

Bupropion Sustained Release and Smoking Cessation

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The identification of nicotine dependence as a psychiatric disorder and increased knowledge of nicotine's neuropharmacologic effects have stimulated researchers to search for new pharmacologic interventions for smoking cessation. After reviewing the efficacy and safety of bupropion sustained release (SR) as an agent for treating smoking cessation, the Food and Drug Administration recently approved the use of bupropion SR for this indication. This paper reviews nicotine's pharmacologic effects and the factors contributing to the development of nicotine dependence, the general principles and strategies for treating nicotine dependence, and the evidence for the efficacy of bupropion SR as a treatment for smoking cessation. The release of bupropion SR as a treatment for smoking cessation may provide clinicians with additional opportunities to address smoking cessation with their patients.

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Cigarette smoking remains the most important preventable contributor to premature death, disability, and unnecessary health expense in the United States.¹ In the United States alone, cigarette smoking accounts for more than 400,000 deaths each year, and, in 1990, tobacco use accounted for 19% of all deaths.² Based on current worldwide smoking patterns, epidemiologists have estimated that about half a billion of the current world population will eventually be killed by tobacco, and about half of them will be 35-69 years of age when they die.³

The overall prevalence of current smoking in the United States in 1994 was 25.5% (28% of men, 23% of women), representing almost 50 million individuals.⁴ The prevalence of smoking is especially high in psychiatric patients; over 50% of all psychiatric patients and over 80% of patients with substance abuse disorders are current smokers.^{5,6} Although the prevalence of smoking has declined dramatically in the United States since the 1960s, since 1990 there has been little to no change in smoking prevalence.⁴ Several factors contribute to the relatively slow decline in smoking prevalence. Although approximately 70% of current smokers say they want to quit smoking,⁴ only about 20% are actively attempting to do so.⁷ Among the 90% of smokers who attempt to quit smoking on their own, only 3%-5% will achieve successful ab-

stinence after 1 year.⁸ Even when smokers utilize pharmacologic agents or seek assistance from formal treatment programs, relapse rates approach 80%.^{9,10} Perhaps the most important reason that individuals have difficulty quitting smoking is the presence of nicotine dependence, as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).⁹ The identification of nicotine dependence as a psychiatric disorder and increased knowledge of nicotine's effects on multiple neurotransmitter systems have stimulated researchers to search for new pharmacologic interventions for treating smoking. Recently, the Food and Drug Administration (FDA) approved bupropion sustained release (SR) as an agent for smoking cessation. Bupropion's efficacy in treating smoking appears to be mediated by its unique pharmacologic profile, particularly its effects on noradrenergic and dopaminergic systems.

The remainder of this paper will review the following: (1) nicotine's pharmacologic effects and the factors contributing to the development of nicotine dependence, (2) the principles and strategies for treating smokers with nicotine dependence, and (3) the evidence for the efficacy of bupropion as a treatment for smoking cessation.

NICOTINE'S PHARMACOLOGIC EFFECTS AND THE DEVELOPMENT OF NICOTINE DEPENDENCE

Nicotine is a powerful pharmacologic agent with a wide variety of stimulant and depressant effects involving the central and peripheral nervous systems.^{1,11} These effects include increases in brain dopamine, serotonin, endogenous opioid peptides, pituitary hormones, catecholamines, and vasopressin.^{1,11,12} The rewarding properties of nicotine may be related to nicotine's stimulatory effects on dopaminergic pathways in the mesolimbic

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Table 1. Diagnostic Criteria for Nicotine Dependence*

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either:
 - a need for markedly increased amounts of the substance to achieve desired effect
 - markedly diminished effect with continued use of the same amount of substance
2. Withdrawal, as manifested by either:
 - the characteristic withdrawal syndrome for the substance
 - the substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is persistent desire or unsuccessful effort to cut down substance use.
5. A great deal of time is spent in activities necessary to obtain the substance or use the substance.
6. Important social, occupational, or recreational activities are given up or reduced because of substance abuse.
7. Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.

