

Continuing Education for Pharmacists

Medications for the Treatment of Nicotine Addiction

This CPE lesson was written by Nazifa Obaidi, 2010 Pharm.D. Candidate, University of Nebraska College of Pharmacy, who has no financial or conflict of interest disclosures.

Goals

The goals of this lesson are to provide background information on the health impact of tobacco use, the incidence of nicotine use, and to review the pharmacotherapy for tobacco cessation.

Objectives

At the conclusion of this lesson, successful participants should be able to:

1. recall the incidence of tobacco use;
2. describe the pharmacological profiles of tobacco cessation therapies; and
3. compare efficacy of treatment options.

Introduction

Tobacco is the leading cause of preventable death in the world. The effects of tobacco kill 5.4 million people a year worldwide, which translates to an average of one person every six seconds, from lung cancer, heart disease and other illnesses.¹ In Nebraska, from 2000 to 2004, an annual average of 2,274 deaths were attributable to smoking.²

According to the CDC, trends in adult smoking in the United States have been declining since the 1950s. Although 46 million American adults smoke cigarettes, 70% of smokers want to quit completely and 40% of smokers attempt to quit each year.^{3,4} In 2008, 18.4% of adult Nebraska residents were cigarette smokers. Even though the use of tobacco

products is decreasing in high-income countries, it is increasing globally.⁵

Current Therapy

There are three general classes of FDA-approved drugs for tobacco cessation: partial nicotinic receptor agonists, psychotropics, and nicotine replacement therapy (NRT). Varenicline (Chantix®) is the only approved partial nicotinic receptor agonist. Bupropion sustained-release (Zyban®) is the only approved psychotrope available. NRT formulations consist of nicotine gum, transdermal patch, lozenge, nasal spray, and oral vapor inhaler. A sublingual tablet is another NRT formulation, but it is not available in the United States.⁶

According to *The Clinical Practice Guidelines for Treating Tobacco Use and Dependence*, published in the *Journal of American Medical Association*, all of the FDA-approved drugs for tobacco cessation are considered first line therapy.⁷ Factors such as clinician familiarity with the medications, contraindications in certain patients, patient preference, previous patient experience with specific agents, and patient characteristics such as history of depression, should be considered when deciding between specific first line therapies.⁷

Partial Nicotinic Receptor Antagonists

Varenicline (Chantix®) Chantix® is the newest medication developed for

tobacco cessation and was approved by the FDA in 2006.

Mechanism of Action. Varenicline is a partial agonist at $\alpha 4\text{-}\beta 2\alpha$ neuronal nicotinic acetylcholine receptors (nAChRs) which are believed to be the site where nicotine exerts its action. Varenicline stimulates low-level agonist activity and competitively inhibits binding of nicotine, therefore, decreases nicotine cravings and withdrawal symptoms. Nicotine increases dopamine levels in the nucleus accumbens and prefrontal cortex. During periods of abstinence from nicotine, cravings are stimulated by low dopamine levels in the mesolimbic system. If a patient relapses and uses tobacco, varenicline reduces the associated reward by occupying nicotine receptor sites.^{8,9}

Dosing/Administration. Varenicline should be titrated over one week with therapy maintained for 12 weeks. Treatment should begin 1 week prior to smoking quit date. Initiate with 0.5 mg daily on days 1 to 3, increase to 0.5 mg twice a day on days 4 to 7, and 1 mg twice a day on day 8 until end of treatment.⁹ For those not smoking at week 12, an additional 12 week course is recommended for relapse prevention.^{6,9} If treatment is unsuccessful, smoking cessation should be attempted again.⁹ For patients with a creatinine clearance (CrCl) ≤ 50 mL/min, titrate to a maximum dose of 0.5 mg twice a day. No dosage adjustments are required in hepatic impairment.⁸

Pharmacokinetics. Varenicline is almost completely absorbed and has a high bioavailability after oral administration. Peak concentration occurs within 3 to 4 hours and steady state is attained after 4 days of multiple dosing. Metabolism of varenicline is minimal with 92% of the drug excreted unchanged in the urine. Food and time of day do not affect the concentration of varenicline.^{8,9}

Adverse Effects. The most common adverse effect of varenicline is nausea (30% vs. 10% placebo in 1 mg twice a day and 16% vs. 11% placebo in 0.5 mg twice a day). Other common adverse effects include sleep disturbances (insomnia, abnormal/vivid dreams), headache and abdominal pain. Rare, but serious side effects, include Steven Johnson's Syndrome and angioedema of the face, mouth, and neck.^{8,9}

