

First-line Pharmacotherapy for Tobacco Use and Dependence

Steve A. Watts, MD, Sara L. Noble, PharmD, Patrick O. Smith, PhD, and Marilyn Disco, PharmD

Editors' Note: *This month we continue the feature - STEPped Care: An Evidence-Based Approach to Drug Therapy. These articles are designed to provide concise answers to the drug therapy questions that family physicians encounter in their daily practice. The format of the feature will follow the mnemonic STEP: safety (an analysis of adverse effects that patients and providers care about), tolerability (pooled dropout rates from large clinical trials), effectiveness (how well the drugs work and in what patient population[s]), and price (costs of drug, but also cost effectiveness of therapy).¹ Hence, the name STEPped Care.*

Since the informatics pioneers at McMaster University introduced evidence-based medicine,² Slawson and colleagues^{3,4} have brought it to mainstream family medicine education and practice. This feature is designed to further the mission of searching for the truth in medical practice. Authors will provide information in a structured format that allows the readers to get to the meat of a therapeutic issue in a way that can help physicians (and patients) make informed decisions. The articles will discourage the use of disease-oriented evidence (DOE) to make treatment decisions. Examples of DOEs include blood pressure lowering, decreases in hemoglobin A_{1c}, and so on. We will include studies that are POEMs - patient-oriented evidence that matters (myocardial infarctions, pain, strokes, mortality, etc) - with the goal of offering our patients the most practical, appropriate, and scientifically substantiated therapies. Number needed to treat to observe benefit in a single patient will also be included as a way of defining advantages in terms that are relatively easy to understand.^{5,6}

At times this effort will be frustrating. Even as vast as the biomedical literature is, it does not always support what clinicians do. We will avoid making conclusions that are not supported by POEMs. Nevertheless, POEMs should be incor-

porated into clinical practice. The rest is up to the reader. Blending POEMs with rational thought, clinical experience, and importantly, patient preferences can be the essence of the art of medicine.

We hope you will find these new articles useful and easy to read. Your comments and suggestions are welcome. You may contact the editors through the editorial office of JABFP. We hope the articles provide you with useful information that can be applied in everyday practice, and we look forward to your feedback.

*Bruce R. Canaday, PharmD
Keith Campagna, PharmD
STEPped Care Feature Editors
John P. Geyman, MD, Editor
Journal of The American Board of Family Practice*

References

1. Shaughnessy AF, Slawson DC, Bennett JH. Separating the wheat from the chaff: identifying fallacies in pharmaceutical promotion. *J Gen Intern Med* 1994;9:563-8.
2. Evidence-based medicine: a new approach to teaching the practice of medicine. Evidence-Based Medicine Working Group. *JAMA* 1992;268:2420-5.
3. Slawson DC, Shaughnessy AF, Bennett JH. Becoming a medical information master: feeling good about not knowing everything. *J Fam Pract* 1994;38:505-13.
4. Shaughnessy AF, Slawson DC, Bennett JH. Becoming an information master: a guidebook to the medical information jungle. *J Fam Pract* 1994;39:489-99.
5. Laupacis A, Sackett D, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988;318:1728-33.
6. Wiffen PJ, Moore RA. Demonstrating effectiveness - the concept of numbers-needed-to-treat. *J Clin Pharm Ther* 1996;21:23-7.

The evidence supporting the use of pharmacologic agents in a comprehensive tobacco treatment plan

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From the Department of Family Medicine (SAW, SLN, POS), and the Department of Pharmacy (MD), University of Mississippi Medical Center, Jackson. Address reprint requests to Steve A. Watts, MD, Department of Family Medicine, University of Mississippi Medical Center, 2500 North State St, Jackson, MS 39216.

is irrefutable. Annually, 70% of smokers see a physician. Of these, 70% wish to quit and 46% attempt to quit.¹⁻³ Primary care clinicians are poised to implement empirically based smoking cessation therapies including providing prescriptive and non-prescriptive smoking cessation aids.

In 1998, a consortium of seven governmental and nonprofit organizations sponsored an update to the 1996 smoking cessation clinical practice guide-

Table 1. Findings and Recommendations of Treating Tobacco Use and Dependence (TTUD).