*Adapted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.²³

system.¹³ Brain circuitry centered around these pathways appears to be the substrate for acute positive reinforcement from several psychoactive drugs including cocaine, psychostimulants, and morphine, contributing to their addictive properties.¹⁴ Nicotine also increases attention, memory, and learning in smokers, especially in the setting of low environmental demand, when stimulation is most desirable.¹

Nicotine and Mood Disorders

Nicotine has anxiolytic and antinociceptive effects, and there is evidence that smokers, especially women smokers, are more likely to use cigarettes during stressful situations or in situations involving negative mood.^{1,15} Nicotine's effects on negative mood states in some smokers may help explain the very high prevalence of smoking among patients with depression and other psychiatric disorders.^{5,6} Other lines of evidence support an important relationship between nicotine dependence and mood disorders. Major depression is more common among smokers than nonsmokers, and a first episode of depression is more likely among smokers who meet criteria for nicotine dependence.^{5,16} Also, findings from both epidemiologic and clinical research demonstrate that a history of clinical depression or the presence of depressive symptoms at the onset of smoking cessation treatment decreases the likelihood of quitting smoking.^{5,17,18} Moreover, patients with associated depression who attempt to quit smoking develop withdrawal and depressive symptoms of greater severity than patients without depressive histories or symptoms.^{17,19} The emergence of depressive symptoms during smoking cessation appears to portend failure.⁵ In some patients, acute episodes of depression may actually be pro-

Table 2. Diagnostic Criteria for Nicotine Withdrawal*

- A. Daily use of nicotine for at least several weeks.
- B. Abrupt cessation of nicotine use, or reduction in the amount of nicotine used, followed within 24 hours by four (or more) of the following signs:
 1. dysphoric or depressed mood
 2. insomnia
 3. irritability, frustration, or anger
 4. anxiety
 5. difficulty concentrating
 6. restlessness
 7. decreased heart rate
 8. increased appetite or weight gain
- C. The symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- D. The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

*Reprinted from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.²³

voked by smoking cessation.²⁰⁻²² The strong relationship between nicotine dependence and depression has led to clinical trials of antidepressants for smoking cessation. The effectiveness of bupropion as a treatment for smoking will be discussed below.

Nicotine as a Drug of Abuse

Nicotine rapidly accumulates in the brain after cigarette smoking, achieving maximum brain concentrations within several seconds.¹ The rapid accumulation of nicotine in the brain in combination with nicotine's effects on brain activity and function provides optimal conditions for the development of drug dependence.¹ Acute and chronic tolerance to many effects of nicotine contributes to an increase in cigarette consumption, as individuals smoke more to obtain desired effects of nicotine.^{1,11}

The characteristics and patterns of chronic nicotine use have much in common with the use of other psychotropic drugs: humans will self-administer nicotine in the laboratory to reproduce desired effects; patterns of relapse to smoking after smoking cessation are quite similar to the patterns noted after treatment for other forms of drug abuse and dependence; chronic nicotine use produces tolerance; and a withdrawal state is noted with abstinence.^{1,9,11}

Nicotine is among the drugs that produce psychoactive substance dependence, as defined by DSM-IV criteria.²³ Eighty-seven percent of adult daily smokers are believed to meet criteria for nicotine dependence.⁹ The diagnosis of nicotine dependence by these criteria requires evidence for any three of seven criteria. The criteria are listed in Table 1. A nicotine withdrawal syndrome, defined by DSM-IV criteria listed in Table 2, is experienced by approximately 50% of smokers who make a serious attempt to quit smoking.^{23,24} In addition, craving, a desire for sweets, and impaired performance on vigilance tasks can

Table 3. Recommendations of the AHCPR Smoking Cessation Clinical Practice Guideline*

Effective smoking cessation treatments are available, and every patient who smokes should be offered one or more of these treatments.

It is essential that clinicians determine and document the tobacco-use status of every patient treated in a health care setting.

Brief cessation treatments are effective, and at least a minimal intervention should be provided to every patient who uses tobacco.

A dose-response relation exists between the intensity and duration of a treatment and its effectiveness. In general, the more intense the treatment, the more effective it is in producing long-term abstinence from tobacco.

Three treatment elements, in particular, are effective, and one or more of these elements should be included in smoking cessation treatment:

- Nicotine replacement therapy
- Social support (clinician-provided encouragement and assistance)
- Skills training/problem solving (techniques on achieving and maintaining abstinence)

Effective reduction of tobacco use requires that health care systems make institutional changes that result in systematic identification of, and intervention with, all tobacco users at every visit.

