



Smoking Cessation Agents

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS^{1,2,3,4,5,6,7}

Drug	Manufacturer	Indication(s)
Nicotine Replacement Therapies (NRT)		
nicotine chewing gum; buccal OTC (Nicorette®)	generic, GlaxoSmithKline	For use as an aid to smoking cessation treatment
nicotine lozenge OTC	generic	For use as an aid to smoking cessation treatment
nicotine inhaler (Nicotrol Inhaler®)	Pfizer	For use as an aid to smoking cessation treatment
nicotine nasal spray (Nicotrol® NS®)	Pfizer	For use (not to exceed six continuous months) as an aid to smoking cessation for the relief of nicotine withdrawal symptoms as a part of a comprehensive behavioral smoking cessation program.
nicotine transdermal OTC (Nicoderm CQ®)	generic, GlaxoSmithKline	For use as an aid to smoking cessation as part of comprehensive behavioral smoking cessation program.
Non-Nicotine Replacement Therapies (Non-NRT)		
bupropion sustained release tablets (Buproban®, Zyban®)	generic, Teva, GlaxoSmithKline	For use as an aid to smoking cessation treatment
varenicline tablets (Chantix®)	Pfizer	For use as an aid to smoking cessation treatment

OVERVIEW

Cigarette smoking is the leading preventable cause of death and is responsible for about one in five deaths annually, or about 443,000 deaths per year.⁸ An estimated 49,000 of tobacco-related deaths are the result of secondhand smoke exposure. Approximately 70 percent of smokers have a desire to quit completely and nearly 40 percent attempt to quit each year. Discontinuing smoking often requires multiple attempts. Most attempts are unsuccessful because they are unaided. Relapse is often caused by stress, weight gain, and withdrawal symptoms. Examples of common nicotine withdrawal symptoms include irritability, anxiety, difficulty concentrating, and increased appetite.

The 2008 Clinical Practice Guidelines for Treating Tobacco Use and Dependence from the Agency for Healthcare Research and Quality or AHRQ (formerly Agency for Healthcare Policy and Research) states: All smokers who are trying to quit should be offered medication, except when contraindicated or for specific populations for which there is insufficient evidence of effectiveness (e.g., pregnant women, smokeless tobacco users, light smokers, and adolescents).⁹ All seven of the FDA-approved medications for treating tobacco use are recommended as first-line therapies in these guidelines: bupropion sustained-release (SR) (Buproban, Zyban), nicotine gum (Nicorette, Thrive), nicotine inhaler (Nicotrol), nicotine lozenge, nicotine nasal spray (Nicotrol NS), nicotine patch (Nicoderm CQ), and varenicline (Chantix). Clinicians should consider varenicline 2 mg daily or the combination of nicotine patch plus another form of nicotine replacement therapy (NRT) to be more effective than the nicotine patch alone. Among first-line medications, evidence exists that combining the nicotine patch long-term (18 - 24 weeks) with either nicotine gum or nicotine nasal spray increases long-term abstinence rates relative to placebo treatments. Shorter term use of the nicotine patch (12 weeks) with the nicotine inhaler, or bupropion sustained-release also increases long-term abstinence rates relative to placebo treatments. However, combining varenicline with NRT agents has been associated with higher rates of

adverse effects (e.g., nausea, headaches). Unfortunately, there are no well-accepted algorithms to guide optimal selection among the first-line medications. The higher-dose preparations of nicotine gum, patch, and lozenge have been shown to be effective in highly dependent smokers.¹⁰ Also, there is evidence that combination NRT therapy may also be particularly effective in suppressing tobacco withdrawal symptoms.¹¹ Therefore, it may be that NRT combinations are especially helpful for highly dependent smokers or those with a history of severe withdrawal. Other pragmatic factors that may influence therapy selection include the likelihood of adherence, presence of dentures when considering use of the gum, and dermatitis when considering use of the patch.

Second-line medications are medications, for which there is evidence of effectiveness for treating tobacco dependence, but they have a more limited role than first-line medications because the FDA has not approved them for a tobacco dependence treatment indication and there are more concerns about potential toxicities than exist with first-line medications.¹² Although second-line agents will not be included in this review, the AHRQ guidelines suggest they should be considered only when a patient is unable to use any first-line medications due to contraindications or when no other first-line options have proven to be helpful.

Any medication that has resulted in sustained abstinence from tobacco use in an initial attempt may be helpful to the patient in any subsequent attempts to quit, especially if the medication was tolerable and/or easy to use. However, it is more difficult to draw any firm conclusions from prior failure with a medication.

The success or failure of smoking cessation is influenced by the quality, intensity and frequency of supportive care often offered through formal smoking cessation programs.¹³ There are several smoking cessation treatment strategies that have proven to be effective. These brief clinical interventions include counseling, use of over the counter (OTC) and prescription NRTs (e.g., nicotine gum, nasal spray, inhaler, lozenge and patch) as well as use of prescription Non-NRTs like bupropion SR (Buproban, Zyban) and varenicline (Chantix).

PHARMACOLOGY^{14,15,16,17}

Nicotine, the chief alkaloid in tobacco products, binds stereo-selectively to nicotinic-cholinergic receptors at the autonomic ganglia, in the adrenal medulla, at neuromuscular junctions, and in the brain. Two types of central nervous system (CNS) effects are believed to be the basis of nicotine's positively reinforcing properties. A stimulating effect is exerted mainly in the cortex via the locus ceruleus, and a reward effect is exerted in the limbic system. At low doses, the stimulant effects predominate while at high doses the reward effects predominate.

