Smoking Cessation Agents
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Nicotine Replacement Therapies (NRT)		
nicotine chewing gum; buccal OTC (Nicorette®)[1]	generic, GlaxoSmithKline	For use as an aid to smoking cessation treatment
nicotine lozenge OTC (Nicorette®)[2]	generic, GlaxoSmithKline	For use as an aid to smoking cessation treatment
nicotine inhaler (Nicotrol Inhaler®)[3]	Pfizer	For use as an aid to smoking cessation treatment
nicotine nasal spray (Nicotrol® NS®)[4]	Pfizer	For use (not to exceed 6 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®)[5]	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 (Zyban®)*[6]	generic, GlaxoSmithKline	For use as an aid to smoking cessation treatment
varenicline tablets (Chantix®)[7]	Pfizer	For use as an aid to smoking cessation treatment

* GlaxoSmithKline has announced Zyban tablets will be discontinued; distribution is expected to cease in July 2019. Product may be available until supplies are depleted.[8]

OVERVIEW

Cigarette smoking is the leading preventable cause of death and is responsible for about 1 in 5 deaths annually, or about 480,000 deaths per year in the United States.[9] More than 41,000 of tobacco-related deaths are the result of secondhand smoke exposure. Approximately 70% of smokers have a desire to quit completely, and 55% have made a quit attempt in the past 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 (AHRQ) 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).[10] All 7 of the Food and Drug Administration (FDA)-approved medications for treating tobacco use are recommended as first-line therapies in these guidelines: bupropion sustained-release (SR) (Zyban), nicotine gum (Nicorette), nicotine inhaler (Nicotrol), nicotine lozenge (Nicorette), 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 NRT to be more effective than the nicotine patch alone. Among first-line medications, evidence exists that combining the nicotine patch long-term (18 to 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.[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 agents for which there is evidence of effectiveness for treating tobacco dependence, but which 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, which include clonidine and nortriptyline, 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 (Zyban) and varenicline (Chantix). The 2012 American Society of Clinical Oncology (ASCO) Tobacco Cessation Guide for Oncology Providers states that treatment efficacy depends on delivery success, and therefore consideration should be given to medical contraindications of pharmacologic treatments (e.g., use of transdermal methods for patients with oral cancers).[14] Data also suggests that combining nicotine products with faster delivery (e.g. gum, lozenge) with slower nicotine delivery method (e.g. transdermal) may improve relief of withdrawal symptoms and increase the likelihood of long-term success.

In their 2015 guidelines, the United States (US) Preventative Services Task Force (USPSTF) recommended that clinicians ask all adults, including pregnant women, about tobacco use and to advise current users to stop using tobacco, and provide behavioral interventions, including approved pharmacotherapy for tobacco use cessation (Level A recommendation).[15] However, evidence is not sufficient to assess benefits versus risks of pharmacotherapy use in pregnant women. In April 2020, the USPSTF issued a recommendation for school-aged children and adolescents who have not started to use tobacco stating that primary care clinicians are recommended to provide interventions (e.g., education or brief counseling), in order to prevent tobacco use initiation in these individuals (Level B recommendation).[16] However, for school-aged children and adolescents who use tobacco, it was concluded the current evidence is inadequate to determine the benefits versus risks of primary care-feasible interventions regarding tobacco cessation (Level I [insufficient] recommendation).

According to the American College of Cardiology (ACC), one-third of deaths in the US attributed to smoking are due to cardiovascular disease (CVD).[17] The ACC 2018 Expert Consensus Decision Pathway on Tobacco Cessation Treatment states that all smokers, regardless of age, duration and heaviness of smoking can benefit from smoking cessation, even those who have already developed CVD. The role of the practitioner is key in the success of smoking cessation. Prescribers must assess, advise, and offer treatment options that work best for the individual. Prescribers should actively connect patients to behavioral support resources and offer pharmacotherapy to each patient, with few exceptions. A combination of pharmacotherapy and behavioral interventions (e.g., cognitive behavior therapy, motivational interviewing) is most effective for cessation. First-line pharmacotherapy for patients with stable CVD in an outpatient setting is varenicline (Chantix) or combination nicotine replacement therapy (NRT) which is comprised of a nicotine patch (Nicoderm CQ) plus nicotine gum (Nicorette), lozenge (Nicorette) or spray (Nicotrol NS), depending on patient's preference. Second-line therapy for patients with stable CVD consists of bupropion (Zyban) or a single NRT product. If a single agent is not effective, the following combinations can be used: varenicline plus a single NRT, varenicline plus bupropion, or bupropion plus a single agent NRT.