Drug Interactions. No clinically significant interactions have been reported with varenicline use.⁸

Contraindications/Precautions. Varenicline use should be avoided in patients with a known hypersensitivity to varenicline. Patients should discontinue varenicline and seek medical help if a skin rash appears with mucosal lesions. Use with caution in renal impairment since varenicline is substantially excreted by the kidneys and can increase toxicity (see dosing/administration). Safe and effective use has not been established in children and adolescents less than 18 years of age. Varenicline is not recommended in this patient population. In 2009, a black box warning label was added to varenicline outlining the serious

neuropsychiatric effects and advising patients to immediately report agitation, depressed mood, and atypical changes in behavior or thoughts of suicidal ideation.^{8,9} A cohort nested observational study in the United Kingdom (n = 80,660) was conducted to determine whether varenicline was associated with an increased risk of suicidal behavior. It was concluded that there was no clear evidence of an increased risk with varenicline compared with other smoking cessation therapies. The study had limited power so risk could not be ruled out.¹⁰

Advantages. Relief from nicotine cravings and symptoms of withdrawal are attributed to varenicline's unique mechanism of action. Based upon the efficacy demonstrated in clinical trials, patients who can tolerate this medication may be more likely to abstain from tobacco use as compared to other therapies.

Psychotropes

Bupropion SR (Zyban®) Bupropion SR, initially approved as an atypical anti-depressant, is the first non-nicotine agent FDA-approved in the treatment of tobacco dependence.¹¹

Mechanism of Action. The exact mechanism of action of bupropion SR in tobacco cessation is unknown, but it is thought to be related to inhibition of noradrenergic or dopaminergic neuronal uptake in the mesolimbic system.^{8,12} It also appears to be a weak antagonist at nicotinic receptors.⁶ Bupropion SR decreases cravings for cigarettes and decreases symptoms of nicotine withdrawal.¹³

Dosing/Administration. Bupropion SR should be initiated 1 to 2 weeks prior to the chosen smoking quit-day.

If patients have not quit smoking after the 7th week of therapy, they are generally considered non-responsive to treatment with bupropion SR.⁸

As monotherapy or in combination with NTS, the patient should be instructed to initiate bupropion SR 150 mg daily for the first three days, then the dose should be 150 mg twice a day for the remainder of the treatment period (7 to 12 weeks) with doses at least 8 hours apart. Maximum daily dose should not exceed 300 mg/day.⁸ Combined therapy of Zyban® and nicotine transdermal system (NTS) received FDA approval in 1999.^{8,11} Patients should initiate bupropion SR 1 to 2 weeks before the scheduled quit-day and NTS should be initiated on the scheduled quit day. Bupropion SR should be continued for 7 to 12 weeks and most NTS can be continued for 8 to 20 weeks. Dose tapering is not necessary when discontinuing treatment with bupropion SR in smoking cessation.^{8,11}

Pharmacokinetics. Bupropion SR is a racemic mixture with an oral bioavailability of around 5% to 20% in animal models. The oral bioavailability of bupropion SR has not yet been determined in humans. Peak plasma concentrations are obtained within 3 hours after administration of bupropion SR. Although food slightly affects absorption, it is not clinically significant.^{8,9}

Adverse Effects. Common adverse effects from bupropion SR include insomnia which occurs in 30% to 40% of patients, and dry mouth which occurs in 10% of patients.^{7,8} Other possible adverse effects include nervousness/difficulty concentrating,

rash, constipation and seizures. The possibility of seizures is 1/1,000 or 0.1%.^{6,8}

Drug Interactions. Although the combination of NTS and bupropion SR is utilized, it can cause a clinically significant increase in blood pressure and it is recommended to monitor blood pressure. Concurrent use of bupropion SR with drugs that decrease the seizure threshold such as anti-depressants, antipsychotics, cocaine, psychostimulants (e.g., amphetamine, dextroamphetamine and stimulant weight-loss medications), sodium phosphate monobasic monohydrate, sodium phosphate dibasic anhydrous, theophylline, tramadol, and systemic corticosteroids, should be avoided altogether or used with caution.^{8,11}

Contraindications/Precautions.