Bupropion SR (Buproban, Zyban) is a relatively weak inhibitor of the neuronal uptake of norepinephrine and dopamine and does not inhibit monoamine oxidase or the re-uptake of serotonin. The mechanism by which bupropion SR enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms.

Varenicline (Chantix) has high affinity and selectivity for $\alpha_4\beta_2$ neuronal nicotinic acetylcholine receptors where its binding is believed to produce agonist activity while simultaneously preventing nicotine binding to these receptors. As a result of blocking the ability of nicotine to stimulate the central nervous mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward

experienced with smoking is blunted. Varenicline also binds with moderate affinity to the serotonin (5-HT₃) receptor.

PHARMACOKINETICS^{18,19,20,21,22,23}

Drug	Bioavailability (%)	Half-Life (hrs)	Protein Binding (%)	Metabolism
Nicotine Replacement Therapies (NRTs)				
nicotine chewing gum; buccal (Nicorette, Thrive)	50 – 90	Initial: 2 – 3 min Terminal: 0.5 - 2	nr	Liver (extensive first-pass)
nicotine lozenge	nr	nr	nr	nr
nicotine inhaler (Nicotrol Inhaler)	53		nr	Liver (extensive first-pass)
nicotine nasal spray (Nicotrol NS)	53 ± 16	1-2	<5	Liver (majority) kidney and lung
nicotine transdermal (Nicoderm CQ)	unknown	4	nr	Liver (extensive first-pass)
Non-Nicotine Replacement Therapies (Non-NRTs)				
bupropion SR (Buproban, Zyban)	not determined	21	84	Liver (majority) three active metabolites
varenicline (Chantix)	90	24	≤20	Minimal Renal (92 percent unchanged in urine)

CONTRAINDICATIONS/WARNINGS^{24,25,26,27,28,29}

Nicotine Replacement Therapies (NRTs)

Use of nicotine in any form is contraindicated in patients with known hypersensitivity or allergy to nicotine or to any component of the formulation.

Nicotine may cause irritation in the airway and nasal mucosa. Use of nicotine nasal spray (Nicotrol NS) in patients with severe reactive airway disease is not recommended due to reports of exacerbation of bronchospasm in patients with pre-existing asthma. In patients with chronic nasal disorders (nasal polyps, rhinitis, sinusitis and allergy), nicotine nasal spray (Nicotrol NS) is not recommended. Although nicotine inhaler (Nicotrol) has not been studied in asthma or chronic pulmonary disease, it should be used with caution in patients with bronchospastic disease.

Therapy with nicotine gum (Nicorette Gum) should be stopped if oral ulcers occur.

The risks of nicotine replacement in patients with cardiovascular and peripheral vascular diseases as well as select gastrointestinal diseases should be weighed against the benefits of including nicotine replacement in a smoking cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias,

vasospastic diseases (Buerger's disease, Prinzmetal's variant angina and Raynaud's phenomena), or peptic ulcer disease should be evaluated carefully before nicotine replacement is initiated.

varenicline (Chantix) and bupropion SR (Zyban)

Bupropion SR (Buproban, Zyban) is contraindicated in patients with seizure disorder, hypersensitivity to any of the medication components, and in patients using any other medication containing bupropion due to the dose dependent incidence of seizure. It is also contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa due to higher incidence of seizures reported in patients treated for bulimia with the immediate-release bupropion formulation. Bupropion SR is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines) and should not be administered concurrently with a monoamine oxidase inhibitor (MAOI). At least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with bupropion SR. **Treatment with bupropion SR should not be initiated in a patient who is being treated with reversible MAOI's such as linezolid or intravenous methylene blue.**

Varenicline (Chantix) is contraindicated in patients who have a known history of hypersensitivity reactions or skin reactions to varenicline.

Varenicline is associated with an increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. Even though smoking itself is a risk factor for cardiovascular events, in an efficacy and safety study in 700 smokers aged 35 to 75 years with stable, documented cardiovascular disease (other than, or in addition to, hypertension), varenicline use for 12 weeks was associated with an increase in angina pectoris, nonfatal myocardial infarction, need for coronary revascularization, and new diagnosis of peripheral vascular disease or admission for a procedure for the treatment of peripheral vascular disease over a one year period.

Patients who take varenicline should be aware of the symptoms of cardiovascular toxicities including: shortness of breath or trouble breathing, new or worsening chest pain, and new or worse pain in legs when walking, and should be cognizant that symptoms may present for an extended period after varenicline has been discontinued.

Serious neuropsychiatric events including, but not limited to, depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients on non-nicotine replacement therapies (Non-NRT) and appear as boxed warnings for varenicline and bupropion SR. Some reported cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking a Non-NRT who continued to smoke. All patients being treated with either of these agents should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide, have been reported in some patients attempting to quit smoking. When symptoms were reported, most were during treatment, but some were following discontinuation. These events have occurred in patients with and without preexisting psychiatric disease. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of the non-NRTs; therefore, the safety and efficacy of these products in such patients have not been established. Advise patients

and caregivers to discontinue use of the drug and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in behavior or thinking that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation occurs, however, if symptoms persisted, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of these agents should be weighed against the benefits of their use.

Although bupropion SR is not indicated for the treatment of depression, it contains the same ingredients as Wellbutrin[®], Wellbutrin[®] SR and Wellbutrin[®] XL. Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Zyban formulation is not approved for use in pediatric patients. Screening for bipolar disorder should be performed when initiating treatment with an antidepressant, including bupropion in any formulation, since major depressive episode may be the initial presentation of bipolar disorder. Bupropion SR is not indicated for the treatment of bipolar depression.