In 2020, the American Thoracic Society (ATS) published new clinical practice guidelines on initiation of pharmacotherapy for tobacco dependence in adults.[18] The guidance maintains all patients who are using tobacco should receive treatment for dependence, and not only be encouraged to discontinue tobacco use. Strong recommendations include 1) preference for use of varenicline over a nicotine patch; 2) preference for varenicline over bupropion; 3) use of varenicline rather than a nicotine patch in adults with comorbid psychiatric condition(s); 4) starting varenicline in adults even if they are not ready to quit; and 5) using controller therapy for an extended duration of more than 12 weeks. Conditional recommendations include 1) the combination of a nicotine patch with varenicline over use of varenicline alone and 2) use of varenicline over electronic cigarettes.

PHARMACOLOGY[19,20,21]

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 (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[22,23,24,25,26,27]

Drug	Bioavailability (%)	Half-Life (hrs)	Protein Binding (%)	Metabolism
Nicotine Replacement Therapies (NRTs)				
nicotine chewing gum; buccal (Nicorette)	50 – 90	Initial: 2 – 3 min Terminal: 0.5 - 2	nr	Liver (extensive first-pass)
nicotine lozenge (Nicorette)	nr	nr	nr	nr
nicotine lozenge	nr	2.3	nr	nr
nicotine inhaler (Nicotrol Inhaler)	53	1-2	<5	Liver (majority), kidney, and lung
nicotine nasal spray (Nicotrol NS)	53 ± 16	1-2	<5	Liver (majority), kidney, and lung
nicotine transdermal (Nicoderm CQ)	unknown	3-4	nr	Liver (extensive first-pass)
Non-Nicotine Replacement Therapies (Non-NRTs)				
bupropion SR (Zyban)	not determined in humans	21	84	Liver (majority) 3 active metabolites
varenicline (Chantix)	90	24	≤20	Minimal Renal (92% unchanged in urine)

CONTRAINDICATIONS/WARNINGS[28,29,30,31,32,33]

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 as it is associated with irritant effects. 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 (CV) 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 [MI] and/or angina pectoris), diabetes, seizures, hypersensitivity, serious cardiac arrhythmias, vasospastic diseases (Buerger's disease, Prinzmetal's variant angina, and Raynaud's phenomena), or peptic ulcer disease, including esophagitis and active

gastric ulcers (due to delayed ulcer healing) should be evaluated carefully before nicotine replacement is initiated.

varenicline (Chantix) and bupropion SR (Zyban)

Bupropion SR (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, sedatives (including benzodiazepines), barbiturates, or antiepileptic drugs. Bupropion SR 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 MAOIs, 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.

Serious neuropsychiatric events including, but not limited to, depression, mania, psychosis, hallucinations, paranoia, delusions, anxiety, panic, homicidal or suicidal ideations, suicide attempt, and completed suicide have been reported in patients on non-NRT and appear as 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 pre-existing psychiatric disease. Patients with serious psychiatric illness, such as schizophrenia, bipolar disorder, and major depressive disorder, did not participate in the pre-marketing 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 post-marketing cases, resolution of symptoms after discontinuation occurs; however, if symptoms persist, 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. Previously, this warning was a boxed warning; however, the FDA removed this boxed warnings for these medications in 2016 following an evaluation of the EAGLES trial (described below). The warning for neuropsychiatric adverse effects remains.[34]

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.

Bupropion SR may increase blood pressure. Prior to initiating therapy, blood pressure should be monitored, as well as during the course of therapy, especially if used concomitantly with nicotine replacement.

There have been reports of seizures in patients treated with varenicline. Patients had either no history of seizures or had a history of seizure disorder that was remote or well-controlled. In most cases, the seizure occurred within the first month of therapy. Potential risks and benefits should be considered in patients with a history of seizure disorder before prescribing varenicline. Varenicline should be discontinued immediately if a seizure occurs.