Absolute contraindications to bupropion SR include seizure disorders, bulimia, anorexia, and concurrent administration with MAOI therapy. Issued in 2004, Bupropion SR contains a black box warning concerning the increased risk of suicidal ideation in pediatric and young adult patients.⁸ In 2009, another black box warning was issued outlining the serious neuropsychiatric effects of bupropion SR such as changes in behavior, agitation, hostility, depressed mood, and suicidal ideation in patients with and without previous psychiatric disorders. There is a possibility for exacerbation of psychiatric disorders such as schizophrenia when bupropion SR is utilized for smoking cessation.¹¹

Advantages. Bupropion SR can delay and/or decrease the weight gain that is associated with smoking cessation.

It is also an effective treatment for smokers with a history of depression.⁶

Nicotine Replacement Therapy

(NRT) The aim of NRT is to replace some of the nicotine from tobacco in order to reduce nicotine withdrawal symptoms and reduce the motivation to smoke. NRT provides an alternative source of reinforcement and cognitive effects compared to the nicotine from tobacco.⁶ A Cochrane Review found that 17% of smokers who had used nicotine replacement therapy successfully quit at follow-up versus 10% of smokers in the control group.¹⁴ The choice of a specific NRT is mostly determined by patient preference, adverse effects, and price.⁶ Patients should discontinue smoking and all other forms of tobacco when initiating NRT.⁸

Mechanism of Action. Nicotine has both stimulant and depressant actions and is classified as a stimulant of nicotinic receptors of autonomic ganglia. Inhaled nicotine is quickly absorbed into the bloodstream where it passes the blood brain barrier. Once in the brain, nicotine binds to nicotine receptors and stimulates release of neurotransmitters such as dopamine.¹⁵ When nicotine is administered in low sustained doses, it desensitizes nicotine receptors and acts like a nicotine receptor antagonist.⁸

Contraindications/Precautions.

Nicotine has cardiovascular side effects which can cause peripheral vasoconstriction, tachycardia and elevated blood pressure. NRT should be used with caution in patients with underlying cardiovascular disease such as recent myocardial infarction (within the past 2 weeks), serious cardiac arrhythmias, and serious or

worsening angina.⁸ NRT products may be appropriate for use in these patients under medical supervision. Nicotine can delay the healing of ulcers and should be used with caution in active peptic ulcer disease. Nicotine is relatively contraindicated in patients with a history of esophagitis, hiatal hernia, or gastroesophageal reflux disease because these conditions can be exacerbated by nicotine's pharmacologic effects.^{8,9} Formulation-specific contraindications are listed separately, if applicable, under individual NRT products.

Drug Interactions. Nicotine has been reported to enhance the cardiovascular effects of adenosine which may result in an increase in chest pain and heart rate and a decrease in blood pressure. NRT and tobacco products should be avoided prior to stress testing and studies where adenosine will be used. Through its neuro-endocrine effects, nicotine may increase cortisol and catecholamine levels and may potentiate the effects of adrenergic agonists and ergot alkaloids. Dosage adjustments may be needed if significant changes in nicotine levels occur.^{8,9}

Tobacco induces CYP450 enzymes and can increase the metabolism of other drugs. When a patient discontinues smoking, even if utilizing NRT, concentrations of certain drugs such as caffeine, clozapine, oxazepam, olanzapine, pentazocine, phenothiazines, propoxyphene, propranolol (and possibly other beta-adrenergic blockers), theophylline, tricyclic antidepressants, and warfarin, may be affected. A decreased dosage of these drugs may be required at the cessation of smoking.^{8,9}

Nicotine Transdermal Patch
(*Nicoderm CQ*[®], *Habitrol*[®],
ProStep[®], *Nicotrol*[®]) Transdermal
patches were FDA-approved in
November 1991 and are available
OTC and with a prescription.

Dosing/Administration.