1. Tobacco dependence is a chronic condition that often requires repeated intervention. However, effective treatments exist that can produce long-term or even permanent abstinence
2. Because effective tobacco dependence treatments are available, every patient who uses tobacco should be offered at least one of these treatments:
 - a. Patients *willing* to try to quit tobacco use should be provided treatments determined to be as effective in this guideline
 - b. Patients *unwilling* to try to quit tobacco use should be provided a brief intervention designed to increase their motivation to quit
3. It is essential that clinicians and health care delivery systems (including administrators, insurers, and purchasers) institutionalize the consistent recognition, documentation, and treatment of every tobacco user seen in a health care setting
4. Brief tobacco dependence treatment is effective, and every patient who uses tobacco should be offered at least brief treatment
5. There is a strong dose-response relation between the intensity of tobacco dependence counseling and its effectiveness. Treatments involving person-to-person contact (via individual, group, or proactive telephone counseling) are consistently effective, and their effectiveness increases with treatment intensity (eg, minutes of contact)
6. Three types of counseling and behavioral therapies were found to be especially effective and should be used with all patients attempting tobacco cessation:
 - a. Provision of practical counseling (problem solving, skills training)
 - b. Provision of social support as part of treatment (intra-treatment social support)
 - c. Help in securing social support outside of treatment (extra-treatment social support)
7. Numerous effective pharmacotherapies for smoking cessation now exist. Except in the presence of contraindications, these should be used with all patients attempting to quit smoking:
 - a. Five *first-line* pharmacotherapies were found that reliably increase long-term smoking abstinence rates:
 1. Bupropion SR
 2. Nicotine gum
 3. Nicotine inhaler
 4. Nicotine nasal spray
 5. Nicotine patch
 - b. Two *second-line* pharmacotherapies were determined to be as efficacious and may be considered by clinicians if first-line pharmacotherapies are not effective.
 1. Clonidine
 2. Nortriptyline
 - c. Over-the-counter nicotine patches are effective relative to placebo, and their use should be encouraged
8. Tobacco dependence treatments are both clinically effective and cost-effective relative to other medical and disease prevention interventions. As such, insurers and purchasers should ensure that:
 - a. All insurance plans include as a reimbursed benefit the counseling and pharmacotherapeutic treatments found to be as effective in this guideline
 - b. Clinicians are reimbursed for providing tobacco dependence treatment just as they are reimbursed for treating other chronic conditions

line entitled, *Treating Tobacco Use and Dependence* (TTUD).⁴ TTUD synthesizes the tobacco dependence treatment literature from 1975 through 1998 and provides an evidence-based tobacco treatment clinical practice guideline.⁵ A tobacco cessation consensus statement in the *Journal of the American Medical Association* (JAMA) endorses and encourages using the TTUD guideline.⁶ The JAMA synopsis of TTUD focuses on a practice strategy known as the 5As: ask, advise, assess, assist, and arrange. The 5A strategy is based on a multicomponent treatment approach including effective behavioral therapies and pharmacotherapies. The key recommendations of TTUD are presented in Table 1.

This review updates subsequent evidence supporting the use of pharmacologic therapies in tobacco dependence treatment based on literature published between 1 January 1999 and 16 January 2001. First-line pharmacologic interventions (namely, nicotine patch, nicotine gum, nicotine inhalers, nicotine nasal spray, and bupropion) and combination therapies are reviewed. MEDLINE, PubMed, and the Cochrane Database of Systematic Reviews were searched using search terms related to smoking cessation. Studies were selected if continuous prevalence measurements of abstinence from tobacco use after follow-up of 5 months or longer was reported. One trial comparing nicotine gum, nicotine patch, nasal spray, and inhaler was

included. Although only 12 weeks in duration, no other studies were found comparing all four nicotine replacement products in a head-to-head study. Furthermore, the conclusions from this study add considerably to the evidence for the use of these treatments in smoking cessation treatment programs.

Nicotine Patch as a Smoking Cessation Aid

Nicotine patches have been available since 1991 and available without a prescription since 1999. Twenty-seven studies in TTUD established that transdermal nicotine patch therapy approximately doubles long-term abstinence rates compared with placebo (odds ratio 1.9, Table 2).⁶ Three additional studies not included in the TTUD guideline show a doubling of abstinence rates for over-the-counter (OTC) nicotine patch therapy when compared with placebo.⁷ In an OTC nicotine patch therapy intent-to-treat study, Hays et al⁸ randomized 958 subjects to a placebo-controlled trial of no-cost, 22-mg, 24-hour patch therapy or an open-label trial of the same therapy with patches purchased by the participants. Patients included in the study were self-selected but received no adjuvant behavioral treatment as a smoking cessation aid. Self-help written material was provided.