An extensive evaluation of CV risk with varenicline suggests that patients with underlying CV disease may be at an increased risk; however, these risks must be weighed against the benefits of smoking cessation. CV risk associated with varenicline has been assessed in randomized controlled trials and meta-analyses. In a smoking cessation trial in patients with stable CV disease, CV events were rare; however, nonfatal MI and stroke occurred more frequently in the treatment group compared to placebo. All-cause and CV mortality was lower in the treatment group, compared to placebo. Patients should be instructed to consult with their healthcare providers if new or worsening CV symptoms arise and to seek immediate medical attention if they have signs and symptoms of MI or stroke.

Varenicline has been associated with hypersensitivity reactions, including angioedema, in post-marketing reports. Clinical symptoms included swelling of the face, mouth, extremities, and neck. 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. Most nausea complaints are mild to moderate and often transient; however, for some patients, it was persistent over several months.

Somnambulism has been reported with varenicline, including cases with harmful behavior to self, others, or property.

Increased intoxicating effects of alcohol while taking varenicline has been reported post-marketing. Unusual or aggressive behavior, that the patient may not remember, has also occurred post-marketing. Patients should be advised to reduce their alcohol consumption until they know whether varenicline affects their tolerance for alcohol.

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

Risk Evaluation and Mitigation Strategy (REMS)[35,36]

Risk Evaluation and Mitigation Strategies (REMS) were required for bupropion SR (Zyban) and varenicline (Chantix) which included medication guides to inform patients of the risk of neuropsychiatric adverse events. Based on a phase 4, randomized, double-blind, placebo-controlled study in subjects with and without histories of psychiatric disorders REMS requirements were removed in December 2016 for Chantix and in May 2017 for bupropion SR (Zyban).

DRUG INTERACTIONS[37,38,39]

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 is primarily metabolized to hydroxybupropion by CYP450 2B6 isoenzyme. The potential exists for a drug interaction between bupropion 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, co-administration 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 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 may decrease digoxin plasma concentration, and digoxin levels should be monitored.

Bupropion 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 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 is required, bupropion should be stopped immediately and patients should be monitored for 2 weeks or until 24 hours after the last dose of linezolid or methylene blue, whichever comes first. Treatment with bupropion 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[40,41,42]

Drug	Dry Mouth	Headache	Insomnia	Nausea
bupropion SR (Zyban)	11 (5)	reported	31 (21)	9 (4)
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 (CV) Events[43]

Although smoking is a risk factor for CV events, in a study of varenicline in 700 subjects aged 35 to 75 years with stable, documented CV disease (other than, or in addition to, hypertension), varenicline use for 12 weeks was associated with an increase in a variety of CV events, as compared to placebo, over a 1-year period. A summary of adjudicated events from this study is shown in the following table.

Adjudicated CV 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 (MI)	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 Events[44,45]

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.

The FDA sponsored 2 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 EAGLES trial, described in more detail below, assessed the risk of neuropsychiatric adverse effects in patients with or without a neuropsychiatric history. While these adverse effects may still occur with agents in this class, the risk was not higher than the risk with placebo.[46] The FDA determined that the risk was lower than originally suspected and the boxed warning for this risk was removed from their labeling (although a warning for these adverse effects remain).

Chronic Obstructive Pulmonary Disease (COPD)[47]

In a placebo-controlled study in smokers with mild to moderate COPD receiving varenicline 1 mg twice daily for 12 weeks, adverse events through 1 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 Dependence[48]

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[49,50,51]

Pediatrics

Safety and effectiveness of these products in pediatric patients have not been established. Keep nicotine nasal spray (Nicotrol NS) and nicotine inhaler (Nicotrol Inhaler) out of the reach of children and pets. Suspected nicotine poisoning in a child is considered a medical emergency and should be managed immediately.

The safety and efficacy of varenicline (Chantix) were evaluated in patients 12 to 19 years of age. In this population, varenicline did not improve continuous abstinence rates at weeks 9 through 12 of therapy, as compared with placebo. The safety profile of varenicline was consistent with previous results reported in adult studies. Use of varenicline is not recommended in patients less than 16 years of age.

