

Managing Nicotine Addiction

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Abstract: Nicotine addiction has been identified as the primary contributor to continued widespread tobacco use worldwide. Although the health benefits of smoking cessation are well publicized, few smokers successfully quit on a long-term basis. A number of pharmacological agents have been shown to approximately double long-term smoking cessation rates and have, therefore, been recommended as first-line therapy for the treatment of nicotine dependence in the clinical practice guidelines recently released by the Agency for Healthcare Research and Quality (AHRQ). These include the currently available dosage forms of nicotine replacement therapy (gum, patch, nasal spray, and inhaler) and bupropion. Other agents that have exhibited some efficacy in increasing smoking cessation rates are nortriptyline and clonidine. All pharmacological treatments are most effective in conjunction with behavioral therapy. Other approaches to treating tobacco use disorder now being investigated include additional ways to administer nicotine, a vaccine to prevent nicotine from crossing the blood-brain barrier, and agents that alter the metabolism of nicotine. This review summarizes the characteristics of nicotine addiction, reviews the pharmacological agents currently used to treat tobacco use disorder, and describes possible approaches to treat nicotine dependence in the future.

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It has been estimated that, in 1999, approximately 23.5 percent of adults in the United States were current smokers.¹ The health consequences of smoking and the health benefits of smoking cessation have been well publicized, yet only a slight decrease in smoking prevalence has been reported since 1993.^{1,2} The physical addiction to nicotine is a key factor in continued tobacco use and should be addressed when considering therapies for the treatment of cigarette or other tobacco products. Since the 1980s, several pharmacological agents have been introduced to treat this addiction. These agents have proven efficacious and, as a result, have been recommended for almost all smokers—the primary exceptions being those with medical contraindications and those who smoke only a few cigarettes per day.^{3,4} Pharmacological interventions are most effective when combined with behavioral interventions, so most studies evaluating the use of pharmacotherapy generally incorporate at least limited behavioral therapy within the study protocol.⁴ This review will describe the characteristics of nicotine addiction, pharmacological agents currently used to treat tobacco use disorder, and future research directions.

Nicotine Addiction

Addiction is defined as a situation in which a drug unreasonably controls behavior.⁵⁻⁸ The primary

criteria for drug dependence are highly controlled or compulsive use of a drug with psychoactive effects and the presence of drug-reinforced behavior. Additional criteria are stereotypic patterns of use, use despite harmful consequences, relapse following abstinence, and recurrent drug cravings. Dependence-producing drugs often produce “tolerance,” physical dependence, and pleasant effects.⁹

Smoking fits these definitions of an addictive behavior.⁶⁻⁷ Approximately 40 percent of smokers attempt to quit annually, yet less than 5 percent do.^{1,10} Most smoking cessation attempts fail within the first two weeks; on average, four or more attempts are necessary before long-term cessation is achieved.^{2,8} Even in patients with cardiovascular disease, cancer, or chronic obstructive pulmonary disease where stopping smoking is critical to halt further deterioration of their medical condition, fewer than 50 percent quit.¹¹⁻¹⁴

The agent largely responsible for maintaining smoking addiction is nicotine.^{8,9} Animal models demonstrate nicotine’s addictive potential, and several lines of evidence suggest that nicotine is addictive in humans as well.¹⁵ In addition to the difficulty in quitting, research shows that smokers adjust their smoking habits to maintain relatively stable concentrations of nicotine, that the reinforcing effects of nicotine are blocked by pretreatment with the nicotine receptor antagonist mecamylamine, and that quitting smok-

ing is associated with cravings and a characteristic withdrawal syndrome.^{5,16,17}

Nicotine's neurobiological effects are complex and not entirely understood. Nicotine binds to nicotinic acetylcholine receptors located in the brain, autonomic ganglia, and neuromuscular junctions.⁸ Such binding leads to the release of a number of neurotransmitters and hormones including dopamine, serotonin, norepinephrine, acetylcholine, vasopressin, and beta-endorphin.^{8,18,19} The release of these substances modulates many of the subjective, cognitive, and behavioral effects associated with smoking, such as increase in pleasure, improved mood, increased attention, enhanced cognition and motor performance, and weight loss.^{8,18,19}

Chronic use of nicotine results in the development of "tolerance," which decreases the effect of a given dose of the drug.^{19,20} Tolerance is the result of morphological changes in the brain, such as receptor desensitization and inactivation as well as upregulation of receptor number.^{8,18,21} As a result of this neuroadaptation, cessation of tobacco use results in a withdrawal syndrome, characterized by depressed mood, insomnia, irritability, frustration or anger, anxiety, difficulty concentrating, restlessness, decreased heart rate, and increased appetite or weight gain.⁵ These symptoms generally peak at one week and gradually decrease over time, sometimes eventually reaching lower levels than were experienced while smoking.²² Thus, nicotine addiction is maintained not only by the subjective positive effects that smokers experience, but also by the desire to avoid the negative symptoms associated with nicotine withdrawal.