Transdermal patches are available in several different doses and deliver between 5 mg and 22 mg of nicotine over a 16 to 24-hour period.¹⁴ Patches should be applied intact to an area of clean, dry, hairless and non-irritated skin on the upper body or upper outer part of the arm. After applying the patch, it should be pressed firmly with palm of hand for about 10 seconds to ensure adherence.¹³ *Habitrol*[®] *Nicoderm*[®] and *ProStep*[®] brands should be worn for 24 hours and then removed and disposed of by folding the patch onto itself. *Nicotrol*[®] should be applied after waking and removed before bedtime. If they are applied correctly, patches are not affected by showering, swimming, or exercise.^{8,9}

Pharmacokinetics. Nicotine is well absorbed through the skin. However, the extent of absorption is not known. In general, peak nicotine plasma concentrations occur within 4 to 12 hours after application of a patch with a continuous release of nicotine over 16 to 24 hours.^{6,8} Time to peak plasma concentrations vary within the

Table 2 Usage for Nicotine Gum ^{7,8}	
Weeks	Usage
1 - 6	1 piece every 1 to 2 hours
7 - 9	1 piece every 2 to 4 hours
10 - 12	1 piece every 4 to 8 hours

various transdermal products. *Habitrol*[®] concentrations peak within 5 to 6 hours after application of the patch, *Nicoderm*[®] in 4 hours, and *ProStep*[®] in 9 hours. Nicotine from a transdermal system has an elimination half-life of 3 to 4 hours.^{8,9}

Adverse Effects. Among the most common side effects of the transdermal patch is mild skin irritation such as itching, burning, and tingling within the first hour at the placement site as well as insomnia.^{6,7} Other possible side effects include vivid dreams or sleep disturbances and headache.⁸

Contraindications/Precautions. Use of the nicotine patch may cause skin irritation in people with certain conditions such as eczema, psoriasis, or atopic dermatitis. Since some nicotine patches contain aluminum or other metals that can overheat and cause skin burns, they should be removed prior to MRI procedures.⁸

Advantages. One advantage of utilizing a transdermal patch is the

consistent nicotine levels delivered over a 24 hour period; thereby, resulting in fewer compliance issues.¹³ Patches are also relatively easy to use and conceal.

Nicotine Polacrilex Gum
(*Nicorette*[®]) *Nicorette*[®] was

approved as an OTC product by the FDA in January 1984.

Dosing/Administration. Nicotine gum is available in 2 mg and 4 mg strengths and come in a variety of flavors including original, cinnamon, fruit, mint, and orange. For patients who smoke ≥ 25 cigarettes per day, the 4 mg strength gum is recommended with a maximum of 24 pieces per day.^{8,13} For patients who smoke < 25 cigarettes per day, the 2 mg strength gum is recommended with a maximum of 24 pieces per day. Patients should chew the gum slowly until a tingling sensation or peppery taste occurs. In order to allow absorption of the nicotine from the oral mucosa, the gum should then be "parked" inside the mouth between the cheek and gum until the tingle or peppery taste fades. This process should be repeated for around 30 minutes and the gum should not be swallowed. It is recommended to use at least 9 pieces of gum per day for the first 6 weeks in order to improve the likelihood of quitting. Certain acidic foods and beverages like coffee, wine, juices and soft drinks, can reduce the effectiveness of nicotine

Table 1 Dosing for NicoDerm CQ [®] Transdermal Patch ⁸	
Light Smoker (≤ 10 cigarettes/day)	Heavy Smoker (> 10 cigarettes/day)
14 mg for 6 weeks then 7 mg for 2 weeks	21 mg for 6 weeks then 14 mg for 2 weeks then 7 mg for 2 weeks

gum. Therefore, it is recommended to not eat or drink for 15 minutes prior to or while using nicotine gum.^{8,17}

Pharmacokinetics. Peak nicotine plasma concentrations occur within 15 to 30 minutes after the start of chewing the gum.

Adverse Effects. Common side effects from utilizing nicotine gum include mouth soreness, hiccups, dyspepsia, and jaw pain.^{6,7,8} Adverse effects that are associated with incorrect chewing technique such as chewing gum too rapidly and can cause excessive release of nicotine include light headedness, nausea and vomiting, and throat and mouth irritation.

Contraindications/Precautions. It is best to avoid nicotine gum in patients with temporomandibular joint (TMJ) disease or mouth and throat inflammation. Use with caution in patients with certain dental work such as dentures since nicotine gum is stickier than regular chewing gum and may stick to dental work.^{8,9}

Advantages. Nicotine gum is a short acting NRT that offers flexible dosing and is attainable without a prescription.

Nicotine Polacrilex Lozenge (Commit®) Nicotine lozenge (Commit®) was approved on October 31, 2002 by the FDA for smoking cessation. It contains buffering agents to enhance buccal absorption of the nicotine.