Pregnancy

Bupropion (Zyban) is Pregnancy Category C. While previously Pregnancy Category C, labeling for varenicline (Chantix) was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR); and label states that available data have not suggested an increased risk for major birth defects following exposure to varenicline in pregnancy. 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. However, moderate and severe renal impairment are anticipated to impact the clearance of nicotine and/or its metabolites delivered via nicotine inhaler (Nicotrol Inhaler) or by the nicotine nasal spray (Nicotrol NS); therefore, dose reduction and monitoring for adverse events (e.g., nausea or dizziness) associated with increased levels of nicotine should be considered.

Bupropion SR should be used with caution in patients with renal impairment (glomerular filtration rate: less than 90 ml/min), 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 impairment (Child Pugh Score 7 to 15). 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. In mild hepatic impairment (Child Pugh Score 5 to 6), a reduction in dose and/or frequency should be considered.

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 with potential for increased adverse reactions) should be anticipated. Furthermore, for the nicotine inhaler (Nicotrol Inhaler) and nicotine nasal spray (Nicotrol NS) pharmacokinetic studies in patients with moderate to severe hepatic impairment have demonstrated reduced nicotine clearance; therefore, a dose reduction as well as monitoring for adverse reactions (e.g., nausea or dizziness) associated with increased nicotine levels should be considered.

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[52,53,54,55,56,57,58,59]

Drug	Dosage in Adults	Special Dosing Considerations	Availability
Nicotine Replacement Therapies (NRTs)			
nicotine chewing gum; buccal OTC (Nicorette, Quit)*	Adults smoking less than 25 cigarettes daily: 2 mg Adults smoking 25 or more cigarettes daily: 4 mg *Max of 24 pieces daily 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 ▪ Weeks 1 to 6:1 piece every 1 to 2 hours ▪ Weeks 7 to 9: 1 piece every 2 to 4 hours ▪ Weeks 10 to 12: 1 piece every 4 to 8 hours Chew 1 piece of gum at a time During first 6 weeks of therapy: Chew at least 9 pieces per day for improved outcomes	2 mg and 4 mg chewing gum
nicotine lozenge OTC (Nicorette, Quit)*	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 *Max of 20 lozenges daily *Max of 5 lozenges in 6 hours	12-Week Schedule: ▪ Weeks 1 to 6: 1 lozenge every 1 to 2 hours ▪ Weeks 7 to 9: 1 lozenge every 2 to 4 hours ▪ Weeks 10 to 12 1 lozenge every 4 to 8 hours Do not chew or swallow lozenge Use beyond 6 months is not recommended Gradually reduce dose over 12 weeks During first 6 weeks of therapy: Use at least 9 lozenges per day for improved outcomes	2 mg and 4 mg lozenges
nicotine inhaler (Nicotrol Inhaler)	Initial: 24 to 64 mg (6 to 16 cartridges) daily for up to 12 weeks	After 3 months, gradually reduce dose over 6 to 12 weeks Use beyond 6 months is not recommended	10 mg/cartridge (4 mg delivered/cartridge)
nicotine nasal spray (Nicotrol NS)	Initial: 1 or 2 doses per hour, as needed, whenever patient feels the need to smoke Maintenance: 8 to 40 doses daily for 3 to 6 months (1 dose = 2 sprays total or 1 spray in each nostril)	Min 8 mg daily or 16 sprays Max 5 doses or 10 sprays per hour Max 40 mg daily or 80 sprays (slightly less than a ½ bottle) Do not spray the eyes during administration of the nasal spray	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)

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

Quit is a branded generic approved under an abbreviated new drug application (ANDA).

Dosages (continued)