Safety and Tolerability

Transdermal nicotine patch therapy in the Hays et al trial was generally safe and well tolerated, with no new adverse effects reported. Most common adverse effects were patch site skin reactions and sleep disturbance in the active treatment groups. Cardiovascular adverse events were experienced by

16 of 958 participants (1.6%), with five of these events resulting in hospitalization or emergency care.⁸ Cardiovascular events were reported more in the active treatment study arms. It should be noted, however, that several randomized controlled trials support the nicotine patch usage in patients with cardiovascular disease.^{9–12} Withdrawal symptom scores did not differ significantly between the groups across the 6-week treatment phase. There were no differences in dropout rates across the three groups. Week 6 dropout rates were 46%, 43%, and 42% in the placebo, active nonpaying, and open-label paying groups, respectively.⁸

Efficacy

Both the paying and nonpaying groups receiving active patch therapy had significantly higher smoking cessation rates than the placebo group at the end of 6 and 24 weeks. Abstinence was measured by both self-report and biochemical assessment. Quit-rates were 16.8% (placebo 9.6%) at week 6 and 8.7% (placebo 4.3%) at week 24 for the blinded nonpaying groups confirmed by expired carbon monoxide measurements ($P < .05$), resulting in a number needed to treat (NNT) of 14 and 23 at weeks 6 and 24, respectively. Quit rates in the open-label paying group were 19.0% at week 6 and 10.8% at week 24.⁸ Positive correlation for success included a lower Fagerstrom test for nicotine dependence score, fewer cigarettes per day at baseline, male sex, absence of other household smokers, and long periods of previous abstinence from cigarettes. These findings support the efficacy of nicotine patches when obtained without a prescription. These data also support the conclusion of the

Table 2. Meta-analysis: Efficacy, Estimated Abstinence Rates, and Number Needed to Treat for First-line Pharmacotherapy in the Treatment of Tobacco Use and Dependence.

Pharmacotherapy	Number of Studies	Estimated Odds Ratio (95% CI)*	Estimated Abstinence Rate (95% CI)*	Number Needed to Treat
Placebo	2	2.1 (1.5, 3.0)	17.3	9.0
Bupropion sustained release			30.5 (23.2, 37.8)	
Placebo	13	1.5 (1.3, 1.8)	17.1	11.0 (2 mg)
Nicotine gum			23.7 (20.6, 26.7)	9.4 (4 mg)
Placebo	4	2.5 (1.7, 3.6)	10.5	8.1
Nicotine inhaler			22.8 (16.4, 29.2)	
Placebo	3	2.7 (1.8, 4.1)	13.9	6.0
Nicotine nasal spray			30.5 (21.8, 39.2)	
Placebo	27	1.9 (1.7, 2.2)	10.0	23.0
Nicotine patch			17.7 (16.0, 19.5)	

*From *Treating Tobacco Use and Dependence*, US Department of Health and Human Services, June 2000.

previous meta-analyses in TTUD of an approximate doubling (odds ratios of 2.1–2.6, Table 2) of smoking cessation with active patch use when compared with placebo.^{13–16}

Price

The average price for treatment using nicotine patches ranges from \$3.50 to \$3.89 per day and depends on the strength of the product (Table 3). The nicotine patch can be worn unobtrusively and delivers a constant level of nicotine. Wearing the patch only during waking hours is as effective as wearing it continuously. Eight weeks of patch therapy is as effective as longer courses, and there is no evidence that tapered therapy is better than abrupt withdrawal. High-dose patch use shows marginal efficacy compared with the standard-dose patch. No current evidence supports the routine use of the nicotine patch at doses higher than 22 mg/24 h. A repeated course of therapy in relapsed patients results in minimal additional probability of quitting.¹⁷

Nicotine Gum as a Smoking Cessation Aid

Nicotine gum has been available since 1984 and available without a prescription since 1996. Thir-

teen nicotine gum studies met TTUD inclusion criteria. Since TTUD was published, two clinical trials using nicotine gum and a 5-year follow-up of nicotine gum data from the Lung Health Study have been published.^{18–20} Abstinence was biochemically confirmed in all three studies.