Due to the dose-dependent seizure risk associated with bupropion SR, clinicians should not prescribe doses over 300 mg daily for smoking cessation. Additionally, certain predisposing factors may also increase seizure risk including history of head trauma or prior seizure, presence of severe hepatic cirrhosis, CNS tumor, and use of concomitant medications that lower the seizure threshold (e.g., antipsychotics, antidepressants, theophylline, and corticosteroids). Additionally, certain patient specific risks may potentiate seizures including excessive use of alcohol or sedatives; addiction to opiates, cocaine or stimulants; use of OTC stimulants and anorectics; and use of oral hypoglycemics or insulin in the treatment of diabetes. Bupropion SR should not be restarted in patients who experience a seizure during therapy. For patients with severe hepatic impairment, bupropion SR dose should not exceed 150 mg every other day due to the substantially elevated peak bupropion levels and drug accumulation.

Varenicline has been associated with hypersensitivity reactions including angioedema in postmarketing reports. In addition, there have also been reports of serious skin reactions including Stevens-Johnson Syndrome and erythema multiforme. Patients are instructed to immediately discontinue varenicline and seek medical attention if they experience any of these symptoms. There have also been reports of traffic accidents, near-miss traffic incidents, or other accidental injuries in patients who use varenicline. Therefore, caution should be exercised when driving, operating machinery, or engaging in any potentially hazardous activity until it is known how varenicline will affect an individual patient. Nausea is the most common adverse event reported with varenicline. Although most nausea complaints are mild to moderate and often transient; however, for some patients it was persistent over several months.

Pupillary dilation that occurs following use of many antidepressants including bupropion may trigger angle-closure glaucoma in patients with untreated anatomically narrow angles.

DRUG INTERACTIONS^{30,31,32,33}

Smoking cessation, with or without nicotine replacement, may alter the pharmacokinetics of certain concomitant medications.

Drugs that May Require a Decrease in Dose at Cessation of Smoking	Possible Mechanism
acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol or other beta-blockers, theophylline	De-induction of hepatic enzymes upon smoking cessation.
insulin	Increase of subcutaneous insulin absorption with smoking cessation.
adrenergic antagonists (e.g., prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation.
Drugs that May Require an Increase in Dose at Cessation of Smoking	Possible Mechanism
adrenergic agonists (e.g., isoproterenol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation.

Bupropion SR is primarily metabolized to hydroxybupropion by CYP450 2B6 isoenzyme. The potential exists for a drug interaction between bupropion SR and substrates or inhibitors/inducers of CYP2B6 isoenzyme such as orphenadrine, thiotepa, cyclophosphamide, ticlopidine, and clopidogrel. In addition, *in vitro* studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir and efavirenz inhibit the hydroxylation of bupropion.

Bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied. Therefore, coadministration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. Unless the drug is activated by CYP2D6, in which case decreased efficacy should be considered. Bupropion is also extensively metabolized, including via CYP2B6, and may be affected by CYP2B6 inhibitor/inducers. For example ritonavir and efavirenz have been shown to result in significant decreased exposure to bupropion and various bupropion metabolites. Additionally, bupropion SR should be used with extreme caution in combination with other drugs which lower the seizure threshold including antipsychotics, antidepressants, theophylline, systemic steroids, and others.

Bupropion SR given concurrently with amantadine or levodopa has resulted in a higher incidence of adverse effects in patients; concurrent therapy should be taken with caution, using small initial doses and gradual dose increases.

Concomitant use of bupropion SR with reversible MAOIs, such as linezolid or methylene blue, may increase the risk of hypertensive reactions. In cases where urgent treatment with linezolid or methylene blue are required, bupropion SR should be stopped immediately and patients should be monitored for two weeks or until 24 hours after the last dose of linezolid or methylene blue, whichever comes first. Treatment with bupropion SR may be restarted 24 hours after the last dose of linezolid or methylene blue.

Varenicline 1 mg twice daily and transdermal nicotine 21 mg/day for up to 12 days did not affect the nicotine pharmacokinetics, however, the incidence of adverse reactions, including nausea, headache, vomiting, dizziness, dyspepsia, and fatigue, for the combination were greater than for nicotine replacement therapy alone.

ADVERSE EFFECTS^{34,35,36,37}

Drug	Dry Mouth	Headache	Insomnia	Nausea
bupropion SR (Buproban, Zyban)	11 (5)	reported	31 (21)	nr
nicotine nasal spray (Nicotrol NS)	<1	18 (15)	nr	5 (5)
varenicline (Chantix)	4 -6 (4)	15 -19 (13)	18-19 (13)	16 – 30 (10)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all-inclusive. Incidences for the placebo group are indicated in parentheses. nr=not reported

Assessment of adverse events in patients who participated in controlled clinical trials is complicated by the occurrence of signs and symptoms of nicotine withdrawal in some patients and nicotine excess in others. The incidence of adverse events is confounded by the many minor complaints that smokers commonly have, by continued smoking of many patients, and the local irritation from both active drug and the pepper placebo. No serious adverse events were reported during the trials.

Risk of angle-closure glaucoma has been reported with antidepressants including bupropion.

Cardiovascular Events^{38,39}

Although smoking is a risk factor for cardiovascular events, in a study of varenicline in 700 subjects aged 35 to 75 years with stable, documented cardiovascular disease (other than, or in addition to, hypertension), varenicline use for 12 weeks was associated with an increase in a variety of cardiovascular events as compared to placebo over a one year period. A summary of adjudicated events from this study is shown in the following table.