Drug	Dosage in Adults	Special Dosing Considerations	Availability
Nicotine Replacement Therapies (NRTs) *(continued)*			
nicotine transdermal OTC (Nicoderm CQ)	Adults smoking ≥ 10 cigarettes daily: Start with 21 mg daily for first 6 weeks then decrease to 14 mg daily for next 2 weeks then 7 mg daily for next 2 weeks Adults smoking < 10 cigarettes daily: Start with 14 mg daily for first 6 weeks then decrease to 7 mg daily for next 2 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: ▪ 7 mg/24 hr ▪ 14 mg/24 hr ▪ 21 mg/24 hr ▪ 21 mg – 14 mg – 7 mg/24 hr system kit
Non-Nicotine Replacement Therapies (Non-NRTs)			
bupropion SR (Zyban)	Initiate 1 to 2 weeks prior to quit date First 3 days: 150 mg daily Maintenance Dose: 150 mg twice daily, at least 8 hours apart	For smoking cessation, doses above 300 mg/day should not be used	150 mg SR tablets
varenicline tablets (Chantix)	Initiate 1 week prior to stop smoking date or, alternatively, begin varenicline dosing and then quit smoking between days 8 and 35 of treatment ▪ 0.5 mg once daily on days 1 to 3 ▪ 0.5 mg twice daily on days 4 to 7 ▪ 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 For patients unable or unwilling to quit abruptly, a gradual approach may be used: begin dosing and reduce smoking by 50% within the first 4 weeks, by an additional 50% in the next 4 weeks, and continue reducing with the goal of complete abstinence by 12 weeks; then continue treatment for an additional 12 weeks, for a total of 24 weeks of treatment	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 An additional attempt of therapy is recommended for those who fail to quit smoking or relapse when factors contributing to the failed attempt have been addressed For patients unable or unwilling to quit abruptly, a gradual approach may be used; however, patients may attempt to quit smoking sooner than the recommended dosing schedule	0.5 mg and 1 mg tablets Packages include: Starting Month Pack Pack includes 1 card of 0.5 mg x 11 tablets and 3 cards of 1 mg x 14 tablets Continuing Month Pack Pack includes 4 cards of 1 mg x 14 tablets

Patients should set a "target quit date" within the first 2 weeks of treatment with bupropion SR, generally in the second week. Treatment with bupropion SR should be continued for 7 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 after the 7 to 14 weeks 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 7 to 12 weeks of treatment should be considered for ongoing therapy with bupropion SR. Counseling should ensue throughout treatment with bupropion SR and for a period of time once therapy has been discontinued.

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% 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 and/or 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.

bupropion sustained-release (Zyban) versus nicotine transdermal

A 9-week, randomized, placebo-controlled trial was conducted to compare 4 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.[60] Treatment with bupropion SR was initiated at 150 mg daily while the patient was still smoking and was increased after 3 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 1 week when the patient reached the target quit date. During weeks 8 and 9 of the study, nicotine transdermal was tapered to 14 and 7 mg daily, respectively. Quitting, defined as total abstinence during weeks 4 through 7, was determined by patient daily diaries and verified by expired air carbon monoxide (CO) levels. In this study, patients treated with any of the 3 treatments achieved greater 4-week abstinence rates than patients treated with placebo. Continuous abstinence rates after 12 months were 30% (95% CI, 24 to 35) in the bupropion SR group, 33% (95% CI, 27 to 39) for patients treated with the combination at 26 weeks compared with 13% (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 5 smoking cessation interventions in adults who were motivated to quit smoking.[61] A total of 1,504 adults who smoked at least 10 cigarettes per day during the last 6 months were randomized to 1 of the following: nicotine lozenge, nicotine patch, bupropion SR, nicotine patch plus nicotine lozenge, bupropion SR plus nicotine lozenge, or placebo. All patients received 6 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 7 days?") and confirmed by measurement of expired CO at 1 week after quit date (post-quit), end of treatment (8 weeks post-quit), and 6 months post-quit. All treatments, except nicotine lozenge, produced higher rates of initial cessation than placebo, and all treatments except nicotine lozenge at 1 week had higher 7-day point-prevalence abstinence rates at 1 week, end of treatment, and 6 months post-quit. All treatments differed from placebo when examined without protection for multiple comparisons (odds ratios [OR], 1.63 to 2.34). With such protection, only the nicotine patch plus nicotine lozenge (OR, 2.34, p<0.001) produced significantly higher abstinence rates at 6 months post-quit than did placebo. Adverse effects were similar to those reported in other studies of smoking cessation.