Dosing/Administration. Nicotine lozenges are available in 2 mg and 4 mg strengths and come in sugar-free mint flavor. Dosing for the nicotine lozenge is based on the “time to first

cigarette” (TTFC) which is used as an indicator of nicotine addiction.¹⁸ People who smoke their first cigarette of the day within 30 minutes of waking should use the 4 mg lozenge and those who smoke their first cigarette after 30 minutes of waking require the 2 mg lozenge. One lozenge every 1 to 2 hours should be used for the first 6 weeks of treatment. Then, reduce to 1 lozenge every 2 to 4 hours for weeks 7 to 9 of treatment and 1 lozenge every 4 to 8 hours for weeks 10 to 12.^{8,9} The recommended duration of therapy is 12 weeks with a maximum of 20 lozenges per day. The lozenge should be placed inside the mouth and allowed to dissolve slowly over 20 to 30 minutes with occasional rotation to different areas of the mouth.¹³ It should not be chewed or swallowed. For maximal results, at least 9 lozenges should be used daily during the first 6 weeks. Certain acidic foods and beverages like coffee, wine, juices and soft drinks, can reduce the effectiveness of the nicotine lozenge. It is recommended not to eat or drink for 15 minutes prior to or while using nicotine lozenge.^{6,7}

Pharmacokinetics. Nicotine from the lozenge is readily absorbed through the buccal mucosa. Systemic absorption is slower than from a cigarette or the inhaled and nasal NRTs. Although pharmacokinetic data is not available for the nicotine lozenge, one study found that nicotine lozenges delivered around 25% more nicotine than nicotine gum. This was because the lozenge dissolves completely whereas the gum may retain some nicotine.^{16,18}

Adverse Effects. Common adverse effects associated with the nicotine lozenge include nausea, hiccups,

cough, heartburn, headache, flatulence, insomnia, and mouth and throat irritation.^{8,18}

Contraindications/Precautions. No specific contraindications are reported for nicotine lozenge.⁸ Refer to general NRT contraindications/precautions.

Advantages. It is claimed that the best indicator for nicotine dependence is TTFC, which is how lozenges are dosed, rather than the number of cigarettes smoked, which is how the gum is dosed.¹⁶ The lozenge offers another flexible dosing schedule that can be used in acute situations as a rescue medication for cravings. Also, there are no precautions reported in TMJ patients, as with the nicotine gum.¹⁸

Oral Inhaler (Nicotrol®)

On May 5, 1997, the FDA-approved Nicotrol® inhaler, a prescription-only oral inhalation system.

Dosing/Administration. Nicotrol® inhaler is available as a 10 mg/cartridge inhalation system with each cartridge delivering 4 mg of nicotine. The recommended initial dose is 24 to 64 mg (6 to 16 cartridges) per day for up to 12 weeks followed by a gradual reduction in dosage over a period 6 to 12 weeks.⁶ Use for more than 6 months is not recommended.⁷ Patients should be instructed to place a cartridge into the mouthpiece and then inhale into back of throat or puff in short breaths. The nicotine in each cartridge will be used up after about 20 minutes of active puffing. Once a cartridge is opened, it retains potency for 24 hours.⁸

Pharmacokinetics. After oral inhalation, nicotine is rapidly

absorbed through the respiratory tract and mucous membranes. Additionally, there is a slower oral absorption of nicotine through the buccal mucosa with peak nicotine plasma concentrations occurring within 15 minutes after inhalation.^{8,9}

Adverse Effects. The most common adverse effects from the oral inhaler are mouth and throat irritation and cough.⁶ Other possible adverse effects include dyspepsia, hiccups, headache, and rhinitis.⁸

Advantages. The inhaler formulation mimics the hand-to-mouth motion and puffing behaviors of smoking and is useful as a behavioral coping mechanism.^{6,16}

Nasal Inhaler (Nicotrol® NS)

Dosing/Administration. Nicotrol® NS is a prescription-only aqueous solution of nicotine available as a 10mg/mL nasal spray. The recommended dosage is 1 spray (containing 0.5 mg nicotine per spray) into each nostril 1 to 2 times hourly as needed whenever the patient feels the need to smoke, with a maximum of 10 sprays (5 doses) per hour.^{6,7} For best results, patients should use at least 16 sprays (8 doses) daily for the first 6 to 8 weeks. Therapy should be continued for up to 3 months. Increased duration of therapy does not improve outcomes and safety of use greater than 6 months has not been established.⁸ Instruct patients to prime the nasal pump before the first use, then blow nose, tilt head back slightly and insert tip of bottle into nostril as far as comfortable. Patients should breathe through the mouth and then actuate spray into nostril.