The potential for abuse or addiction to a drug is generally determined by the magnitude of the positive reinforcing effects and the speed of drug delivery to the brain.¹⁸ Typically, the relationship between drug dose and the reinforcing effect of the drug is characterized by an inverted U-shaped curve.^{15,18} Administration of an addictive drug will increase until its toxicity reduces the overall desirable effects and therefore decreases its reinforcing effects.^{15,18} Generally, the more quickly the drug is delivered to the brain, the greater the potential for abuse.²³ Nicotine from a smoked cigarette reaches the brain in ten to twenty seconds, with initial arterial nicotine concentrations far surpassing venous concentration.^{19,24,25} Such rapid delivery contributes to its high abuse potential. Smokeless tobacco and nicotine gum, which take longer to reach the brain, have somewhat less abuse potential, and the nicotine patch, which is very slowly absorbed, has minimal abuse potential.²³

Current and future pharmacological treatments aim to reduce tobacco use by targeting the mechanisms that reinforce tobacco use. Some treatments use agents that mimic the reinforcing effect of nicotine or reduce the negative effects (such as craving or withdrawal symptoms) associated with abstinence. Strategies being considered for future therapies include using agents that block the reinforcing effects of nicotine, prevent nicotine from crossing the blood-brain barrier, and alter the metabolism of nicotine.

Nicotine Replacement Therapies

Currently, four dosage forms of nicotine replacement therapy (NRT) are marketed in the United States: gum, patch, inhaler, and nasal spray. A nicotine lozenge is marketed in some countries in Europe. Each of these agents, by supplying an alternative source of nicotine, attempts to facilitate the smoking cessation attempt by decreasing the craving and withdrawal symptoms while achieving some perceived positive effects. Although NRT is appropriate for most smokers, caution should be taken when patients who use these products have had a myocardial infarction within the preceding two weeks, have serious arrhythmias, or have serious or worsening angina pectoris.³ Use of NRT during pregnancy is discussed later in this review.

Although there are differences in patient preference and tolerability, short-term quit rates for the four dosage forms are similar. Clinical practice guidelines recently released by the Agency for Healthcare Research and Quality (AHRQ) list each form as a first-line therapy for the treatment of nicotine dependence.^{3,26} The AHRQ recommendations are based on meta-analyses conducted on all trials meeting certain criteria. To be included in the meta-analyses, studies had to be randomized, placebo, or comparison controlled trials that provided follow-up results at least five months after the quit date and had been published in peer-reviewed journals in English.³ The efficacy of the AHRQ-recommended pharmacotherapies is summarized in Table 1 along with each's recommended dosage range, treatment duration, and common adverse effects. Quit rates and odds ratios provided by this analysis should not be compared across products. Differences in various aspects of the studies included in the analysis (such as study design, availability of adjunctive behavioral therapy, and

study population) limit the usefulness of direct comparisons. Despite similarities among the four dosage forms, important differences should be taken into account when selecting one for a given patient.

Nicotine Gum

Nicotine gum was the first available dosage form of nicotine replacement agents and is consequently the best studied to date. Nicotine from the gum is absorbed buccally with peak concentrations attained at about thirty minutes.²⁷ To ensure maximal absorption, patients should be counseled that nicotine gum should not be chewed in the way one chews regular chewing gum. Nicotine gum should be intermittently chewed slowly and then placed between the cheek and gum, allowing nicotine to be absorbed through the oral mucosa.²⁸ Since an acidic environment impairs the buccal absorption of nicotine, all food and beverages except water should be avoided for at least fifteen minutes before and during chewing.²⁹ To ensure that sufficient gum is used, initially nicotine gum should be used on a scheduled basis, with at least one piece chewed every one to two hours.³

More than fifty studies have been published assessing the efficacy of nicotine gum.³⁰ A number of meta-analyses have summarized these studies, the

most recent of which was based on thirteen studies assessing the efficacy of 2 mg nicotine gum. This analysis found that, relative to placebo, the odds ratio of successfully quitting using nicotine gum was 1.5 (95 percent CI: 1.3-1.8), which corresponded to a quit rate of 17.1 percent and 23.7 percent in the placebo and nicotine patch group, respectively.³ These results were the basis for the AHRQ recommendation that nicotine gum be considered a first-line therapy for tobacco use disorder.³ Earlier, meta-analyses also found nicotine gum to be an effective aid to smoking cessation.³¹⁻³⁴