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.[62] 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 2 groups over weeks 9 to 12 (71.4% versus 78.6% in the varenicline and nicotine patch groups, respectively), and weeks 9 to 24 (64.3% versus 71.4%, respectively). The frequencies of inability to concentrate at 2, 4, and 8 weeks, and wakeful nights at 2 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 1 case in the nicotine patch group, respectively. Conversely, there were no cases of skin allergy in the varenicline group while there were 9 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.[63] 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% and 65.7% of patients in the transdermal nicotine replacement and varenicline groups, respectively. The primary outcomes were confirmed by exhaled CO for the last 4 weeks of treatment, at week 24 and at week 52. Self-reported continuous abstinence rates at the last 4 weeks of treatment were 55.9% for varenicline and 43.2% for transdermal nicotine replacement (OR, 1.7; 95% CI, 1.26 to 2.28; p<0.001). The week 52 continuous abstinence rate was 26.1% for varenicline and 20.3% for transdermal nicotine replacement (OR, 1.4; 95% CI, 0.99 to 1.99; p=0.056). Nausea was reported by 37.2% and 9.7% of patients receiving varenicline and transdermal nicotine replacement, respectively. The manufacturer of varenicline supported the study.

nicotine patch versus varenicline (Chantix) versus combination nicotine therapy (patch and lozenge)

A randomized, open-label trial compared the efficacy of nicotine patch versus varenicline (including 1 pre-quit week) and combination nicotine therapy for 12 weeks (n=1,086).[64] Patients assigned varenicline received 0.5 mg once daily for 3 days, 0.5 mg twice daily for 3 days, and 1 mg twice daily thereafter for 11 weeks, while those assigned nicotine patch received 21 mg/day for 8 weeks, 14 mg/day for 2 weeks, and 7 mg/day for 2 weeks (alternative regimen available for those smoking ≤ 10 cigarettes/day). The combination

treatment group received the nicotine patch as described and 2 or 4 mg nicotine lozenges based on morning smoking latency with instructions to use at least 5 lozenges/day for 12 weeks unless intolerable. Six counseling sessions were also offered. The primary outcome was CO confirmed, self-reported 7-day abstinence at 26 weeks, while secondary outcomes included CO confirmed, self-reported initial abstinence, prolonged abstinence at 26 weeks, and point-prevalence abstinence at 4, 12, and 52 weeks. The mean number of cigarettes smoked per day was 17 and the average number of years smoking was 28.6 years. Approximately 84% provided 12-month follow up data. There were no statistically significant differences between groups in any abstinence measure at either 26 or 52 weeks. Percentages of 7-day CO confirmed, self-reported abstinence at 26 weeks ranged from 22.8% to 26.8%. However, adverse effects (e.g., vivid dreams, insomnia, nausea, constipation, sleepiness, indigestion) were more frequent with varenicline than with either nicotine regimen.

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.[65] 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 CO. Patients were also evaluated at end of treatment (EOT) at 12 weeks and at a 6-month follow-up. Although statistically insignificant, there was a trend for higher quit rates for nicotine transdermal versus nicotine lozenge at EOT (24.3% versus 18.7%; p=0.1) and at 6 months (15.6% versus 10.9%; p=0.1). 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.