Adjudicated cardiovascular events during the 52-week study period:

Cardiovascular Event	On Treatment (Weeks 1 – 11)		Off Treatment (Weeks 13 – 52)	
	varenicline	placebo	varenicline	placebo
	n=353	n=350	n=353	n=350
Nonfatal myocardial infarction	4 (1.1)	1	3 (0.8)	2 (0.6)
Nonfatal stroke	2 (0.6)	0		
Need for coronary revascularization			7 (2)	2 (0.6)
Angina	13 (3.7)	7 (2)		
Hospitalization for angina pectoris			6 (1.7)	4 (1.1)
New diagnosis of peripheral vascular disease (PVD) or admission for a procedure for the treatment of PVD			5 (1.4)	2 (0.6)
Transient Ischemic Attack (TIA)			1 (0.3)	0

Neuropsychiatric Adverse Events⁴⁰

Some patients have experienced changes in behavior, hostility, agitation, depressed mood, and suicidal thoughts or actions while using varenicline. Some patients had these symptoms soon after they began taking varenicline, and others developed them after several weeks of treatment, or after stopping treatment.

FDA sponsored two observational studies of neuropsychiatric adverse events with varenicline. One was conducted by the Department of Veterans Affairs' (VA) and the other by the Department of Defense (DoD). Both were retrospective cohort studies either evaluating the incidence of mental health hospitalizations among over 28,000 veterans using varenicline or nicotine replacement therapy (NRT) or comparing the acute (30-day) rates of hospitalizations for neuropsychiatric adverse events among new users of varenicline (n=19,933) and NRT patch (n=15,867). Although neither study found a measurable increase in psychiatric hospitalizations with varenicline versus NRT, these results should be interpreted with the limitations of both studies in mind. The sample sizes in both studies were too small to assess rare, idiosyncratic events. Focusing on psychiatric hospitalizations is a useful approach for assessing the risk of serious neuropsychiatric adverse events, but it does not allow an assessment of less severe neuropsychiatric events that did not result in a psychiatric hospitalization (in the periods studied). Although the studies did not find a difference in psychiatric hospitalization risk between varenicline and NRT, they do not exclude the possibility that both treatments carry a similar risk. The manufacturer of varenicline is currently conducting a large safety clinical trial of varenicline to assess neuropsychiatric adverse events as outcomes. Results from this trial are expected in 2017.

Chronic Obstructive Pulmonary Disease⁴¹

In a placebo controlled study in smokers with mild-to-moderate COPD receiving varenicline 1 mg twice daily for 12 weeks adverse events through one year were similar to those seen in studies that were conducted for varenicline's initial approval in 2006, and no new safety concerns were identified.

Drug Abuse and Dependence⁴²

Nicotine NS has a dependence potential intermediate between other nicotine-based therapies and cigarettes. This is the result of differences between cigarettes, nicotine NS, nicotine gum and nicotine patches in pharmacokinetic and dosing characteristics commonly associated with abuse and dependence. Nicotine NS is distinct from other nicotine-based smoking cessation therapies in its greater speed of onset, greater capacity for self-titration of dose, and frequent and rapid fluctuations in plasma nicotine concentration.

SPECIAL POPULATIONS^{43,44,45,46}

Pediatrics

Safety and effectiveness of these products in pediatric patients have not been established. Keep nicotine nasal spray (Nicotrol NS) out of the reach of children and pets.

Pregnancy

Bupropion SR and varenicline are Pregnancy Category C. Nicotine replacement therapies are Pregnancy Category D. The effect of nicotine delivery by Nicotrol NS has not been examined in pregnancy.

Renal Impairment

Nicotine replacement therapy does not require dosage adjustment in the renally impaired.

Bupropion SR should be used with caution in patients with renal impairment, and a reduced frequency of dosing should be considered as bupropion and the metabolites of bupropion may accumulate in such patients to a greater extent than usual.

Varenicline is substantially eliminated by renal glomerular filtration along with active tubular secretion. Dose reduction is not required in patients with mild to moderate renal impairment. However, for patients with severe renal impairment (estimated creatinine clearance <30 mL/min), and for patients with end-stage renal disease undergoing hemodialysis, dosage adjustment is needed.

Hepatic Impairment

Bupropion SR should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency of dosing is required, as peak bupropion levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients.

No dosage adjustment of varenicline is necessary for patients with hepatic impairment.

The pharmacokinetic profile of nicotine has not been studied extensively in special populations including those with hepatic impairment. However, given that nicotine is metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites.

Elderly

No overall differences in safety or effectiveness have been observed between older and younger subjects treated with bupropion SR.

No dosage adjustment of varenicline is recommended for elderly patients.

Studies of nicotine replacement therapies have not included sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.

DOSAGES^{47,48,49,50,51,52,53,54,55}

Drug	Dosage in Adults	Special Dosing Considerations	Availability
Nicotine Replacement Therapies (NRTs)			
nicotine chewing gum; buccal OTC (Nicorette, Thrive)	Adults smoking less than 25 cigarettes daily: 2 mg Adults smoking 25 or more cigarettes daily: 4 mg *Max of 24 pieces daily	12-Week Schedule <ul style="list-style-type: none"> ▪ Weeks 1 to 6: One piece every one to two hours ▪ Weeks 7 to 9: One piece every two to four hours ▪ Weeks 10 to 12: One piece every four to eight hours Chew one piece of gum at a time	2 mg and 4 mg chewing gum
nicotine lozenge OTC	Dosage is dependent on time to first cigarette: If first cigarette is 30 minutes or later after awakening = 2 mg If first cigarette is within 30 minutes of awakening = 4 mg	12-Week Schedule: <ul style="list-style-type: none"> ▪ Weeks 1 to 6: One lozenge every one to two hours ▪ Weeks 7 to 9: One lozenge every two to four hours ▪ Weeks 10 to 12: One lozenge every four to eight hours Do not chew or swallow lozenge. Use beyond six months is not recommended. Gradually reduce dose over twelve weeks	2 mg and 4 mg lozenges
nicotine inhaler (Nicotrol Inhaler)	Initial: 24 to 64 mg (6 to 16 cartridges) daily for up to twelve weeks	After three months gradually reduce dose over six to twelve weeks. Use beyond six months is not recommended	10 mg/cartridge