Currently, two doses of nicotine gum are available (2 mg and 4 mg), neither of which requires a prescription in the United States. Both doses have been reported to improve smoking cessation rates; however, the 4 mg dose appears to be more effective among highly dependent smokers. A meta-analysis in which the 2 mg and 4 mg doses of nicotine gum were compared found that among highly dependent smokers, those using the 4 mg gum had 21 percent greater success at cessation than those using the 2-mg gum.³¹ Interestingly, for smokers low in nicotine dependence, the 2 mg gum may be more effective than the higher dosage.^{30,31} An advantage of nicotine gum over some other therapies is that it has been shown, in a dose-dependent manner, to delay but not

Table 1. Summary of drugs recommended in current AHRQ clinical practice guidelines*

Drug	Quit Rates (percent)		OR (95 percent CI)	Recommended Dosage Range	Recommended Duration	Common Adverse Effects
	PBO	Drug (95 percent CI)				
<i>First-Line Agents</i>						
2 mg Nicotine Gum	17.1	23.7 (20.6–26.7)	1.5 (1.3–1.8)	Up to 24 pieces per day	12 weeks	Mouth soreness, hiccups, dyspepsia, jaw ache
Nicotine Patch	10.0	17.7 (16.0–19.5)	1.9 (1.7–2.2)	1 patch per day	8 weeks	Skin reactions, insomnia
Nicotine Nasal Spray	13.9	30.5 (21.3–39.2)	2.7 (1.8–4.1)	8 to 40 doses per day	3 to 6 months	Nasal irritation, transient changes in sense of smell or taste
Nicotine Inhaler	10.5	22.8 (16.4–29.2)	2.5 (1.7–3.6)	6 to 16 cartridges per day	Up to 6 months	Irritation of mouth or throat, coughing, rhinitis
Bupropion	17.3	30.5 (23.2–37.8)	2.1 (1.5–3.0)	150 mg daily x 3 days, then 150 mg twice daily	7 to 12 weeks	Insomnia, dry mouth, headache, tremor, agitation
<i>Second-Line Agents</i>						
Nortriptyline	11.7	30.1 (18.1–41.6)	3.2 (1.8–5.7)	75 to 100 mg per day	10 to 12 weeks	Dry mouth, sedation, nervousness, urinary retention, tremor, lightheadedness
Clonidine	13.9	25.6 (17.7–33.6)	2.1 (1.4–3.2)	0.15 to 0.75 mg per day	3 to 12 weeks	Dry mouth, sedation, orthostatic hypotension

*Quit rates and odds ratios based on meta-analyses performed by AHRQ.³

prevent the weight gain normally associated with stopping smoking.^{35,36}

Patients using the nicotine gum are generally encouraged to discontinue use after approximately three months. However, it has been found that 10 to 25 percent of successful abstainers continue to use the gum for a year or longer.³⁰ Although patients should not be encouraged to use nicotine gum indefinitely, any risks associated with its long-term use are small relative to the risks associated with continued smoking.³⁰

Nicotine Patch

With the application of the nicotine patch, nicotine concentrations increase gradually over six to ten hours, then remain steady for seven to eight hours before gradually declining.³⁷ Unlike the other three dosage forms, the patch must be used on a scheduled basis because of its release characteristics. The nicotine patch should be applied once daily on a different skin site—a relatively hairless location on the upper body typically between neck and waist.

The efficacy of the nicotine patch has been assessed in numerous studies and summarized in several meta-analyses.^{3,31,33,38-40} The most recent meta-analysis, reported in the AHRQ guidelines, was based on twenty-seven studies meeting their inclusion criteria.³ This analysis found that, relative to placebo, the odds ratio of successfully quitting when using the nicotine patch is 1.9 (95 percent CI: 1.7-2.2) which corresponded to a quit rate of 10.0 percent and 17.7 percent in the placebo and nicotine patch group, respectively.³ A meta-analysis of studies assessing the use of over-the-counter nicotine patches found similar increases in quit rates when a nicotine patch is used relative to placebo (OR 1.8; 95 percent CI: 1.2-2.8). However, this analysis was based on the results of only three studies.³

Nicotine patches are available in forms designed to be worn for either sixteen or twenty-four hours; the sixteen-hour patches are applied in the morning and removed at bedtime. The efficacy of these patches has been found to be equivalent, although theoretically the twenty-four hour patch may be preferable for smokers with strong early morning cravings.³⁸ Conversely, the sixteen-hour patch may be more useful in patients who experience sleep disturbances or vivid dreams while using the patch. Decreasing the dose of the nicotine patch prior to discontinuation has not been found to result in higher cessation rates.³⁸

Nicotine Nasal Spray

Currently the nicotine nasal spray is available only by prescription. Absorption of nicotine administered via the nasal spray is faster than that achieved with any of the other nicotine dosage forms (although slower than from smoking a cigarette).⁴¹ Peak arterial plasma concentrations are reached approximately five minutes after administration.⁴²

