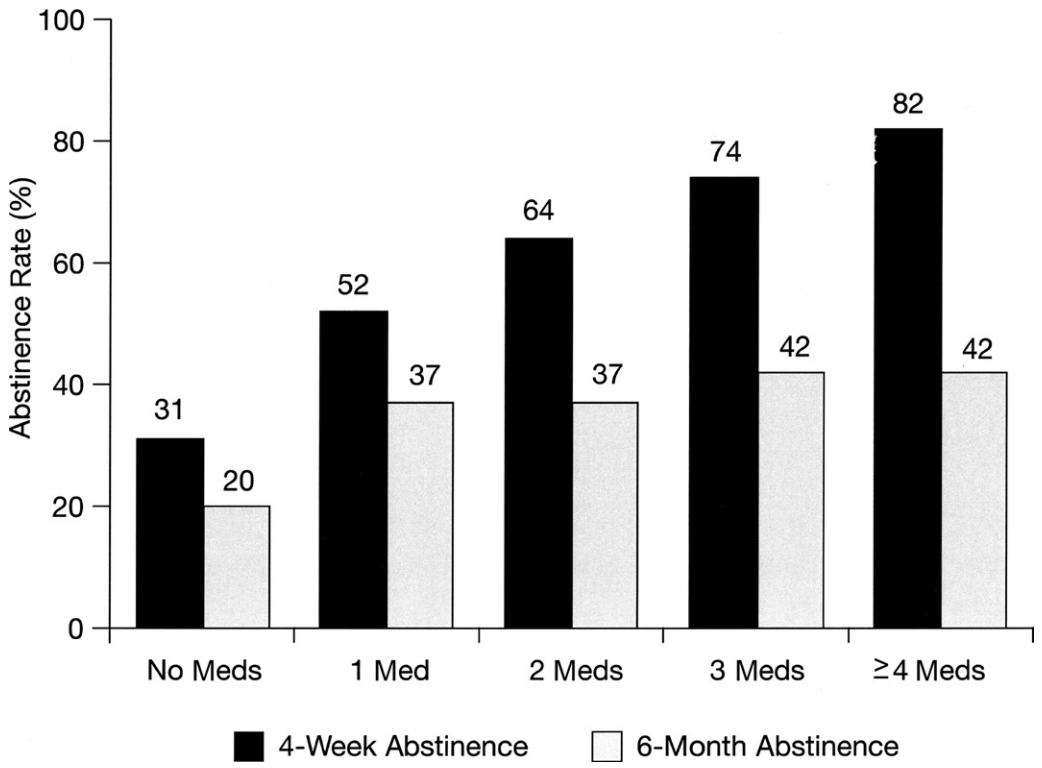

Figure 3 Abstinence rates by number of medications used (n = 790) at the Tobacco Dependence Clinic–New Jersey, 2001 to 2003. (Reprinted with permission from *Prev Med*.[62])

vaccines in general and include tenderness, injection-site induration, erythema, fever, and aching.[67,74]

SUMMARY

Given the serious consequence of tobacco smoking and the chronic nature of nicotine dependence, consistent use of effective therapies to aid smoking cessation is vital. The DHHS guidelines recommend that, unless contraindicated, all patients who smoke ≥10 cigarettes per day should use pharmacotherapy on every quit attempt. As such, clinicians have an important role in screening for patients in need of tobacco dependence treatment and to recommend appropriate pharmacologic agents that are proved to reliably increase abstinence rates for smokers who are willing to quit. First-line agents for smoking cessation therapy include NRT, bupropion, and varenicline. Both NRT and bupropion have been proved to approximately double the rate of abstinence versus placebo, and both are generally well tolerated by smokers. Overall, NRT offers low abuse potential and adherence advantages owing to the different routes of administration available. Bupropion may be particularly effective for smokers with a history of depression. Bupropion, however, carries the risk of more serious adverse events than NRT. Varenicline, a novel agent whose development was based on the neurobiology of nicotine addiction, has recently become available and appears to offer certain advantages over other currently available treatments for tobacco dependence. Varenicline provides superior efficacy for achieving abstinence over placebo and bupropion, is well tolerated, and has a low abuse potential. As was true for nicotine gum, the nicotine patch, and bupropion, the approval and advertising of varenicline will prompt increased patient- and clinician-initiated discussions of smoking cessation.

For patients who cannot tolerate or do not respond to first-line treatments, nortriptyline, a tricyclic antidepressant agent, or clonidine, an antihypertensive drug, can be considered. Both of these drugs have similar efficacy to the first-line agents. Their adverse event profiles, however, preclude their routine use for first-line therapy. New drug therapies, such as vaccines, are being developed based on current knowledge of the neurobiology of tobacco smoking and may offer further improvement in smoking cessation outcomes in the future.

The choice of pharmacologic therapy should be based on each patient's particular medical and psychosocial circumstances, as well as on adverse event profiles and patient preferences for route and schedule of administration. Although the use of the pharmacologic approaches available for smoking cessation substantially improves the likelihood of achieving successful abstinence, the best outcomes for cessation are achieved when pharmacologic agents are combined with behavioral approaches to treatment, such as tobacco dependence counseling. These behavioral approaches are outlined in detail by Niaura[82] elsewhere in this supplement.

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AUTHOR DISCLOSURES

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