Dosages (continued)

Drug	Dosage in Adults	Special Dosing Considerations	Availability
Nicotine Replacement Therapies (NRTs)			
nicotine nasal spray (Nicotrol NS)	Initial: One or two doses per hour, as needed whenever patient feels the need to smoke Maintenance: Eight to 40 doses daily for three to six months (one dose = two sprays total or one spray in each nostril)	Min 8 mg daily or 16 sprays Max five doses or ten sprays per hour Max 40 mg daily or 80 sprays (slightly less than a ½ bottle)	Box of four 10 mL bottles (10 mg/mL) (Each 10 mL bottle contains 200 applications and each actuation delivers approximately 0.5 mg nicotine)
nicotine transdermal OTC (Nicoderm CQ)	Adults smoking ≥ 10 cigarettes daily: Start with 21 mg daily for first four weeks then decrease to 14 mg daily for next two weeks then 7 mg daily for next two weeks Adults smoking < 10 cigarettes daily: Start with 14 mg daily for first six weeks then decrease to 7 mg daily for next two weeks	Patch should be applied to intact skin. After transdermal nicotine has been in place for 24 hours, remove and apply a new patch to an alternate skin site. Do not reuse the same skin sites for at least one week.	Transdermal patch: <ul style="list-style-type: none"> ▪ 7 mg/24 hr ▪ 14 mg/24 hr ▪ 21 mg/24 hr
Non-Nicotine Replacement Therapies (Non-NRTs)			
bupropion SR (Buproban, Zyban)	Initiate one to two weeks prior to quit date First three days: 150 mg daily Maintenance Dose: 150 mg twice daily, at least eight hours apart	For smoking cessation, doses above 300 mg/day should not be used	150 mg SR tablets
varenicline tablets (Chantix)	Initiate one week prior to stop smoking date or alternatively, begin varenicline dosing and then quit smoking between days 8 and 35 of treatment <ul style="list-style-type: none"> ▪ 0.5 mg once daily on days one to three ▪ 0.5 mg twice daily on days four to seven ▪ 1 mg twice daily for a total of 12 weeks An additional 12 weeks of treatment is recommended for successful quitters to increase likelihood of long-term abstinence	Reduce the dose in patients with severe renal impairment (estimated creatinine clearance <30 mL/min). Starting dose should be 0.5 mg daily with titration to a maximum of 0.5 mg twice daily	0.5 mg and 1 mg tablets Packages include: Starting Month Pack Pack includes one card of 0.5 mg x 11 tablets and three cards of 1 mg x 14 tablets Continuing Month Pack Pack includes four cards of 1 mg x 14 tablets

Avoid eating or drinking 15 minutes prior to or during chewing of nicotine gum or using nicotine lozenges.

Patients should set a “target quit date” within the first two weeks of treatment with bupropion SR, generally in the second week. Treatment with bupropion SR should be continued for seven to 12 weeks; longer treatment should be guided by the relative benefits and risks for individual patients. If a patient has not made significant progress towards abstinence by the seventh week of therapy with bupropion SR, it is unlikely that he or she will quit during that attempt, and treatment should probably be discontinued. Conversely, a patient who successfully quits after seven to 12 weeks of treatment should be considered for ongoing therapy with bupropion SR.

CLINICAL TRIALS

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

Due to paucity of data in the literature, open labeled trials have been included. Also, some of the study populations consist of small numbers of patients.

varenicline (Chantix) and bupropion SR (Zyban) and placebo

In a randomized, double-blind, parallel-group trial, 1,025 healthy patients who were smokers (≥ 10 cigarettes per day) were enrolled to assess the safety and efficacy of varenicline for smoking cessation compared to bupropion SR and placebo.⁵⁶ Patients had fewer than three months of smoking abstinence in the past year. Patients were randomized to varenicline 1 mg twice daily, bupropion SR titrated to 150 mg twice daily or placebo for 12 weeks with 40 weeks of non-drug follow-up. The completion rates for the 52-week study were 60.5 percent for varenicline, 56 percent for bupropion SR, and 54 percent for placebo. The primary outcome was the exhaled carbon monoxide – confirmed four-week rate of continuous abstinence for weeks nine through 24 and weeks nine through 52. For the first time period, the four-week continuous abstinence rates were 44 percent for varenicline (versus placebo; odds ratio: 3.85; 95%CI, 2.7 to 5.5; $p < 0.001$), 29.5 percent for bupropion SR (versus varenicline; OR, 1.93; 95% CI, 1.95 to 4.91; $p < 0.001$) and 17.7 percent for placebo. Bupropion SR was significantly more efficacious than placebo (OR, 2.0; 95% CI, 1.38 to 2.89; $p < 0.001$). For the time period out to 52 weeks, continuous abstinence rates were 21.9 percent for varenicline versus 8.4 percent for placebo (OR, 3.09; 95% CI, 1.95 to 4.91; $p < 0.001$) and compared to bupropion SR with 16.1 percent (OR, 1.46; 95% CI, 0.99 to 2.17; $P = .057$). Common adverse events were nausea for varenicline (28.1

percent versus placebo 8.4 percent) and insomnia for bupropion SR (21.9 percent versus 12.8 percent for placebo). The manufacturer of varenicline supported the study.