Among the various NRT dosage forms, nicotine nasal spray is associated with the greatest frequency of adverse effects. Over 75 percent of users initially report moderate to severe nasal irritation or other related symptoms such as runny nose, throat irritation, and coughing.³⁰ Generally, the symptoms decrease with time although they may not dissipate entirely. A study comparing the efficacy of the four available dosages of nicotine found that a greater number of subjects randomized to nicotine spray did not use the recommended amount due to adverse effects than subjects randomized to any other nicotine dosage form.²⁶ Potential advantages of nicotine nasal spray include a more rapid relief of craving than observed after administration of other NRTs, possibly increased efficacy in highly dependent smokers, and some evidence suggesting that the spray may delay though not prevent the weight gain normally associated with quitting smoking.^{43,44} If nicotine nasal spray is used as a single agent, patients should be encouraged, at least initially, to use the spray regularly and to use at least eight doses per day.⁴⁵

Like the other dosage forms, nicotine nasal spray has been shown to be effective in increasing smoking cessation rates. A recent meta-analysis showed an odds ratio of 2.7 (95 percent CI: 1.8, 4.1) when compared to placebo corresponding to quit rates of 13.9 percent and 30.5 percent in the placebo and nasal spray groups, respectively.³ However, the quick absorption of nicotine raises questions about the addictive potential of this dosage form. Several studies have found that smokers continue to use nasal spray up to a year after initiating treatment; still, the health impact of continued use of the nicotine spray is small relative to continued smoking.^{30,44,46}

Nicotine Inhaler

Currently in the United States, nicotine inhalers require a prescription. Smokers are instructed to puff on the inhaler as they would on a cigarette, with each puff delivering a small amount of nicotine. Al-

though inhaled, most of the absorption of nicotine occurs via the buccal route.⁴⁷ An acidic environment in the mouth may therefore impair nicotine's absorption, and it is suggested that eating or drinking anything but water for at least fifteen minutes before and during inhalation be avoided.³ A potential advantage of the nicotine inhaler is that it comes closest to mimicking the behavioral aspects of smoking and therefore may be preferred by some patients. Initially, patients should use the inhaler regularly and use at least six cartridges per day.⁴⁸

The efficacy of nicotine inhalers has been assessed in several studies, four of which were combined in a meta-analysis that found an odds ratio of successful cessation of 2.5 (95 percent CI: 1.7, 3.6) when using a nicotine inhaler relative to placebo.³ These results corresponded to quit rates of 10.5 percent and 22.8 percent in the placebo and nicotine inhaler groups, respectively.³

Non-Nicotine Replacement Therapies

Bupropion

Bupropion sustained release (SR) is, at this time, the only non-nicotine medication approved for marketing in the United States as an aid to smoking cessation. Also an effective antidepressant, its mechanism of action remains uncertain although it is thought that both its antidepressant and smoking effects are mediated through the inhibition of norepinephrine and dopamine re-uptake by bupropion and/or its metabolites.⁴⁹⁻⁵¹ Bupropion is generally well tolerated; its most common side effects are dry mouth, headache, and insomnia. A dose-related incidence of seizures has been reported, so it should not be used by individuals at increased seizure risk (with a history of seizure disorder, on medication known to lower seizure threshold, etc.) or by those with a history of an eating disorder.

The efficacy of bupropion has been confirmed in several large studies.⁵²⁻⁵⁴ Smoking rates are known to be higher among those with depression than in the general population. Therefore, to ensure that any effects seen were independent effects of the drug and were not secondary to the resolution of depressive symptoms, these studies excluded subjects with a major depressive episode at the time of enrollment.⁵⁵⁻⁵⁷

A dose response study enrolling 615 subjects suggested that bupropion's effects are dose-dependent, with 300 mg per day being the most effective.⁵⁴ Consequently, all subsequent large smoking studies utilized the 300 mg daily dose. In the dose response study, quit rates among subjects receiving 300 mg of bupropion were significantly ($p < 0.001$) higher six weeks following their smoking quit date than in those receiving placebo (24.4 percent vs. 10.5 percent, respectively). Quit rates in the 100 and 150 mg group were 13.7 percent and 18.3 percent, respectively. One year after their quit date, those who had received 150 mg or 300 mg continued to have significantly higher quit rates than those who had received placebo (22.9 percent and 23.1 percent vs. 12.4 percent, respectively). The efficacy of bupropion in this study was independent of a past history of major depression.⁵⁸ A study in patients with mild to moderate chronic obstructive pulmonary disease confirmed that bupropion is effective in increasing both short- and long-term (twenty-six week) quit rates in this population as well.⁵²

To study the usefulness of continuing treatment beyond the recommended seven to twelve weeks, 429 smokers who had successfully quit after seven weeks of open-label bupropion were randomized to receive either an additional forty-five weeks of bupropion or placebo.⁵⁹ The proportion of those initially successful subjects who were not smoking at the end of treatment (55.1 percent vs. 42.3 percent; $p = 0.008$) and six months after the end of treatment (47.7 percent vs. 37.7 percent; $p = 0.034$) was higher in the bupropion than the placebo group. One year after the end of treatment, quit rates were no longer different between the two groups (41.6 percent vs. 40.0 percent; $p > 0.05$). The median time to smoking relapse was sixty-five days for the placebo group and 156 days for the bupropion group.