*From reference 10.

occur.^{24,25} The signs and symptoms of the nicotine withdrawal syndrome can appear within 2 hours after the last use of tobacco, usually peak between 24 and 48 hours after cessation, and usually last from a few days to 4 weeks, although craving and hunger can persist for months.²⁴ The mean decrease in heart rate is 8 beats per minute, and the mean weight gain is 2–3 kg.²⁴

TREATMENT OF NICOTINE DEPENDENCE

In the last year, two important guidelines have been released to assist clinicians in delivering effective smoking cessation interventions: the *Clinical Practice Guideline on Smoking Cessation*, released in April 1996 by the Agency for Health Care Policy and Research (AHCPR)¹⁰; and the *Practice Guideline for the Treatment of Patients with Nicotine Dependence*, released in October 1996 by the American Psychiatric Association (APA).⁹ The AHCPR guideline is intended primarily for the use of primary care providers, while the APA guideline was created principally for psychiatrists. The recommendations of both of these guidelines will be briefly reviewed in the following sections. It should be noted that neither of these guidelines made specific recommendations regarding the use of bupropion, as data regarding bupropion's efficacy were not available for review when the APA and the AHCPR guideline panels conducted their deliberations.

The AHCPR Guideline's Recommendations

The principal recommendations of the AHCPR Smoking Cessation Guideline Panel, listed in Table 3, are based on evidence that is primarily derived from meta-analyses of published randomized controlled trials.¹⁰ The findings of the AHCPR Panel include the following: (1) the use of sys-

tems that identify and document smoking status result in significantly higher rates of smoking cessation interventions by clinicians, as well as higher quit rates among patients who smoke; (2) brief advice (less than 3 minutes) by a clinician significantly increases quit rates by about 30% compared with the absence of such advice; (3) smoking cessation interventions delivered by any type of health care provider increase cessation rates, and interventions delivered by multiple types of providers increase the likelihood of smoking cessation by a factor of almost four, suggesting that smoking cessation interventions should be delivered by as many clinicians and types of clinicians as feasible; and (4) there is a strong "dose-response" relationship between the intensity of person-to-person contact and successful smoking cessation outcome.¹⁰ Although even brief counseling significantly increases quit rates, cessation rates approach 20% (compared with 8.8% for a no contact reference group) for 10 minutes or more of counseling during a single clinical contact.¹⁰

Based on their analyses of the scientific literature, the AHCPR Panel also found evidence that three specific types of behavioral and psychosocial interventions are efficacious: (1) problem solving/skills training; (2) social support provided within the treatment setting; and (3) aversive smoking procedures.¹⁰ Finally, the AHCPR Panel also found that nicotine gum and transdermal nicotine are efficacious as smoking cessation interventions regardless of the intensity of adjuvant psychosocial interventions.¹⁰

In addition to providing recommendations for clinicians, the AHCPR Panel also recommended that health care systems (1) implement a tobacco-user identification system in every clinic, (2) provide education and resources to promote provider intervention, (3) dedicate staff to providing smoking cessation interventions and assessing the effectiveness of treatment, (4) promote hospital policies that support smoking cessation services, (5) include smoking cessation treatment as paid services for all subscribers of health insurance packages, and (6) reimburse fee-for-service clinicians for delivery of effective smoking cessation treatments.¹⁰ The inclusion of specific recommendations for coverage and reimbursement of smoking cessation services is unusual for an AHCPR guideline and reflects the failure of the health insurance industry to provide adequate coverage for this crucially important preventive service.

The APA Guideline's Recommendations

In contrast to the AHCPR guideline, the APA Practice Guideline for the Treatment of Nicotine Dependence was developed specifically for psychiatrists.⁹ Although the recommendations of the APA guideline largely parallel those of the AHCPR, the APA guideline includes additional recommendations that focus on the management of psychiatric patients. Also, the APA Working Group was more inclusive when considering scientific evidence regarding the

Table 4. Recommendations of the APA Practice Guideline for the Treatment of Patients With Nicotine Dependence*