Safety and Tolerability

The tolerability of nicotine gum is high. Approximately one third of abstinent patients at 1 year were still using nicotine gum in a study of high- and low-dependence smokers. Low-dependence smokers (n = 263) were defined as patients who scored 0 to 3 on the heaviness of smoking index, and high-dependence smokers (n = 345) scored 3 to 6. The index assesses dependence based on two questions: the number of cigarettes smoked per day, and the time of waking to the first cigarette. High-dependence smokers reported more adverse events, such as nausea, vomiting, dizziness, and palpitations, at rates of 1.4%, 2.8%, and 5.6% with placebo, 2-mg, and 4-mg strength gum, respectively. Only 1.8% of low-dependence smokers on 4-mg gum reported any of the above adverse effects. Three participants withdrew because of adverse events; 2 patients experienced nausea and

Table 3. Cost of Drug Therapy.

Drug	Cautions	Adverse Effects	Dosage	Duration	Approximate Cost per Day*
Sustained-release bupropion	History of seizure or eating disorder	Insomnia Dry mouth	150 mg every morning for 3 days, then 150 mg twice a day. Start 1–2 weeks before quit date	7–12 weeks up to 6 months for maintenance	\$3.21 (\$1.60 per tablet)
Nicotine gum		Dyspepsia Mouth soreness	1–24 cigarettes per day: 2-mg gum, up to 24 pieces per day 24 cigarettes per day: 4-mg gum, up to 24 pieces per day	Up to 12 weeks	\$5.23 for 10, 2-mg pieces \$5.90 for 10, 4-mg pieces
Nicotine inhaler		Local irritation of mouth and throat	6–16 cartridges a day	Up to 6 months	\$9.71 for 10 cartridges
Nicotine nasal spray		Nasal irritation	8–40 doses a day	3–6 months	\$4.90 for 12 doses
Nicotine patch		Local skin reaction Insomnia	21 mg/24 h 14 mg/24 h 7 mg/24 h 15 mg/16 h	4 weeks, then 2 weeks, then 2 weeks 8 weeks	\$3.89 (21 mg) \$3.70 (14 mg) \$3.50 (7 mg) \$3.83 (15 mg)

Chart used with permission from Prescriber's Letter, PO Box 8190 Stockton, CA 95208 (Tel: 209-472-2240, E-mail: mail@pletter.com, www.prescribersletter.com).

*Average wholesale price obtained from 2001/Drug Topics Red Book, Montvale, NJ.

vomiting, and 1 patient with asthma experienced breathing difficulties.¹⁸

An open-label trial of 2-mg nicotine gum with intermittent diet therapy (n = 137) vs a control group (n = 150) was completed in overweight female smokers.¹⁹ In this study 86 women discontinued treatment during the 12 months of treatment, 35 in the diet group and 51 in the control group. The authors did not state the reasons for withdrawal but only that none were due to adverse events.

The Lung Health Study²⁰ was a study of 5,887 smokers with impaired lung function who were offered access to 2-mg nicotine gum and a smoking cessation program (n = 3,923) or a list of community resources for smoking cessation. Participants were evaluated at 1 year and then reevaluated at 5 years to determine whether certain variables from the 1-year assessment period were indicative of success at the 5-year mark. In this study there were very few patients lost to follow-up. At the completion of the study 97% of participants in the intervention group and 96% in the usual care group were enrolled. A total of 98 patients (2.5%) in the smoking intervention group died during the 5-year period of causes not attributed to the use of the gum. Negative predictors were the number of previous quit attempts in men older than 49 years of age and the use of smoking to cope with emotions. Adverse events attributed to gum use were not included in the final analysis.

Efficacy

In the TTUD studies using nicotine gum, the mean abstinence rate at 6 months was 23.7% vs 17.1% using placebo. The number needed to treat was 15. Garvey et al,¹⁸ in a study using nicotine gum, assigned high- and low-dependence smokers to placebo, 2-mg, or 4-mg strength gum for 2 months with a tapering schedule based on gum usage. Participants also received brief counseling at each follow-up visit. The combined quit rates at 1 year were 8.4% with placebo, 17.3% with 2-mg, and 19.7% with 4-mg doses. The differences in cessation rates were statistically significant compared with placebo for both the 2-mg and 4-mg strength gum. The number needed to treat using the 2-mg gum was 11.2, whereas the number needed to treat using the 4-mg gum was 9.4. Evidence suggests the 4-mg strength is more effective

than 2-mg strength in highly dependent smokers, ie, smoking more than 25 cigarettes a day.