A study comparing bupropion, nicotine patch, and a combination of both therapies found that four-week quit rates were higher in all treatment groups relative to placebo.⁵³ Thereafter, only the bupropion and combined treatment groups were significantly superior to placebo. At the end of treatment, approximately 12, 24, 34, and 36 percent in the placebo, nicotine patch, bupropion, and combined treatment groups, respectively, had not smoked since their quit date; and one-year quit rates were 5.6, 9.8, 18.4, and 22.5 percent, respectively. This study suggests that long-term quit rates in subjects receiving bupropion are superior to those receiving the nicotine patch.

However, the limited long-term efficacy of the nicotine patch in this study contrasts with findings of most other research that has generally found both short- and long-term benefits.³ Further comparison studies are necessary to conclude whether bupropion is indeed superior to nicotine replacement therapy.

Due to the well-documented efficacy of bupropion in increasing quit rates, this agent is currently recommended as a first-line pharmacotherapy in the AHRQ clinical practice guideline.³ Additionally, bupropion has been shown to delay the weight gain associated with stopping smoking. Although one study suggests that long-term quit rates are higher with bupropion than the nicotine patch, further evidence is necessary before it can be conclusively determined that this is indeed the case.⁵³ Previous failed smoking cessation attempts using bupropion should not preclude another attempt once the smoker is motivated to try again.⁶⁰

Nortriptyline

Nortriptyline is one of the two agents recommended as second-line pharmacotherapy in the most recent AHRQ clinical practice guidelines.³ This agent is an effective antidepressant in the tricyclic antidepressant (TCA) class of medications and is thought to exert its therapeutic effects via the inhibition of the re-uptake of norepinephrine and serotonin with a greater effect on norepinephrine re-uptake.⁶¹ Side effects of the TCAs are related to their blocking muscarinic cholinergic receptors (dry mouth, blurred vision, constipation, and urinary retention), H₁ histamine receptors (sedation, drowsiness, weight gain), and alpha₁ adrenergic receptors (orthostatic hypotension).⁶² Although nortriptyline can exhibit any of the side effects described, it is among the least sedative of the TCAs and is thought to be least frequently associated with postural hypotension.⁶² Because TCAs can cause cardiac conduction delays that can result in arrhythmias in susceptible individuals or in overdose situations, nortriptyline should be avoided in patients at risk.⁶¹ The availability of nortriptyline in lower cost generic formulations may be an important factor for some patients.

The efficacy of nortriptyline as a smoking cessation aid has been assessed in two double-blind placebo controlled studies, each enrolling approximately two hundred patients.^{63,64} As with bupropion, subjects with a major depressive episode at the time of enrollment were excluded to ensure that any effect seen was independent of nortriptyline's antidepressant

effect. Both studies demonstrated that nortriptyline significantly increased smoking cessation rates when compared to placebo. Hall et al. reported six-month quit rates of 24 percent vs. 12 percent for nortriptyline- and placebo-treated subjects, respectively, while Prochazka et al. reported one-year quit rates of 14 percent vs. 3 percent favoring nortriptyline over placebo.^{63,64}

These two studies evaluating a total of 413 subjects suggest that nortriptyline is likely to be useful in assisting smokers with the smoking cessation attempt. The lack of a smoking cessation indication and its side effect profile resulted in nortriptyline being recommended as second-line therapy in the AHRQ clinical practice guidelines.³

Clonidine

Clonidine is currently recommended as another second-line pharmacotherapy in the AHRQ clinical practice guidelines.³ It is an alpha₂ adrenergic agonist commonly used as an antihypertensive. Stimulating alpha₂ receptors results in decreased release of norepinephrine, thereby reducing sympathetic activity.⁶⁵ Due to the possibility of a withdrawal reaction characterized by sympathetic rebound resulting in large blood pressure increases, clonidine must be tapered off slowly when discontinued.⁶⁵ Clonidine is useful for the treatment of withdrawal symptoms that emerge upon the discontinuation of opiates or alcohol probably by decreasing sympathetic overactivity that characterizes these withdrawal syndromes.^{66,67} Despite a number of published studies assessing its effect, the role of clonidine in assisting with smoking cessation attempts is still relatively unclear.