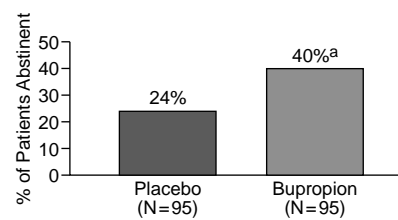
| Recommended Treatments | |
|------------------------|---|
| Psychosocial therapies | |
| | Multicomponent behavioral therapy [I] |
| | Skills training/relapse prevention [II] |
| | Stimulus control [II] |
| | Rapid smoking [II] |
| | Self-help materials [II] |
| Somatic therapies | |
| | Nicotine gum [I] |
| | Transdermal nicotine [I] |
| | Nicotine gum or transdermal nicotine + behavioral therapy [I] |
| | Nicotine gum + transdermal nicotine [I] |
| | Clonidine [II] |
| | Nicotine nasal spray [II] |
| Promising therapies | |
| | Intensive behavioral therapy [III] |
| | Educational/supportive groups [III] |
| | Exercise [III] |
| | Hypnosis [III] |
| | Nicotine inhaler [III] |
| | Antidepressants [III] (includes bupropion) |
| | Anorectics [III] |
| | Bupirone [III] |
| | Higher-than-normal dose transdermal nicotine [III] |
| | Mecamylamine [III] |
| | Sensory replacement [III] |

*Adapted from reference 9. The numerals in brackets refer to the strength of the APA Nicotine Dependence Guideline Working Group's recommendation. These levels are defined as follows:

I = Recommended with substantial confidence based on multiple randomized controlled trials; II = Recommended with moderate confidence based on few positive studies or less consistent data from multiple sources; and III = Recommended with lower confidence based on individual circumstances or expert opinion.

efficacy of interventions. Therefore, several interventions not mentioned in the AHCPR guideline are listed as effective or promising in the APA guideline. The interventions recommended by the APA guideline are listed in Table 4. Included among the recommended therapies in the APA, but not the AHCPR guideline, are nicotine nasal spray, clonidine, the combination of nicotine gum and transdermal nicotine and two nonpharmacologic therapies, stimulus control, and self-help materials. Nicotine nasal spray has been approved by the FDA and is available by prescription, whereas nicotine gum and transdermal nicotine are now available over-the-counter. Meta-analyses have demonstrated that nicotine replacement with gum or patch increases long-term quit rates by a factor of 1.4–2.6 when compared with placebo, even when provided with no adjuvant behavioral therapy.^{9,10,26–31} Long-term abstinence rates of 25%–40% can be achieved when nicotine replacement is provided in combination with group-based behavioral treatment,^{27,32} whereas long-term abstinence rates of 10%–20% are achieved when nicotine replacement is provided with brief counseling in primary care settings.^{32,33} Nicotine nasal spray appears to produce similar outcomes.^{9,31,34}

Antidepressants (including bupropion), anorectics, bupirone, mecamylamine, the nicotine inhaler, exercise, and

Figure 1. 4-Week Smoking Cessation Outcomes of Bupropion Versus Placebo in a Veterans Hospital Outpatient Setting.*

*From reference 36.

^ap < .02 vs placebo.

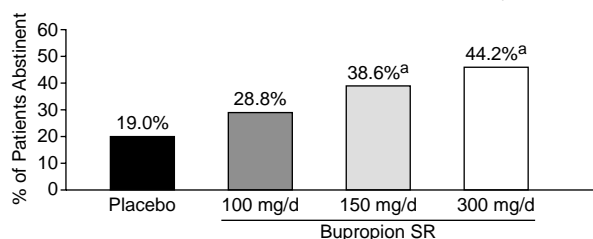
hypnosis are among the treatments listed as promising in the APA guideline.⁹ The reader is referred to the APA guideline for a discussion of the evidence supporting the use of these treatments. The APA guideline also provides useful recommendations regarding the timing of smoking cessation attempts in psychiatric patients and provides an excellent overview of behavioral and psychotherapeutic strategies for motivating patients to quit smoking and successfully treating smokers when they are ready to quit.⁹

Bupropion as a Treatment for Smoking Cessation

As noted previously, the relationships between nicotine dependence and mood disorders led researchers to consider antidepressants as potential treatments for smoking cessation. Bupropion is an antidepressant that exhibits both noradrenergic and dopaminergic activity. Ferry and Burchette³⁶ first noted spontaneous quitting in patients treated with bupropion for depression at a Veterans Administration hospital clinic in California. After an open trial of bupropion suggested efficacy for smoking cessation, Ferry and Burchette conducted the first randomized controlled trial of bupropion in a sample of 190 nondepressed veterans (84% male; all smoked > 20 cigarettes per day; all had failed previous quit attempts). In a presentation at the annual meeting of the American Psychiatric Association in 1994, Ferry and Burchette reported the results of this double-blind placebo controlled trial of 12 weeks of 300 mg/day of bupropion (Figure 1). Each patient also received weekly group behavioral treatment for 16 weeks. Efficacy was assessed using a criterion of 4 weeks of continuous abstinence during the medication phase, confirmed by salivary cotinine measurement. Forty percent of the bupropion group achieved 4-week abstinence compared with 24% in the placebo group (p < .02).³⁶