Pharmacokinetics. After nasal inhalation, nicotine is rapidly absorbed through the respiratory tract and mucous membranes. Peak nicotine plasma concentrations occur within 4 to 15 minutes after nasal administration. Approximately 53% of a dose (2 sprays) reaches systemic circulation.^{8,9}

Adverse Effects. Common adverse effects of the nicotine nasal spray are rhinitis, throat and nasal irritation, sneezing, headache, and cough. Side effects usually subside after 3 to 7 days with regular use.^{8,9}

Advantages. More rapid delivery of nicotine is obtained through a nasal spray therefore providing faster relief of withdrawal symptoms.^{6,16}

Clinical Trials/Comparison

One clinical trial indicates that the combination of bupropion SR with NTS results in abstinence rates of 51% at week 10 following a 4-week quit program. However, one year after the target quit-date, the bupropion SR and NTS combination is not significantly better at maintaining abstinence than the use of bupropion SR alone.¹⁹ Nicotine abstinence rates in clinical trials after 6 weeks of monotherapy with bupropion SR were 44.2% for bupropion SR 300 mg per day versus 19% with placebo. At one year, the abstinence rate was superior to placebo for those patients receiving bupropion SR at 300 mg per day or 150 mg per day, but not for the 100 mg per day dosage.⁸

According to a 2004 Cochrane Review which included over 40,000 people, treatment with bupropion SR doubled the quit rate compared with placebo.^{6,14} After reviewing 132 trials

of NRT, the authors of the Cochrane Review concluded that all forms combined of NRT increased chances of quitting smoking by 50% to 70% in heavy smokers who are highly motivated to quit.¹⁴ Quit rates were generally found to be similar in comparison trials of bupropion SR with NRT.⁶

Varenicline has been shown to be superior over placebo and bupropion SR. One randomized controlled trial comparing varenicline versus bupropion or placebo, found 43.9% of participants on varenicline remained continuously abstinent from smoking compared to 17.6% in the placebo group and 29.8% in the bupropion SR group.¹² The most common adverse event of varenicline reported in the trial was nausea with a frequency of 29.4%.^{8,12} Table 3 summarizes odds ratios for all pharmacotherapy agents for tobacco cessation.

Second Line Drugs

Second line therapies such as clonidine, an antihypertensive, and nortriptyline, a tricyclic antidepressant, should be considered after treatment failure or in patients with contraindications to first-line agents.²⁰ Neither nortriptyline nor clonidine has an FDA-approved indication for tobacco dependence treatment and each has an increased incidence of side effects versus first-line treatments. However, both clonidine and nortriptyline have been shown to be efficacious.¹⁷

Clonidine is available as a transdermal patch (Catapres® TTS) and tablets. One dosage regimen for clonidine is 0.1 to 0.4 mg daily or 0.1 mg once weekly transdermally for 3 to 6 weeks. Treatment should begin 3 days prior to or on the quit day.⁸ Dose should be

Table 3
Odds ratios of abstinence with first- and second-line smoking cessation therapy^{6,14}

Therapies	Odds Ratio (95% CI/# of trials)
First-line	
NRT:	
Gum	1.43 (1.33 to 1.53)/53 trials
Patch	1.66 (1.53 to 1.81)/41 trials
Inhaler	1.90 (1.36 to 2.67)/4 trials
Lazenge	2.00 (1.63 to 4.45)/6 trials
Nasal Spray	2.02 (1.49 to 2.73)/4 trials
Varenicline	3.85 (2.70 to 5.50)/2 trials
Bupropion SR	2.06 (1.77 to 2.40)/19 trials
Second-line	
Nortriptyline	2.14 (1.49 to 3.06)/6 trials
Clonidine	1.89 (1.30-2.74)/6 trials

tapered prior to discontinuation of medication to circumvent rebound hypertension. The most common adverse effects are dry mouth, dizziness, sedation, constipation, erythema, contact dermatitis, and postural hypotension.⁹

Treatment with nortriptyline should begin 10 to 28 days prior to quit date at a dose of 25 mg daily. Gradually titrate to 75 mg to 100 mg daily and continue therapy for 8 to 12 weeks. Dose should be tapered prior to discontinuation of medication. Common adverse effects associated with nortriptyline therapy are sedation, dry mouth and constipation.⁶