An open-label trial of 2-mg nicotine gum with intermittent diet therapy (n = 137) vs a control group (n = 150) was completed in overweight female smokers.¹⁹ Participants met for 11 behavioral counseling sessions during a 16-week period, and the diet group received a modified, fasting low-calorie liquid diet for three 2-week intervals (weeks 1–2, 7–8, and 13–14). The quit rates at 1 year were 28% in the diet-gum group vs 16% in the control group ($P = .02$). The number needed to treat in the diet and therapy trial was 12.5. At 1 year, no difference in weight gain was found between nonsmokers in the diet group and nonsmokers in the control group. Successful quitters during the 16-week period used 7.8 pieces per day in the diet group and 8.3 pieces per day in the control group. Forty-seven percent of 201 patients at 1 year of follow-up were still using the 2-mg strength gum. Rhinitis and headache were the most common side effects reported (diet group – 59%, control group – 37%). The number needed to harm for rhinitis and headache in the dieters was 4.5.

At 1 year 35% (n = 1,338) of participants were abstinent. At 5 years 22% (n = 835) of patients remained abstinent. Regression analysis indicates that patients using the gum after 1 year were less likely to remain abstinent at 5 years. Cessation rates for these latest trials were similar to those reported in TTUD.

Price

The price for treatment using nicotine gum is highly competitive and comparable to that of the nicotine patch (Table 3). High-dependence smokers used approximately two more pieces of gum per day during the first 60 days of treatment.¹⁸ This amount would potentially increase the cost of treatment by 20% or an additional \$31.00 per month for 2-mg strength and an additional \$35.40 for 4-mg strength gum.

Nicotine Inhaler and Nicotine Nasal Spray as Smoking Cessation Aids

The nicotine nasal spray and inhaler were introduced to the US market in 1997 and 1998, respectively, as prescription smoking cessation medications. Whereas the patch and the gum were well

established as smoking cessation aids, the inhaler was designed to ameliorate behavioral activity associated with tobacco dependence.

Safety and Tolerability

Most safety concerns with the nicotine inhaler and spray involve use in pregnancy, during lactation, and in cardiovascular disease. As with all nicotine-replacement therapy, pregnant smokers should be encouraged to quit without pharmacologic treatment. Prescription nicotine-replacement therapy products are classified as category D for use during pregnancy. The Food and Drug Administration has recently revised the warning concerning nicotine-replacement medicine during pregnancy stating, "Smoking can seriously harm your child. Try to stop smoking without using any nicotine-replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known."²¹ Nicotine-replacement medicine should be avoided during lactation. Those patients who have had a recent myocardial infarction (within 2 weeks), a serious arrhythmia, or worsening angina pectoris should use nicotine inhalers and spray cautiously and only under the direction of their physician.

Nicotine inhalers and nasal spray use is limited by nasal and airway reactions. There is less irritation with the inhaler than with the nasal spray. Forty percent of patients using the nicotine inhaler experience mouth and throat irritation ie, coughing 32%, and rhinitis 23%. The nicotine nasal spray, however, was associated with moderate to severe nasal irritation in 94% of the users in the first 48 hours and in 81% after 3 weeks. The nicotine inhalers and nicotine nasal spray should be prescribed carefully to patients with perennial rhinitis, history of recurrent epistaxis, acute rhinosinusitis, and severe reactive airway disease.²¹ The incidence of side effects for both the inhaler and the nasal spray is directly proportional to the amount of product used by the patient. Recommended doses for the nicotine inhaler ranges from 6 to 16 cartridges per day and for the nicotine nasal spray, from 8 to 40 sprays per day. Although many of the side effects subside within the first few days of use, clinicians should warn patients about the relatively high incidence of mild side effects, such as nasal irritation, cough, and rhinitis.²¹