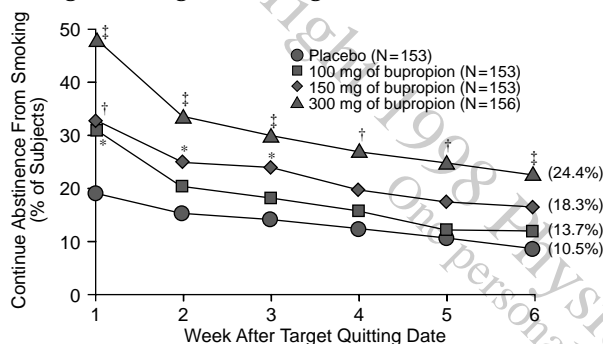
Subsequently, a multisite placebo-controlled, dose-response trial of a sustained-release form of bupropion was conducted among 615 subjects (55% female; mean age = 44; mean smoking rate = 27 cigarettes/day; 94% with a previous serious attempt to quit smoking).³⁷ Patients were randomly assigned to one of four conditions: (1) placebo, N = 153; (2) bupropion SR 100 mg/day,

Figure 2. End-of-Treatment 1-Week Abstinence Rates in a Bupropion Sustained Release Dose-Response Study.*



*Data from reference 38.
^a $p < .001$ vs placebo.

Figure 3. Rates of Confirmed Continuous Abstinence From the Target Quitting Date Through the End of Treatment^a



^aFrom reference 38, with permission. Self-reported abstinence was confirmed by a finding of an expired carbon monoxide concentration of 10 ppm or less. All subjects are included at all time points.
^{*} $.01 < p \leq .05$ vs placebo.
[†] $.001 < p \leq .01$ vs placebo.
[‡] $p \leq .001$ vs placebo.

N = 153; (3) bupropion SR 150 mg/day, N = 153; or (4) bupropion SR 300 mg/day, N = 156. Patients received 7 weeks of drug treatment, which was started 1 week before the patient attempted to quit smoking. Patients also received weekly brief counseling during the drug treatment phase and a telephone call 3 days after their target quit day. Carbon monoxide–confirmed 1-week abstinence rates at the end of drug treatment, 6 weeks after the quit day, are displayed in Figure 2. The results suggest a dose-response effect for bupropion SR. Both the 150 mg and the 300 mg doses were significantly more effective than placebo in achieving end-of-treatment abstinence ($p < .001$).³⁸ At the end of 1 year of follow-up, carbon monoxide–confirmed 1-week cessation rates were also significantly higher than placebo for the 150 mg and 300 mg SR conditions (23% versus 12%; $p < .05$).³⁸ The rates of continuous abstinence from the quit date through the end of treatment are presented in Figure 3. The rate of continuous abstinence was significantly greater in the 300 mg bupropion SR condition compared with placebo ($p = .001$).³⁸

Preliminary results of a study combining bupropion SR and transdermal nicotine were reported at the FDA Drug

Table 5. Adverse Events Occurring in $\geq 5\%$ of Subjects Receiving Bupropion SR 300 mg/day in the Dose-Response Study*

| |
|-------------------------|
| Insomnia ^a |
| Headache |
| Dry mouth ^a |
| Dizziness |
| Disturbed concentration |
| Nausea |
| Constipation |
| Abnormal dreams |
| Arthralgia |
| Back pain |

*Data on file, Glaxo Wellcome.

^aSignificantly greater occurrence rate in active treatment vs. placebo; $p < .05$.

Abuse Advisory Committee Meeting, December 12, 1996, in Rockville, Md. (data on file, Glaxo Wellcome). In this multisite study, 893 subjects were randomly assigned to four conditions: (1) placebo patch/placebo pill, (2) placebo patch/bupropion SR 300 mg/day, (3) active 21 mg/day nicotine patch/placebo pill, or (4) active 21 mg nicotine patch/bupropion SR 300 mg/day. As in the dose-response study, subjects received 1 week of bupropion or placebo prior to quitting smoking and 6 weeks of oral drug or placebo after quitting smoking. The 21 mg/day nicotine patch was continued for 6 weeks, and then the dose was tapered to 14 mg/day for 2 weeks before discontinuation. Patients received the same adjuvant therapy as in the dose-response study. Preliminary end-of-treatment (study Week 9) results suggest that bupropion SR 300 mg/day increased quit rates by a factor of 3, compared with placebo, whereas the combination of bupropion SR and nicotine patch increased quit rates by a factor of 4.5. The preliminary results presented at the FDA Drug Abuse Advisory Committee Meeting also suggested that bupropion SR alone significantly outperformed nicotine patch alone at the end of treatment ($p < .01$). However, these results must be viewed with caution, as they are yet unpublished and because only long-term (greater than 6-month) outcomes are considered acceptable when considering the efficacy of smoking cessation treatments.

