PHARMACY Tech Topics™ BY ICHP

Home-Study Continuing Pharmacy Education MODULES for Nationally Certified Pharmacy Technicians

APRIL 2010
VOLUME 15 NUMBER 2

SMOKING CESSATION UPDATE

THIS MODULE MUST BE SUCCESSFULLY COMPLETED BY APRIL 30, 2012 TO RECEIVE CPE CREDIT

Pharmacy Tech Topics™ is provided as a free service to all Pharmacy Technician Members of the American Society of Health-System Pharmacists.

Pharmacy Tech Topics™
VOLUME 15 ISSUE 2
APRIL 2010

SMOKING CESSATION UPDATE

EDITOR: Patricia M. Wegner, Pharm.D., FASHP
DESIGN EDITOR: Barbara J. Yahn

Pharmacy Tech Topics™ (USPS No. 014-766) is published quarterly for $50 per year by the Illinois Council of Health-System Pharmacists, 4055 N. Perryville Road, Loves Park, IL 61111-8653. Phone (815) 227-9292. Periodicals Postage Paid at Rockford, IL and additional mailing offices.

POSTMASTER: Send address changes to:
Pharmacy Tech Topics,™ c/o ICHP, 4055 N. Perryville Road, Loves Park, IL 61111-8653

This module is accredited for 2.5 contact hours of continuing pharmacy education and is recognized by the Pharmacy Technician Certification Board (PTCB).

LEARNING OBJECTIVES

Upon completion of this module, the subscriber will be able to:

1. List five examples of health consequences from cigarette smoking and define the time course for health benefits with smoking cessation.
2. Describe a brief intervention using the 5 A's and 5 R's for a pharmacist to effectively counsel a patient on smoking cessation.
3. Outline the proper technique for using the nicotine gum, patch, inhaler and nasal spray.
4. Explain the role in therapy for the oral agents bupropion sustained release and varenicline.
5. Describe the side effects for each of the first-line agents and list common dosing recommendations for each agent.

Accreditation: Pharmacy Tech Topics™ Modules are accredited for Continuing Pharmacy Education (CPE) credits by the Illinois Council of Health-System Pharmacists. The Illinois Council of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ©2010 Illinois Council of Health-System Pharmacists. Pharmacy Tech Topics™ is a trademark of the Illinois Council of Health-System Pharmacists. The intended audience is pharmacy technicians.

This module will provide **2.5 hours** of continuing pharmacy education credit for certified pharmacy technicians.

ACPE Universal Activity Number: 121-000-10-002-H01-T Type of Activity: Knowledge

Validation Dates: 4/01/10 to 4/30/12

Pharmacy Tech Topics™ APRIL 2010 FACULTY DISCLOSURE

It is the policy of the Illinois Council of Health-System Pharmacists (ICHP) to insure balance and objectivity in all its individually or jointly presented continuing pharmacy education programs. All faculty participating in any ICHP continuing pharmacy education programs are expected to disclose any real or apparent conflict(s) of interest that may have any bearing on the subject matter of the continuing pharmacy education program. Disclosure pertains to relationships with any pharmaceutical companies, biomedical device manufacturers, or other corporations whose products or services are related to the subject matter of the topic.

The intent of disclosure is not to prevent the use of faculty with a potential conflict of interest from authoring a publication but to let the readers know about the relationship prior to participation in the continuing pharmacy education activity. It is intended to identify financial interests and affiliations so that, with full disclosure of the facts, the readers may form their own judgments about the content of the learning activity.

Dr. Susan Winkler's submission has been peer reviewed with consideration and knowledge of these potential conflicts and it has been found to be balanced and objective. The author has no real or apparent conflict(s) of interest that may have any bearing on the subject matter of this continuing pharmacy education program.

Meet the Author

Susan R. Winkler, Pharm.D., BCPS

Susan R. Winkler received her PharmD from the University of Illinois at Chicago College of Pharmacy and completed a PGY-1 residency at the UIC Medical Center. She worked as a clinician educator at UIC for many years in the Neurosurgery ICU and then in the Neurology/Neurosurgery Clinic at both UIC and Jesse Brown VAMC. Dr. Winkler developed and implemented pharmacist-managed smoking cessation clinics at both UIC and Jesse Brown VAMC and served as the Assistant Director of Ambulatory Pharmacy Services at UIC from 2003 – 2007. She subsequently accepted a position as Assistant Dean at Midwestern University Chicago College of Pharmacy and is currently Department Chair and Professor at this institution.