A randomized, double-blind, placebo-controlled trial evaluated the efficacy and safety of varenicline for smoking cessation compared to placebo and bupropion SR in 1,027 adult volunteers who smoked.⁵⁷ Completion rate for the study was 65 percent. Patients were randomized to varenicline titrated to 1 mg twice daily, bupropion SR titrated to 150 mg twice daily, or placebo for 12 weeks. The primary outcome parameter was the continuous abstinence from smoking in the last four weeks of treatment for time period weeks nine to 24 and time period of weeks nine to 52. At the end of treatment, continuous abstinence was achieved by 43.9 percent of varenicline compared to placebo rate of 17.6 percent (OR 3.85; 95% CI, 2.69 to 5.50; $p < 0.001$) and 29.8 percent in the bupropion SR group (OR, 1.90; 95% CI, 1.38 to 2.62; $p < 0.001$). For the first follow-up period, continuous abstinence was achieved by 29.7 percent of varenicline compared to placebo rate of 13.2 percent (OR 2.83; 95% CI, 1.91 to 4.19; $p < 0.001$) and 20.2 percent in the bupropion SR group (OR 1.69; 95% CI, 1.19 to 2.42; $p = 0.003$). For the final time period ending at 52 weeks, continuous abstinence rates were 23 percent for varenicline compared to 10.3 percent with placebo (OR 2.66; 95% CI, 1.72 to 4.11; $p < 0.001$) and 14.6 percent in the bupropion SR group (OR 1.77; 95% CI, 1.19 to 2.63; $p = 0.004$). The most common adverse event with varenicline was nausea (29.4 percent compared to 9.7 percent placebo and 7.4 percent with bupropion SR). The manufacturer of varenicline supported the study.

varenicline (Chantix) and bupropion SR (Zyban) versus varenicline (Chantix) and placebo

A randomized, placebo-controlled, blinded multicenter trial evaluated safety and efficacy of varenicline and bupropion SR ($n = 249$) combination therapy compared to monotherapy with varenicline and placebo ($n = 257$) for 12 weeks in 506 adult smokers.⁵⁸ Completion rate for the study was 62 percent. The primary outcome was abstinence rates measured at week 12, defined as prolonged abstinence from two weeks after the target quit date and 7-day point-prevalence abstinence for the previous seven days. Secondary outcomes were 26 and 52 week prolonged and point-prevalence abstinence rates. Patients were randomized to varenicline titrated to 1 mg twice daily and bupropion SR titrated to 150 mg twice daily or varenicline and placebo. At 12 weeks, prolonged abstinence and seven-day point prevalence abstinence rates for the combination therapy group were 53 percent and 56.2 percent, respectively (OR 1.49; 95% CI, 1.05 to 2.12; $p = 0.03$) compared to 43.2 percent and 48.6 percent, respectively, in the varenicline monotherapy group (OR 1.36; 95% CI, 0.95 to 1.93; $p = 0.09$). At 26 weeks, prolonged abstinence and seven-day point prevalence abstinence rates for the combination therapy group were 36.6 percent and 38.2 percent, respectively (OR 1.52; 95% CI, 1.04 to 2.22; $p = 0.03$) compared to 27.6 percent and 31.9 percent, respectively, in the varenicline monotherapy group (OR 1.32; 95% CI, 0.91 to 1.91; $p = 0.14$). At 52 weeks, abstinence and seven-day point prevalence abstinence rates for the combination therapy group were 30.9 percent and 36.6 percent (OR 1.39; 95% CI, 0.93 to 2.07; $p = 0.11$) compared to 24.5 percent and 29.2 percent, respectively, in the varenicline monotherapy group (OR 1.40; 95% CI, 0.96 to 2.05; $p = 0.08$). Participants in the combination therapy group reported more anxiety and depressive symptoms than the monotherapy group (7.2 percent versus 3.1 percent, and 3.6 percent versus 0.8 percent, respectively). The authors concluded that combination therapy with varenicline and bupropion increased prolonged abstinence in smokers, compared with varenicline alone, but not seven-day point prevalence abstinence at 12 and 26 weeks.

nicotine patch versus varenicline (Chantix)

An open-label, randomized, controlled trial of varenicline (n=16) versus nicotine patch (n=16) was conducted in 32 adult smokers for comparison of efficacy, safety, and withdrawal symptoms.⁵⁹ The primary endpoints were the 12 and 24 week smoking-abstinence rates as well as safety and withdrawal symptoms including stress. No significant difference in abstinence rates was observed between the two groups over weeks 9 to 12 (71.4 percent versus 78.6 percent in the varenicline and nicotine patch groups, respectively), and weeks 9 to 24 (64.3 percent versus 71.4 percent, respectively). The frequencies of inability to concentrate at two, four, and eight weeks, and wakeful nights at two weeks were higher in the varenicline group than in the nicotine patch group. Adverse side-effects associated with a gastrointestinal disorder occurred in 14 cases in the varenicline group compared to only one case in the nicotine patch group, respectively. Conversely, there were no cases of skin allergy in the varenicline group while there were nine cases in the nicotine patch group. The authors concluded that treatment selection requires a balance of time to smoking cessation with expected adverse effects (e.g., psychiatric problems, gastrointestinal problems, skin allergy, etc.).