The FDA Drug Abuse Advisory Committee also reviewed evidence regarding adverse events reported during smoking cessation trials of bupropion SR at the December 1996 meeting (data on file, Glaxo Wellcome). The 300 mg/day dose produced 8%–12% discontinuation rates due to adverse events. The most common reasons for discontinuation were tremor, rash, headache, and urticaria. Adverse events that occurred in 5% or more of subjects receiving active treatment with 300 mg/day SR in the dose-response study are listed in Table 5. Only insomnia and dry mouth were significantly more likely to occur with active treatment than placebo. No seizures were reported in any of the bupropion SR smoking cessation trials, which included a total of 1828 patients. However, pa-

tients were carefully screened in these trials to exclude patients with a personal or family history of seizures, active alcohol or other substance abuse, or a history of head injury.

In summary, the results of clinical trials have demonstrated that bupropion SR is effective in promoting long-term smoking cessation when combined with brief counseling, bupropion SR 300 mg/day produces the highest short-term quit rates of all tested dosages, and bupropion SR is at least as effective as transdermal nicotine. Preliminary evidence also suggests that combined bupropion SR and transdermal nicotine produces higher quit rates than either treatment alone. After reviewing the evidence demonstrating bupropion's efficacy and safety when used to aid smoking cessation, the FDA approved bupropion SR for a smoking cessation indication. Thus, bupropion SR is the first non-nicotine drug treatment for smoking cessation and the only approved smoking cessation treatment available in pill form.

When used for smoking cessation, bupropion SR should be started at 150 mg q.d. for 3 days, then increased to 150 mg b.i.d. and continued 7 to 12 weeks. Bupropion SR should be initiated 1 to 2 weeks before the patient's quit day. Bupropion SR is contraindicated in patients with a seizure disorder, patients concurrently receiving monoamine oxidase inhibitors (MAOIs), and patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion. Clinicians should not prescribe over 300 mg/day for smoking cessation, and concurrent use of medications that may lower the seizure threshold should be avoided.

The effectiveness of bupropion as a smoking cessation treatment may be related to its effects on noradrenergic and dopaminergic systems.³⁵ As discussed previously, the development of nicotine dependence appears to be related to nicotine's stimulatory effects on dopaminergic pathways in the mesolimbic system, pathways also implicated in the development of dependence on other psychoactive substances.^{13,14} Noradrenergic systems are believed to mediate nicotine's effects on concentration and attention and also mediate nicotine withdrawal.^{12,24} Although bupropion's efficacy as an aid for smoking cessation appears to be independent of its antidepressant effects, there is emerging evidence that antidepressants may be particularly helpful as a smoking cessation treatment for patients with coexisting depressive symptoms.^{39,40} When used as an antidepressant, bupropion appears to have a weight-sparing effect,⁴¹ which may also increase its attractiveness to smokers concerned about weight gain after quitting smoking. Research evaluating bupropion SR's efficacy in promoting smoking cessation in subgroups of smokers with depressive symptoms or concerns about weight gain is anticipated in the near future.

The availability of bupropion SR as a new smoking cessation treatment in the spring of 1997, along with the media attention and promotional activity that will undoubtedly accompany the release, is likely to stimulate thousands of smokers to consider quitting. Clinicians should take advantage of this opportunity to motivate patients to quit smoking and assist those smokers ready to quit, utilizing bupropion when appropriate, as well as other effective treatments for smoking cessation. Psychiatrists and other physicians can prepare for this occasion by becoming more familiar with general treatment principles for smoking cessation as published in the AHCP and APA guidelines (see Tables 3 and 4).^{9,10}

Drug names: bupropion SR (Wellbutrin SR, Zyban), buspirone (BuSpar), clonidine (Catapres), mecamylamine (Inversine), nicotine (Habitrol and others).

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