Three meta-analyses have assessed the pooled results of studies in which clonidine's effects on smoking behavior was tested. One of these meta-analyses, based on the results of nine randomized double-blind studies, concluded that clonidine is helpful in increasing quit rates (odds ratio of 2.36, 95 percent CI: 1.69-32.8).⁶⁸ The second reaches a similar conclusion, finding a pooled odds ratio of 2.0 (95 percent CI: 1.3-3.0).⁶⁹ The third meta-analysis, which served as the basis for the AHRQ recommendation, also concluded that clonidine increases quit rates to a greater extent than placebo (estimated odds ratio 2.1; 95 percent CI: 1.4-3.2).³ These meta-analyses suggest that clonidine is effective in promoting smoking cessation in certain populations; however, it is unclear which subset of patients benefits most from it.

Several studies have found that clonidine is effective in increasing quit rates among women but not among men, whereas others have found some efficacy in both male and female smokers.⁷⁰⁻⁷⁵ Still other studies have failed to find that clonidine is superior to placebo in promoting smoking cessation, regardless of gender.⁷⁶⁻⁷⁸

In summary, despite being extensively studied, the role of clonidine as an aid to smoking cessation remains unclear. Clonidine appears to have beneficial effects in some smokers with the greatest benefits possibly occurring in women. Due to this uncertainty, its side effect profile, and the possibility of a withdrawal reaction upon discontinuation, clonidine is considered a second-line pharmacotherapy in assisting smokers with a cessation attempt.

Combined Medications

Despite the documented benefits of nicotine replacement therapy or bupropion in increasing smoking cessation rates, one-year quit rates with these therapies rarely exceeds 25 percent to 35 percent. In order to further increase smoking cessation rates, combination therapy has been investigated, in which either two dosage forms of nicotine are combined or nicotine replacement therapy (NRT) is combined with bupropion.

A number of studies have assessed the efficacy of combining two dosage forms of NRT: in these, the nicotine patch is combined with one of the other three forms (gum, inhaler, or spray).⁷⁹⁻⁸³ With these combinations, the patch provides a basal level of nicotine throughout the day, and the additional dosage form provides nicotine only when cravings or withdrawal symptoms occur. Using the non-patch dosage form on an as-needed basis may therefore reduce nicotine withdrawal symptoms. This may be accomplished both by increasing the amount of administered nicotine and by using the NRT as a behavioral substitute for reaching for a cigarette when one has smoking cravings. Indeed, several studies have found that nicotine withdrawal symptoms are less severe when combination NRT is used relative to using only one.^{79,84}

Studies comparing smoking cessation rates attained with combination NRT also suggest that quit rates are higher in the short term and may be higher in the longer term than those achieved when a single therapy is used. A study in which the nicotine patch

was compared with treatment combining the patch and nicotine gum found significantly higher quit rates in the combination group through the twenty-four week assessment period (27.5 percent and 15.3 percent in the combination and patch groups, respectively).⁸⁰ Smoking cessation rates continued to be higher in the combination group through a one-year period (one-year quit rates of 18.1 percent vs. 12.7 percent), although this was not statistically significant. A study that compared the patch/gum combination to gum alone similarly found significantly higher quit rates with the combination through the twelve-week visit, at which time quit rates were 39.3 percent vs. 28.0 percent in the combination and gum groups, respectively. Again, there was a trend toward higher quit rates in the combination group throughout a one-year period (one-year cessation rates of 24.0 percent and 17.3 percent); however, these differences did not reach statistical significance.⁸¹

Two studies have compared the nicotine inhaler to combination therapy in which the inhaler was used with the patch. One trial found no benefit to the combination; however, the open label design of this study makes the results difficult to interpret.⁸² The second study, which was a randomized, double-blind study comparing this combination to the inhaler alone, found that quit rates were significantly higher through the twelve-week visit (84 percent vs. 62 percent; $p=0.02$).⁷⁹ One-year quit rates were 39 percent vs. 28 percent ($p=0.14$) in the combination and inhaler groups, respectively.

A study comparing the patch and spray combination to the patch alone found both short- and long-term benefits to using combination therapy.⁸³ Abstinence rates at three months and one year were 37.3 percent vs. 25.2 percent ($p=0.045$) and 27.1 percent vs. 10.9 percent ($p=0.001$) in the combination group and patch group, respectively. At six years, quit rates continued to be higher in the combination group (16.2 percent vs. 8.5 percent) but did not reach statistical significance ($p=0.08$). These results should be interpreted with caution since the patch was used for five months and the nasal spray was used for up to a year. Therefore, subjects randomized to the active patch/active spray condition received some form of nicotine replacement for seven months longer than those randomized to the active patch/placebo spray condition.