In a randomized, open-label, Phase 3 trial, varenicline and transdermal nicotine were compared in 746 patients who were smokers (≥ 15 cigarettes per day) over 52 weeks.⁶⁰ Patients were randomized to varenicline titrated to 1 mg twice daily for 12 weeks or transdermal nicotine replacement (21 mg/day reducing to 7 mg/day) for 10 weeks. Follow-up continued through 52 weeks. The study was completed by 62.2 percent and 65.7 percent of patients in the transdermal nicotine replacement and varenicline, respectively. The primary outcomes were confirmed by exhaled carbon monoxide for the last four weeks of treatment, at week 24 and at week 52. Self-reported continuous abstinence rates at the last four weeks of treatment were 55.9 percent for varenicline and 43.2 percent for transdermal nicotine replacement (OR 1.70, 95% CI, 1.26 to 2.28, $p < 0.001$). The week 52 continuous abstinence rate was 26.1 percent for varenicline and 20.3 percent for transdermal nicotine replacement (OR 1.40, 95% CI, 0.99 to 1.99, $p = 0.056$). Nausea was reported by 37.2 percent and 9.7 percent of patients receiving varenicline and transdermal nicotine replacement, respectively. The manufacturer of varenicline supported the study.

nicotine patch versus nicotine lozenge

A randomized, open-label, effectiveness trial compared the effectiveness of transdermal nicotine versus nicotine lozenge for smoking cessation and identified predictors of treatment response at 12 medical sites participating in the National Cancer Institute's Community Clinical Oncology Program.⁶¹ Smokers seeking treatment (n=642) were randomized to 12 weeks of either nicotine transdermal or nicotine lozenge. Smoker characteristics were assessed at baseline, and at the 24-hour point prevalence abstinence confirmed with breath carbon monoxide (CO). Patients were also evaluated at end of treatment (EOT) at 12 weeks and at a six-month follow-up. Although statistically insignificant, there was a trend for higher quit rates for nicotine transdermal versus nicotine lozenge at EOT (24.3 percent versus 18.7 percent, $p = 0.10$) and at six months (15.6 percent versus 10.9 percent, $p = 0.10$). Smoker characteristics identified through a logistic regression model of EOT quit rates showed smokers who preferred nicotine transdermal and had higher quit rates were not reactive to smoking cues and did not use nicotine to alleviate distress or stimulate cognitive function. The authors concluded that nicotine transdermal may be more effective than nicotine lozenge for smokers who do not smoke to alleviate emotional distress or stimulate cognitive function.

bupropion sustained-release (Zyban) versus nicotine transdermal

A nine-week, randomized, placebo-controlled trial was conducted to compare four treatment options: bupropion SR 300 mg daily, nicotine transdermal 21 mg daily, combination of bupropion SR 300 mg daily plus nicotine transdermal 21 mg daily, or placebo.⁶² Treatment with bupropion SR was initiated at 150 mg daily while the patient was still smoking and was increased after three days to 300 mg daily given as 150 mg twice daily. Nicotine transdermal 21 mg daily was added to treatment with bupropion SR after approximately one week when the patient reached the target quit date. During weeks eight and nine of the study, nicotine transdermal was tapered to 14 and 7 mg daily, respectively. Quitting, defined as total abstinence during weeks four through seven, was determined by patient daily diaries and verified by expired air carbon monoxide levels. In this study, patients treated with any of the three treatments achieved greater four-week abstinence rates than patients treated with placebo. Continuous abstinence rates after 12 months were 30 percent (95% CI, 24 to 35) in the bupropion SR group, 33 percent (95% CI, 27 to 39) for patients treated with the combination at 26 weeks compared with 13 percent (95% CI, 7 to 18) in the placebo group. Although the treatment combination of bupropion SR and nicotine transdermal displayed the highest rates of continuous abstinence throughout the study, the quit rates for the combination were not significantly higher ($p>0.05$) than for bupropion SR alone. The prescribing information cautions that none of these comparisons have been replicated and therefore should not be interpreted as demonstrating the superiority of any of the active treatment arms over any other.

bupropion sustained-release (Zyban) versus nicotine transdermal and/or nicotine lozenge

A randomized, double-blind, placebo-controlled trial assessed the relative efficacies of five smoking cessation interventions in adults who were motivated to quit smoking.⁶³ A total of 1,504 adults who smoked at least 10 cigarettes per day during the last six months were randomized to one of the following: nicotine lozenge, nicotine patch, bupropion SR, nicotine patch plus nicotine lozenge, bupropion SR plus nicotine lozenge, or placebo. All patients received six individual counseling sessions. Seven-day point-prevalence abstinence was determined for each participant (question: "Have you smoked at all, even a puff, in the last seven days?") and confirmed by measurement of expired carbon monoxide at one week after quit date (post-quit), end of treatment (eight weeks post-quit) and six months post-quit. All treatments except nicotine lozenge produced higher rates of initial cessation than placebo, and all treatments except nicotine lozenge at one week had higher seven-day point-prevalence abstinence rates at one week, end of treatment, and six months post-quit. All treatments differed from placebo when examined without protection for multiple comparisons (odds ratios, 1.63 to 2.34). With such protection, only the nicotine patch plus nicotine lozenge (odds ratio, 2.34, $p<0.001$) produced significantly higher abstinence rates at six-month post-quit than did placebo. Adverse effects were similar to those reported in other studies of smoking cessation.

SUMMARY

Cigarette smoke can cause serious health problems, numerous diseases, and death. Regardless of the duration of smoking, cessation at any age is beneficial. Tobacco dependence is a chronic condition that often requires repeated interventions, but effective treatments and helpful resources exist.