Pregnancy

Pregnant women should seek medical advice before initiating any smoking cessation pharmacotherapy. The negative effects of cigarette smoking on the fetus have been well established, including low birth weight, an increased risk of spontaneous

abortion, and increased perinatal mortality. Studies in pregnant animals have shown adverse effects to the fetus from intravenous nicotine, including teratogenicity in rats and acidosis, hypercarbia, and hypotension in the rhesus monkey fetus. There have been no adequate, well-controlled studies in pregnant females. Smoking cessation therapy

should only be used in pregnancy if the potential benefits, such as an increase in likelihood of smoking cessation, outweigh the risks to the fetus. Spontaneous abortion has been reported in pregnant women on NRT. Nicotine patches, lozenges, inhalers, and nortriptyline are classified as FDA pregnancy category D, while nicotine gum, bupropion SR, varenicline, and clonidine are classified as FDA pregnancy category C.^{8,9}

Pipeline

NicVAX[®] is a nicotine conjugate vaccine currently in phase II clinical trials which is designed as a smoking cessation aid as well as an aid to prevent relapses. NicVAX[®] is a nicotine derivative that is chemically bound to a selected carrier protein. It is designed to cause the immune system to produce antibodies that bind to nicotine in the bloodstream and prevent it from entering the brain. By blocking the effects of nicotine, the end result is lack of the positive stimulus caused by nicotine. There have been positive and

Table 4
Medication Guidelines²¹

Effective Medication Combination	Medications Not Recommended
Longterm (>14 weeks) nicotine patch + other NRT (gum or spray)	Antidepressants other than bupropion SR and nortriptyline
The nicotine patch + the nicotine inhaler	Selective serotonin re-uptake inhibitors (SSRIs)
The nicotine patch + bupropion SR (Strength of Evidence = A)	Anxiolytics/benzodiazepines/beta-blockers
	Opioid antagonists/naltrexone
	Mecamylamine
	Extended use of medications

promising results from phase I and phase II studies showing safety, tolerability and efficacy of NicVAX®.¹⁵

Conclusion

Tobacco use is the most preventable cause of premature mortality and morbidity in the world. With the addition of bupropion SR and varenicline to the market, a variety of medication therapies are available for those who have decided to quit smoking, giving patients and physicians more flexibility in choosing an appropriate treatment option. Following the most recent smoking cessation guidelines, those who smoke 10 or more cigarettes per day should be encouraged to use first-line smoking cessation therapies such as NRT, bupropion SR, or varenicline (strength of evidence: A).²⁰ If there are contraindications to first-line therapies, second-line therapies of

either clonidine or nortriptyline can be used. Table 4 summarizes effective combination smoking cessation therapies as well as medications not recommended for the treatment of tobacco cessation.

As part of the health care team, pharmacists can provide tobacco cessation and prevention services. This increases quit rates and expands the pharmacist's role in tobacco treatment. One recently published systematic review found evidence that suggests pharmacists are effective in helping smokers stop tobacco use.²²

The next *M&P* continuing education lesson will focus on developing and implementing a smoking cessation program, and will provide guidelines on what topics should be addressed during each smoking cessation meetings between patients and the

pharmacists.

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- Preventable deaths due to non-adherence are estimated to be at least 125,000 each year. Pharmacists should lead the way in educating patients about being adherent to their prescribed medication therapy.
Vermeire, E., et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther.* 2001 Oct;26(5):331-42.
- According to one study, people aged 75 years and older take an average of 7.9 drugs per day. Assure your patients understand the importance of being adherent by discussing their medications with them at each visit.
Marinker M, Blenkinsopp A, Bond C, et al. From Compliance to Concordance: Achieving Shared Goals in Medicine Taking. London, UK: Royal Pharmaceutical Society of Great Britain; 1997.
- With the increasing number of patients with chronic illnesses, there are increased numbers of prescription medications being prescribed. Those patients that are on multiple medications are more likely to miss doses and not take their medications properly. While the list of reasons for non-adherence is long, pharmacists are on a short-list of healthcare professionals that can make a significant impact on this health care crisis. Talk to these patients about ways in order to improve their medication adherence.
- There are many stakeholders in the effort to improve medication adherence and everyone in the health care system has a role to play. Patients are non adherent to medications for a variety of reasons, and need to be educated continuously. Pharmacists, as the medication experts should be leading the way to ensuring optimal medication use. Being among the most accessible members of the health care team, pharmacists are in the position to conduct adherence interventions.
- Patients on multiple medications are more likely to miss doses and not take their medications properly. Talk to these patients about ways in order to improve their medication adherence.
- There are many stakeholders in the effort to improve medication adherence. Pharmacists, as the medication experts should lead the way to ensuring optimal medication use.
- Everyone in the health care system has a role to play in improving prescription medication adherence. Pharmacists, as the medication experts should lead the way to ensuring optimal medication use.