A single study comparing a bupropion/nicotine patch combination to using either therapy alone found that combination therapy was significantly superior to using the patch alone but was not statisti-

cally different from bupropion therapy.⁵³ Rates of point prevalence abstinence at twelve months were 15.6, 16.4, 30.3, and 35.5 percent in the placebo, nicotine patch, bupropion, and combination group, respectively. The lack of long-term efficacy of the nicotine patch is not consistent with other studies demonstrating both short- and long-term benefits of the nicotine patch, so results of this study should be interpreted with caution.

In summary, although there are a limited number of studies assessing combination therapy, most available data suggest that combined NRT increases quit rates in the short term and possibly the long term as well. Although significant increases in long-term cessation rates were not observed with most studies, trends towards higher quit rates were found. Pooling results from four of these studies, Bohadana et al. found an odds ratio for cessation at twelve months using combination therapy relative to single agent NRT of 1.7 (95 percent CI: 1.3-2.3). A meta-analysis based on three of the studies found an odds ratio for successful long-term cessation of 1.9 (95 percent CI: 1.3-2.6).^{79-81,83} Based on this analysis, the AHRQ clinical practice guidelines recommend combining the nicotine patch with a self-administered form of NRT in patients who are unable to quit using a single type of first-line therapy.³ It remains unclear whether higher quit rates result from the benefits of using two distinct nicotine dosage forms or whether benefits occur due to higher overall amounts of nicotine replacement. Further research is necessary to determine whether combining bupropion with NRT results in higher overall quit rates.

Choosing the Appropriate Treatment

The various pharmacological treatments are essentially similar in efficacy although failure with one agent has not been shown to suggest failure with others. The choice of product should, therefore, be based on patient-specific factors such as contraindications, side effect profile of specific products, previous experience with medications (e.g., whether they had positive or negative reactions to the product), patient preference, and the health provider's familiarity with the medication. Smoking history is also an important consideration since highly dependent smokers may respond preferentially to the 4 mg dose of nicotine gum or nasal spray.

Other potential differences among products include cost, ability to delay weight gain, and effectiveness in treating concurrent disease states such as depression. Nortriptyline and nicotine patches are available in generic formulations and therefore usually cost less than other products. Nicotine gum and bupropion have been shown to delay the weight gain commonly associated with smoking cessation, and bupropion and nortriptyline have been shown to be effective antidepressants. All of these may be important considerations when individualizing therapy.

Patients who fail their first attempt should be encouraged to make repeated attempts since multiple quit attempts are often required before long-term success is achieved.⁸ The use of combination therapy should be considered in smokers who were not successful quitters despite the use of monotherapy, since this approach has been shown to improve quit rates.

Treatment of Special Populations: Women, Adolescents, and Smokeless Tobacco Users

Little information is currently available on pharmacological treatment of pregnant women, women in general, and adolescents. Short-term safety studies with pregnant women have shown that use of 2 mg nicotine gum results in less nicotine exposure than smoking approximately twenty cigarettes per day and use of the 21 mg patch results in no greater exposure to nicotine.^{85,86} It would logically follow that use of NRT should then be associated with less toxicity to the fetus than continued smoking because exposure to other tobacco-related toxins such as carbon monoxide is eliminated. The elimination of carbon monoxide is particularly important because this is the primary fetal toxic tobacco-related constituent.⁸⁷

Only one efficacy study has been published on the use of the nicotine patch in pregnant smokers. This study showed that although no significant differences were observed for quit rates between the placebo and active nicotine patch group, the birth weights of babies born to mothers assigned to the active nicotine patch were 186 grams higher than babies of mothers assigned to the placebo patch.⁸⁸

The recent AHRQ guidelines recommend that behavioral counseling be provided to pregnant

women. If counseling is not sufficient, then use of pharmacological agents should be considered, especially if the risk of smoking outweighs the risk of using nicotine products with and without concomitant smoking. Because nicotine replacement products are not without risk to the fetus, the guidelines recommend that pregnant women be monitored for nicotine levels and the lowest effective dose should be used. Nicotine products with intermittent rather than continuous delivery are recommended.³

In general, the efficacy of pharmacological agents in the treatment of women do not differ from the treatment of men. That is, pharmacological treatments are effective in promoting quitting in both women and men. However, some studies have suggested that some nicotine replacement therapies are not as beneficial in women as in men.⁸⁹ One exception is the nicotine inhaler, where women showed higher success rates than men.⁹⁰ These findings must take into consideration that women enrolled in clinical trials tend to do more poorly than men in achieving abstinence.⁸⁹ The effect of gender in response to treatment with bupropion is yet unclear. Interesting research is being conducted on the hormonal influences on physical dependence on nicotine. These results show that women tend to experience greater withdrawal symptoms during the luteal or late luteal phases of the menstrual cycle.^{91,92} However, nicotine patches appear to equally reduce the extent of withdrawal whether the woman quits smoking during the follicular or late luteal phase of her menstrual cycle.⁹³