Efficacy

The TTUD analyzed seven studies and reported abstinence rates of 22.8% and 30.5% (placebo 10.5% and 13.9%) for the nicotine inhaler and the nicotine nasal spray, respectively.⁵ Hajek et al,²² in the first study comparing all four nicotine-replacement therapies, although only 12 weeks in duration, found no difference in effects on withdrawal discomfort, urges to smoke, or abstinence rates. This study further supports the Cochrane Review recommendations that there is minimal direct evidence to recommend one nicotine-replacement therapy than another and that individual preferences should be considered.¹⁷ This outcome held true, despite the relative underuse of the nasal spray and the inhaler, presumably because of medication side effects. All the commercially available forms of nicotine replacement therapy (nicotine gum, patch, nasal spray, and inhaler) increase quit rates approximately 1.5- to 2-fold when utilized in conjunction with at least brief advice. Because all the trials in the meta-analysis of the TTUD included some amount of behavior counseling, at a minimum physician advice and patient education materials should be given to all recipients of smoking cessation medications.¹⁷

Price

The choice of tobacco dependence treatment should reflect behavioral issues, safety, and tolerability profiles, as well as cost considerations. The cost of the use of the inhaler and spray is quite variable. Nicotine inhaler cartridges cost about \$1.00 each. Average usage will range from 6 to 16 cartridges per day or \$5.82 to \$15.52 per day. Nicotine nasal spray is dispensed as a 10-mL pressurized vial containing 100 doses and costs about \$41.00. Average usage will range from 8 to 40 doses per day or \$3.27 to \$16.33 per day (Table 3). At the maximum recommended dose of 40 doses per day, the nicotine nasal spray might increase cost as much as fourfold that of the nicotine patches. If patients were able to limit the number of nicotine cartridges to 8 to 9 per day, however, the cost would be comparable to that of nicotine patches.

Bupropion Use as a Smoking Cessation Aid

Sustained-release bupropion is the first agent that is not nicotine to receive an indication as a smoking cessation aid in the pharmacologic treatment of

tobacco dependence. The exact action of sustained-release bupropion as a smoking cessation aid is unknown. The therapeutic antidepressant action is hypothesized to be through noradrenaline inhibition or dopaminergic reuptake.

Safety and Tolerability

Sustained-release bupropion has a very low abuse potential in humans. Drug interaction evidence suggests a potential interaction for drugs affecting the cytochrome P-450 (CYP) 2D6 isoenzyme. These drugs would include tricyclic antidepressants, selective serotonin reuptake inhibitors, β -blockers, type 1C antiarrhythmic agents, and certain antipsychotic medications. Sustained-release bupropion is generally well tolerated, with insomnia, headache, and dry mouth being the most common side effects. Estimated risk of seizure is 1 in 1000. Sustained-release bupropion is contraindicated in patients who have a history of or a current seizure disorder, anorexia nervosa, or bulimia.

Efficacy

Two randomized placebo-controlled double-blind clinical trials included in TTUD smoking cessation efficacy of sustained-release bupropion.^{23,24} The trials included groups receiving 300 mg/d for 9 and 6 weeks, respectively. This dose was associated with end-of-treatment point prevalence abstinence rates of 60.2% (placebo 33.8%) after 9 weeks of treatment, and 44.2% (placebo 19.0%) after 6 weeks of treatment. Continuous abstinence rates at 12 months were 24.4% (placebo 5.6%) and 18.4% (placebo 10.5%). Number needed to treat for point prevalence abstinence rates was 3.8 and 3.9 for 9- and 6-week administrations, respectively. The number needed to treat for 12-month continuous abstinence rates for 9- and 6-week administrations were 5.3 and 12.7, respectively.

Since the publication of TTUD, Hayford et al²⁴ used a randomized, double-blind, placebo-controlled multidose study of sustained-release bupropion to evaluate efficacy in smokers with a former history of major depression or alcoholism. Doses included 100 mg/d, 150 mg/d, and 300 mg/d, with treatment duration of 7 weeks including physician quit advice with counseling components according to the National Cancer Institute guidelines.²⁵ Point prevalence smoking abstinence for each dose (ie, 100 mg/d, 150 mg/d, and 300 mg/d) and placebo at 7 weeks was 29%, 38%, 44%, and 18%. The num-

bers needed to treat with each respective dose of sustained-release bupropion are 9.1 using 100 mg/d, 5 using 150 mg/d, and 3.9 using 300 mg/d. At 12 months, follow-up point prevalence smoking abstinence was 20% using 100 mg/d and 23% using both 150 mg/d and 300 mg/d. Using placebo, the abstinence rate was 12%. The number needed to treat using 12-month point prevalence abstinence rates were 12.5 (100 mg/d), 9.1 (150 mg/d), and 9.1 (300 mg/d). There were no continuous abstinence rates reported. The efficacy of sustained-release bupropion was independent of having a former history of major depression or alcoholism. These patients were predominately white, highly educated, and seeking treatment for smoking cessation.