Continuing Education for Pharmacists

Quiz and Evaluation

Medications for the Treatment of Nicotine Addition

1. What percent of adult Nebraska residents were cigarette smokers in 2008?
 - a. 5.2%
 - b. 12.5%
 - c. 18.4%
 - d. 40.6%
2. All the following are considered first-line medications for tobacco cessation except:
 - a. Bupropion SR
 - b. Clonidine
 - c. NRT
 - d. Varenicline
3. The most common adverse effect of varenicline is:
 - a. Arrhythmias
 - b. Constipation
 - c. Drowsiness
 - d. Nausea
4. When should a patient be instructed to quit smoking when initiating bupropion SR?
 - a. One to two days after
 - b. One to two weeks after
 - c. One to two months after
 - d. It does not matter when the patient quits smoking
5. What nicotine gum dosage regimen should be initiated for a patient who smokes 20 cigarettes per day?
 - a. 1 piece (2 mg) every 1 to 2 hours
 - b. 1 piece (4 mg) every 1 to 2 hours
 - c. 1 piece (2 mg) every 4 to 8 hours
 - d. 1 piece (4 mg) every 4 to 8 hours
6. Which NRT formulation is not FDA-approved in the United States?
 - a. Gum
 - b. Lozenge
 - c. Patch
 - d. Sublingual tablet
7. Which of the following is true about the nicotine patch?
 - a. The patch should be removed prior to showering
 - b. The patch should be removed prior to MRIs
 - c. The patch can be cut if needed
 - d. The patch should be removed prior to exercise
8. Dosage of which drug should be adjusted when a patient discontinues smoking?
 - a. Atorvastatin
 - b. Celecoxib
 - c. Metformin
 - d. Olanzapine
9. Nicotine gum, bupropion SR, varenicline, and clonidine are classified as FDA pregnancy category _____.
 - a. A
 - b. B
 - c. C
 - d. D
10. (T/F) Currently, there is vaccine being studied for the treatment of tobacco dependence.
 - a. True
 - b. False



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Medication for the Treatment of Nicotine Addiction

This lesson is a knowledge-based CPE activity and is targeted to pharmacists.

GPhA code: J10-08

ACPE#: 0142-9999-10-008-H01-P

Contact Hours: 1.5 (0.15 CEU)

Release Date: 08/01/2010

Expiration Date: 08/01/2013

1. Select one correct answer per question and circle the appropriate letter below using blue or black ink (no red ink or pencil.)

2. Members submit \$4.00, Non-members must include \$10.00 to cover the cost of grading and issuing statements of credit/ Please send check or money order only. Note: GPhA members will receive priority in processing CE.

Statements of credit for GPhA members will be emailed or mailed within four weeks of receipt of the course quiz.

- 1. A B C D 2. A B C D 3. A B C D 4. A B C D 5. A B C D 6. A B C D 7. A B C D 8. A B C D 9. A B C D 10. A B

Activity Evaluation: must be completed for credit

Please rate the following items on a scale from 1 (poor) to 5 (excellent) as to how well the activity:

- 1. Met my educational needs: 1 2 3 4 5
2. Relates to pharmacy practice: 1 2 3 4 5
3. Achieves the stated learning objectives: 1 2 3 4 5
4. Faculty presented the information: 1 2 3 4 5
5. Teaching methods conveyed information: 1 2 3 4 5
6. Post-test aided in assessing my grasp of the information: 1 2 3 4 5
7. Avoided any bias or commercial bias: 1 2 3 4 5
8. How long did it take to complete this activity? _____

A passing grade of 70% is required for each examination. A person who fails the exam may resubmit the quiz only once at no additional charge.

Please check here if you are indicating a change of address [X] Phone #: _____

Name: _____

License Number(s) and State(s): _____ Email Address: _____

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Remove this page from the Journal and mail this completed quiz and evaluation to: GPhA, 50 Lenox Pointe NE, Atlanta, GA 30324.