Few pharmacological treatment studies have been published regarding adolescent smokers. Two open label studies using nicotine patches found the success rate to be quite low in adolescents, with end of treatment abstinence rates of 11 percent and 14 percent and six-month abstinence rates of 5 percent.^{94,95} In a small (N=100), double-blind trial, nicotine patches reduced nicotine withdrawal symptoms compared to placebo patches, but demonstrated no increased efficacy at the end of the ten-week treatment phase (20 percent vs. 18 percent, four-week continuous abstinence).⁹⁶ Evidence to date suggests that nicotine replacements may be used to alleviate withdrawal in adolescents concerned about the withdrawal brought about by quitting, but quit rates will likely be enhanced only with adjunctive psychosocial or cognitive behavioral therapies. Currently, larger studies are being conducted with the nicotine replacement agents and bupropion SR.

Among smokeless tobacco users, nicotine replacements have not uniformly enhanced the treatment efficacy over placebo.⁹⁷⁻⁹⁹ However, one study that examined the effects of nicotine patches dispensed in pharmacies did show relapse rates (use of smokeless tobacco for at least seven consecutive days) were reduced among the active vs. placebo group (33 percent vs. 48 percent, respectively).¹⁰⁰ Furthermore, studies have consistently shown a significant reduction in withdrawal symptoms with nicotine replacements over placebo.^{97,98}

In summary, research data shows that nicotine replacements and bupropion are effective in the treatment of women. Whether nicotine replacements should be used in the treatment of pregnant women must be carefully considered by weighing the potential benefits and risks. To date, the data suggests that smoking is more harmful than the use of nicotine replacement agents. Nonetheless, the pregnant woman must be carefully monitored. Finally, among smokeless tobacco users and adolescents, although no data is available on the efficacy of bupropion SR, existing data on nicotine replacement agents show no enhanced efficacy over placebo, but do show a reduction in withdrawal symptoms. For those adolescent smokers and smokeless tobacco users concerned about experiencing withdrawal during a quit attempt, these products may be useful.

Future Directions in Research

Additional ways to administer nicotine are currently being developed, with some likely to be marketed soon. These products include a nicotine lozenge, a straw nicotine oral delivery system, and products that result in faster delivery of nicotine than existing products.^{101,102} In addition, more targeted therapies are likely to be developed, including medications that target specific nicotinic acetylcholine receptor subtypes responsible for some of the reinforcing effects of nicotine (e.g., $\alpha 4\beta 2$, $\alpha 7$).

Another potential medication includes a nicotine vaccine. Such a vaccine produces antibodies that bind to nicotine so that nicotine cannot cross the blood brain barrier, thus reducing the reinforcing effects of nicotine. This vaccine has undergone preclinical testing with promising results. In rat studies, nico-

tine vaccine injection has reduced brain levels of nicotine compared to a vehicle injection.¹⁰³ Furthermore, animal studies show that nicotine-induced increases in blood pressure and locomotor activity are reduced with the nicotine vaccine and that nicotine-induced relief of nicotine withdrawal symptoms has been attenuated.^{103,104} The advantage of this vaccine is that this medication specifically targets nicotine and does not alter any other central nervous system function.

Recently, interest has been focused on individual differences in activity of the cytochrome P450 2A6 (CYP2A6) enzyme, which metabolizes nicotine. Studies have shown that some individuals inherit a defective CYP2A6 allele.¹⁰⁵⁻¹⁰⁷ These individuals metabolize nicotine more slowly, resulting in reduced number of cigarettes smoked or reduced prevalence in smoking. Investigators have been exploring the effect on tobacco use of methoxsalen, a medication that reduces the metabolism of nicotine. When this medication is combined with oral nicotine, a reduction in smoking is observed compared to a double placebo condition.¹⁰⁸

Finally, pharmacogenetic studies are being conducted that entail treatment matching based on a smoker's genotype. Subpopulations of smokers have been observed to have polymorphisms of the dopamine or serotonin transporter gene or tryptophan hydroxylase gene.¹⁰⁹⁻¹¹¹ These populations of smokers may respond to specific types of treatment more than others.

Conclusions

Nicotine is an addictive drug, particularly when administered in a way that results in immediate delivery to the brain. Various effective pharmacologic treatments are now available; their use has been recommended for all smokers who do not have medical contraindications.³ The use of pharmacological treatment can enhance tobacco cessation success by two- to three-fold. Nicotine addiction is a chronic, relapsing disorder that may require many attempts at quitting smoking and even long-term use of medications. Furthermore, the physical addiction to nicotine is only one aspect of the addiction to tobacco. Therefore, pharmacological treatments are most effective when given in conjunction with advice and assistance, whether the assistance is brief or more intensive, with more intensive treatment leading to greater success.³

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