In adult smokers, the recommended dosage for sustained-release bupropion is 150 mg/d for 3 days and then twice daily with 8 hours between doses for 7 to 12 weeks. A quit date should be set within 2 weeks of beginning bupropion. Recommended administration duration is 7 to 12 weeks with an extended range up to 6 months for those patients continually attempting smoking cessation.²⁶ Sustained-release bupropion, like nicotine-replacement therapy, should be recommended as part of a comprehensive smoking cessation program.

Price

Sustained-release bupropion costs approximately \$1.60/150 mg. Thus, for the initial 3 days of administration, the cost is \$1.60/d, escalating to \$3.20/d as dosage increases to 300 mg. Recommended administration of 7 to 12 weeks would cost \$151.80 to \$264.00. An extended range of 6 months administration would cost \$532.80.

Combination Pharmacotherapy Interventions

Many clinicians anecdotally consider using a nicotine-replacement therapy combination or combination of sustained-release bupropion and nicotine-replacement therapy. Initial clinical trials examining combination strategies have promising results. Only three combination studies were included in TTUD, and these studies contained various combinations of nicotine-replacement therapies under differing conditions. One trial using the combination of nicotine patch and nasal spray compared with the patch alone showed improved efficacy.²⁷

Safety and Tolerability

The safety and tolerability of combination therapies has not been well documented or studied.

Jorenby et al²⁸ compared bupropion with nicotine patch and bupropion combined with nicotine patch. The discontinuance rate for all participants was 34.8%. Participants in the placebo group had the highest rate of discontinued treatment (48.8%). Discontinuance rates were higher for those receiving bupropion and those receiving combined treatment than were those receiving placebo. Relatively few participants discontinued treatment because of adverse events (8.8%). No serious adverse events were attributed to the study medications. There were no significant differences between groups in mean weight gain after 7 weeks. No seizures were reported in any group. Minor nasal irritation was noted in all combinations using the nasal spray (81%).

Efficacy

Sustained-release bupropion alone and sustained-release bupropion with patch had higher abstinence rates compared with nicotine patch alone. Twelve-month abstinence rates were 16.4% for nicotine patch, 30.3% for sustained-release bupropion alone, 35.5% for sustained-release bupropion plus patch, and 15.6% for placebo. There was no significant difference between bupropion and combination therapy. The number needed to treat using the combination of sustained-release bupropion and nicotine patch was 5.0. On their own, these findings are insufficient to define the relative efficacy of the two treatments. Although a lack of strict controls and relatively low number of participants weaken the evidence for the use of combinations, each individual study revealed statistically significant improvement in cessation rates. Physicians may recommend the use of combination nicotine-replacement therapy or nicotine-replacement therapy with sustained-release bupropion, particularly in those patients who have been unable to quit using monotherapy.⁶

Price

The use of two or more agents could be cost prohibitive unless clear evidence surfaces that efficacy is markedly enhanced or it could be shown that patients with comorbidities, such as depression or alcoholism, would have enhanced success.

Summary

First-line pharmacotherapies for tobacco use and dependence (namely, nicotine patch, nicotine gum, nicotine inhaler, nicotine nasal spray, and sustained-release bupropion) are safe and have been empirically determined to be efficacious and should always be considered part of a tobacco treatment intervention program unless contraindicated. Studies published subsequent to the literature synthesized in TTUD support previously determined efficacy of first-line pharmacologic medications for treatment of tobacco use and dependence. Further studies will be necessary to define clearly the efficacy and relative safety of combination treatments.