Cessation medications that have demonstrated efficacy in treating tobacco dependence include: OTC and prescription nicotine replacement therapies in various formulations (e.g., nicotine gum, lozenge, transdermal, nasal spray, or inhaler) and prescription non-nicotine medications (e.g., bupropion

sustained release (Buproban, Zyban) and varenicline tartrate (Chantix). The combination of medication and behavioral therapy is more effective for cessation than either as monotherapy.

REFERENCES

- 1 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 2 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 3 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 4 Available at: <http://www.clinicalpharmacology.com/>. Accessed April 10, 2014.
- 5 Nicotrol [package insert]. New York, NY; Pfizer; December 2008.
- 6 Available at: http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed April 10, 2014.
- 7 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 8 Smoking & Tobacco Use. Fast Facts. CDC/Office on Smoking and Health. Centers for Disease Control and Prevention. Available at: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/fast_facts/index.htm. Accessed April 10, 2014.
- 9 Treating Tobacco Use and Dependence: 2008 Update. Tobacco Use and Dependence Guideline Panel. Rockville (MD): US Department of Health and Human Services; 2008 May. Available at: <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>. Accessed April 10, 2014.
- 10 Hatsukami D, Mooney M, Murphy S. et al. Effects of high dose transdermal nicotine replacement in cigarette smokers. *Pharmacol Biochem Behav*. 2007; 86: 132–9.
- 11 Sweeney CT, Fant RV, Fagerstrom KO. et al. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. *CNS Drugs*. 2001; 15: 453–67.
- 12 Treating Tobacco Use and Dependence: 2008 Update. Tobacco Use and Dependence Guideline Panel. Rockville (MD): US Department of Health and Human Services; 2008 May. Available at: <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>. Accessed April 10, 2014.
- 13 Treating Tobacco Use and Dependence: 2008 Update. Tobacco Use and Dependence Guideline Panel. Rockville (MD): US Department of Health and Human Services; 2008 May Update. Available at: <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>. Accessed April 10, 2014.
- 14 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 15 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 16 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 17 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 18 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 19 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 20 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 21 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 22 Available at: <http://www.clinicalpharmacology.com/>. Accessed April 10, 2014.
- 23 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 24 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 25 Nicorette Gum [labeling]. Parsippany, NJ; GlaxoSmithKline Consumer Healthcare; February 2012.
- 26 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 27 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 28 FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease. June 16, 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm>. Accessed April 5, 2013.
- 29 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 30 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 31 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 32 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 33 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 34 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 35 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 36 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 37 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 38 FDA Drug Safety Communication: Chantix (varenicline) may increase the risk of certain cardiovascular adverse events in patients with cardiovascular disease. June 16, 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm259161.htm>. Accessed April 10, 2014.
- 39 FDA Chantix Supplement Approval Letter. N21-928/S-028. January 20, 2012. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/021928s028ltr.pdf. Accessed April 10, 2014.
- 40 FDA Drug Safety Communication: Safety review update of Chantix (varenicline) and risk of neuropsychiatric adverse events. October 24, 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm276737.htm>. Accessed April 10, 2014.
- 41 FDA Drug Safety Communication: Chantix (varenicline) drug label now contains updated efficacy and safety information. July 22, 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm264436.htm>. Accessed April 10, 2014.
- 42 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 43 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 44 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 45 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.

- 46 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 47 Available at: <http://www.clinicalpharmacology.com/>. Accessed April 10, 2014
- 48 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 49 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 50 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 51 Nicotrol NS [package insert]. New York, NY; Pfizer; June 2010.
- 52 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 53 Chantix [package insert]. New York, NY; Pfizer; February 2013.
- 54 FDA Drug Safety Communication: Chantix (varenicline) drug label now contains updated efficacy and safety information. July 22, 2011; <http://www.fda.gov/Drugs/DrugSafety/ucm264436.htm>. Accessed April 10, 2014.
- 55 Buproban [package insert]. Sellersville, PA; Teva; August 2012.
- 56 Gonazles D, Rennard SI, Nides M, et al for the Varenicline phase 3 study group. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA*. 2006; 296(1):47-55.
- 57 Jorenby DE, Hays JT, Rigotti NA, et al for the varenicline Phase 3 study group. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA*. 2006; 296(1):56-63.
- 58 Ebbert JO, Hatsukami DK, Croghan IT, et al. Combination varenicline and bupropion SR for tobacco-dependence treatment in cigarette smokers: a randomized trial. *JAMA*. 2014; 311(2):155-63. doi: 10.1001/jama.2013.283185.
- 59 Tsukahara H, Noda K, Saku K. A randomized, controlled, open comparative trial of varenicline versus nicotine patch in adult smokers: efficacy, safety and withdrawal symptoms (the VN-SEESAW study). *Circ J*. 2010; 74(4):771-8.
- 60 Aubin HJ, Bobak A, Britton JR, et al. Varenicline Versus Transdermal Nicotine Patch For Smoking Cessation: Results From A Randomised Open-Label Trial. *Thorax*. 2008; 63(8):717-24.
- 61 Schnoll R, Martinez E, Tatum K, et al. Nicotine patch versus nicotine lozenge for smoking cessation: an effectiveness trial coordinated by the Community Clinical Oncology Program. *Drug Alcohol Depend*. 2010; 107(2-3):237-43.
- 62 Zyban [package insert]. Research Triangle Park, NC; Glaxo SmithKline; March 2014.
- 63 Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of five smoking cessation pharmacotherapies. *Arch Gen Psychiatry*. 2009; 66(11):1253-62.