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.[66] Patients had fewer than 3 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% for varenicline, 56% for bupropion SR, and 54% for placebo. The primary outcome was the exhaled CO-confirmed 4-week rate of continuous abstinence for weeks 9 through 24 and weeks 9 through 52. For the first time period, the 4-week continuous abstinence rates were 44% for varenicline (versus placebo; OR, 3.85; 95% CI, 2.7 to 5.5; p<0.001), 29.5% for bupropion SR (versus varenicline; OR, 1.93; 95% CI, 1.95 to 4.91; p<0.001), and 17.7% for placebo. Bupropion SR was significantly more efficacious than placebo (OR, 2; 95% CI, 1.38 to 2.89; p<0.001). For the time period out to 52 weeks, continuous abstinence rates were 21.9% for varenicline versus 8.4% for placebo (OR, 3.09; 95% CI, 1.95 to 4.91; p<0.001) and compared to bupropion SR with 16.1% (OR, 1.46; 95% CI, 0.99 to 2.17; p=0.057). Common adverse events were nausea for varenicline (28.1% versus placebo 8.4%) and insomnia for bupropion SR (21.9% versus 12.8% 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.[67] Completion rate for the study was 65%. 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 4 weeks of treatment for time period weeks 9 to 24 and time period of weeks 9 to 52. At the end of treatment, continuous abstinence was achieved by 43.9% of varenicline compared to placebo rate of 17.6% (OR, 3.85; 95% CI, 2.69 to 5.5; p<0.001) and 29.8% in the bupropion SR group (OR, 1.9; 95% CI, 1.38 to 2.62; p<0.001). For the first follow-up period, continuous abstinence was achieved by 29.7% of varenicline compared to placebo rate of 13.2% (OR, 2.83; 95% CI, 1.91 to 4.19; p<0.001) and 20.2% 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% for varenicline compared to 10.3% with placebo (OR, 2.66; 95% CI, 1.72 to 4.11; p<0.001) and 14.6% 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% compared to 9.7% placebo and 7.4% 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.[68] Completion rate for the study was 62%. The primary outcome was abstinence rates measured at week 12, defined as prolonged abstinence from 2 weeks after the target quit date and 7-day point-prevalence abstinence for the previous 7 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 7-day point prevalence abstinence rates for the combination therapy group were 53% and 56.2%, respectively (OR, 1.49; 95% CI, 1.05 to 2.12; p=0.03) compared to 43.2% and 48.6%, 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 7-day point prevalence abstinence rates for the combination therapy group were 36.6% and 38.2%, respectively (OR, 1.52; 95% CI, 1.04 to 2.22; p=0.03), compared to 27.6% and 31.9%, respectively, in the varenicline monotherapy group (OR, 1.32; 95% CI, 0.91 to 1.91; p=0.14). At 52 weeks, abstinence and 7-day point prevalence abstinence rates for the combination therapy group were 30.9% and 36.6% (OR, 1.39; 95% CI, 0.93 to 2.07; p=0.11) compared to 24.5% and 29.2%, respectively, in the varenicline monotherapy group (OR, 1.4; 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% versus 3.1% and 3.6% versus 0.8%, respectively). The authors concluded that combination therapy with varenicline and bupropion increased prolonged abstinence in smokers, compared with varenicline alone, but not 7-day point prevalence abstinence at 12 and 26 weeks.

bupropion sustained-release (Zyban) versus nicotine transdermal versus varenicline (Chantix) versus placebo

EAGLES: Bupropion SR, varenicline, transdermal nicotine, and placebo were evaluated in a randomized, double-blind, active- and placebo-controlled postmarketing neuropsychiatric safety trial that included

subjects without a history of psychiatric disorder (non-psychiatric cohort, n=4,116) and subjects with a history of psychiatric disorder (psychiatric cohort, n=4,116).[69] Subjects aged 18 to 75 years, smoking 10 or more cigarettes per day were randomized 1:1:1:1 to bupropion SR 150 mg twice daily, varenicline 1 mg twice daily, NRT patch 21 mg per day with taper, or placebo for a treatment period of 12 weeks and were then followed for another 12 weeks post-treatment. The primary composite of neuropsychiatric endpoints occurred in 2.2%, 2.5%, 1.3%, and 2.4% of the non-psychiatric cohort assigned bupropion, nicotine, varenicline, and placebo, respectively. The primary composite of neuropsychiatric endpoints occurred in 6.7%, 5.2%, 6.5%, and 4.9% of the psychiatric cohort assigned bupropion, nicotine, varenicline, and placebo, respectively. No differences were found between placebo and either bupropion or nicotine, but the risk was found to be statistically lower in the non-psychiatric varenicline group compared to both the placebo and bupropion groups.

Although not a primary outcome measure, both the non-psychiatric and psychiatric cohorts treated with placebo had the lowest rate of CO-confirmed abstinence.[70] During weeks 9 through 12 and 9 through 24, varenicline had the highest rate, while bupropion SR and transdermal nicotine had similar intermediate rates of CO-confirmed abstinence. The rates for weeks 9 through 12 of bupropion, varenicline, NRT, and placebo in the non-psychiatric cohort were 26.1%, 38%, 26.4%, and 13.7%, respectively. The rates for weeks 9 through 12 of bupropion, varenicline, NRT, and placebo in the psychiatric cohort were 19.3%, 29.2%, 20.4%, and 11.4%, respectively. The rates for weeks 9 through 24 of bupropion, varenicline, NRT, and placebo in the non-psychiatric cohort were 18.8%, 25.5%, 18.5%, and 10.5%, respectively. The rates for weeks 9 through 24 of bupropion, varenicline, NRT, and placebo in the psychiatric cohort were 13.7%, 18.3%, 13%, and 8.3%, respectively.

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 [Zyban] and varenicline tartrate [Chantix]). The combination of medication and behavioral therapy is more effective for cessation than either as monotherapy.

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