References

1. Physician and other health-care professional counseling of smokers to quit—United States, 1991. *MMWR Morb Mortal Wkly Rep* 1993;42:854–7.
2. Hayward RA, Meetz HK, Shapiro MF, Freeman HE. Utilization of dental services: 1986 patterns and trends. *J Public Health Dent* 1989;49:147–52.
3. Tomar SC, Husten CG, Manley MW. Do dentist and physicians advise tobacco users to quit? *J Am Dent Assoc* 1996;127:259–65.
4. Fiore MC, Bailey WC, Cohen SJ, et al. Smoking cessation. Clinical practice guideline No. 18. Rockville, Md: US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research: 1996. [AHCPR publication No. 96-0692.]
5. Fiore MC, Bailey WC, Cohen SJ, et al. Treating tobacco use and dependence. Rockville, Md: US Department of Health and Human Services, Public Health Service, 2000. [AHQR publication No. 00-0032.]
6. A clinical practice guideline for treating tobacco use and dependence. The Tobacco Use and Dependence Clinical Practice Guideline Panel, Staff, and Consortium Representatives. *JAMA* 2000;283:3244–54.
7. Articles used in tobacco guideline meta-analyses. Tobacco Cessation Guideline. The Virtual Office of the Surgeon General. Available at <http://www.surgeongeneral.gov/tobacco/meta.htm>. Accessed October 2001.
8. Hays JT, Croghan IT, Schroeder DR, et al. Over-the-counter nicotine patch therapy for smoking cessation: results from randomized, double-blind, placebo-controlled, and open label trial. *Am J Public Health* 1999;89:1701–7.
9. Benowitz NL, Gourlay SG. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol* 1997;29:1422–31.
10. Joseph AM, Norman SM, Ferry LH, et al. The safety of transdermal nicotine as an aid to smoking

- cessation in patients with cardiac disease. *N Engl J Med* 1996;335:1792–8.
11. Mahmarian JJ, Moye LA, Nasser GA, et al. Nicotine patch therapy in smoking cessation reduces the extent of exercise-induced myocardial ischemia. *J Am Coll Cardiol* 1997;30:125–30.
 12. Nicotine replacement therapy for patients with coronary artery disease. Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease. *Arch Intern Med* 1994;154:989–95.
 13. Fiore M, Smith S, Jorenby DE, Baker TB. The effectiveness of the nicotine patch for smoking cessation: a meta-analysis. *JAMA* 1994;271:1940–7.
 14. Silagy C, Mant D, Fowler G, Lodge M. Meta-analysis on efficacy of nicotine replacement therapies in smoking cessation. *Lancet* 1994;343:139–42.
 15. Gourlay S. The pros and cons of transdermal nicotine therapy. *Med J Aust* 1994;160:152–9.
 16. Li Wan Po A. Transdermal nicotine in smoking cessation. A meta-analysis. *Eur J Clin Pharmacol* 1993;45:519–28.
 17. Silagy C, Mant D, Fowler G, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Library* 2000;vol?(4).
 18. Garvey A, Kinnunen T, Nordstrom B. Effects of nicotine gum dose by level of nicotine dependence. *Nicotine Tobacco Res* 2000;2:53–63.
 19. Danielsson T, Rossner S, Westin A. Open randomized trial of intermittent very low energy diet together with nicotine gum for stopping smoking in women who gained weight in previous attempts to quit. *BMJ* 1999;319:490–3.
 20. Murray RP, Gerald LB, Lindgren PG, et al. Characteristics of participants who stop smoking and sustain abstinence for 1 and 5 years in the Lung Health Study. *Prev Med* 2000;30:392–400.
 21. Physician's desk reference. Montvale, NJ: Medical Economics, 1999:1829.
 22. Hajek P, West R, Foulds J, Nilsson F, Burrows S, Meadow A. Randomized comparative trial of nicotine polacrilex, transdermal patch, nasal spray, and an inhaler. *Arch Intern Med* 1999;159:2033–8.
 23. Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337:1195–202.
 24. Hayford KE, Patten CA, Rummans TA, et al. Efficacy of bupropion for smoking cessation in smokers with a former history of major depression or alcoholism. *Br J Psychiatry* 1999;174:173–8.
 25. Glynn TJ, Manley MW. How to help your patients stop smoking: a National Cancer Institute manual for physicians. Bethesda, Md: Smoking, Tobacco, and Cancer Program, Division of Cancer Prevention and Control, National Cancer Institute, US Department of Health and Human Services, Public Health Service, National Institutes of Health, 1989. [NIH publication No. 89-3064.]
 26. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. *BMJ* 2000;321:355–8.
 27. Blondal T, Gudmundsson LJ, Olafsdottir I, Gustavsson G, Westin A. Nicotine nasal spray with nicotine patch for smoking cessation: randomised trial with six year follow up. *BMJ* 1999;318:285–8.
 28. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;34:685–91.