Smoking Cessation Update

INTRODUCTION

Cigarette smoking continues to be a public health concern and a leading cause of preventable diseases and death in the United States (U.S.) and worldwide. The number of deaths attributed to cigarette smoking and exposure to secondhand smoke during 2000 – 2004 was over 443,000 annually or nearly one in every 5 deaths.[1] The financial burden of smoking also continues to be high. During this same reporting period, there was an estimated $96.8 billion spent annually due to lost productivity and an additional $96 billion spent annually for smoking-related health care expenditures.[1] Results from the 2008 National Health Interview Survey show that 20.6% of the U.S. population currently smokes: 23.1% of men and 18.3% of women.[2] Nicotine addiction and the smoking habit usually begin at an early age. Since 2003, approximately 21.9% of high school students are current smokers.[3] This percentage has remained stable through 2007, leading to specific concerns about smoking in teenagers and young adults and recommendations to continue to improve prevention efforts in this group. The number of teenagers who begin smoking each year has remained consistent, despite stricter regulations on the sale of cigarettes to minors and the widespread ban on smoking in public places.

The U.S. government has played a continuous role in regulating smoking. The first direct action taken to curb smoking after the U.S. Surgeon General's report in 1964 was the warning mandated on cigarette packages by the Federal Trade Commission. This warning took effect in 1964 and was strengthened in 1969 to read, "Warning: the Surgeon General has determined that cigarette smoking is dangerous to your health." A still stronger sequence of four alternative warnings was developed in 1984. In 1971, cigarette advertising was banned from radio and television, and cities and states initially began to pass laws requiring nonsmoking sections in public places. Many states have now passed laws banning smoking in offices, restaurants, and/or bars.[4]

In 2004, the Surgeon General published a report detailing the health consequences of smoking, which continues to be the leading cause of preventable diseases and death in our society and has negative effects on health at every stage of life.[5] The report identified four major conclusions:

1. Smoking harms nearly every organ in the body, causing many diseases and adversely affecting smokers' general health.
2. Quitting smoking has immediate as well as long-term benefits, reducing the risk for diseases caused by smoking and improving health in general.

3. Smoking cigarettes with lower machine-measured levels of tar and nicotine does not provide any clear benefit to health or minimize risks to health.
4. The list of diseases caused by smoking has been expanded to include abdominal aortic aneurysm; acute myeloid leukemia; cataract; pneumonia; periodontitis (gum disease); and cervical, kidney, pancreatic, and stomach cancer. This is in addition to previously recognized diseases such as lung cancer, chronic obstructive lung disease (emphysema), cardiac-related diseases (eg., heart attack), and complications during pregnancy.

Cigarette smoking is a major cause of atherosclerotic disease and is considered a major risk factor for heart disease. Smokers have a 2 to 4 times greater chance of developing coronary artery disease and suffering a stroke than nonsmokers. Smoking narrows blood vessels, reducing circulation and resulting in smokers' having a 10 times greater risk of peripheral vascular disease. Smoking causes 90% of lung cancer deaths in men and 80% of lung cancer deaths in women. The risk of dying from lung cancer is 23 times higher among men who smoke cigarettes, and about 13 times higher among women who smoke cigarettes compared with those who have never smoked.[6]

Cigarette smoking increases the risk of ischemic episodes, aortic aneurysm, and peripheral vascular disease. While the risk is directly related to the number of cigarettes smoked, even someone who smokes only 1 to 4 cigarettes a day has a substantially greater risk.[7] Women who smoke and take oral contraceptives have a considerably greater risk of developing cardiovascular disease than women who have not smoked or used oral contraceptives.[8] Also, women who smoke have a greater risk of developing postmenopausal osteoporosis.[9]

Recent research has focused on the effects of environmental tobacco smoke (secondhand smoke) on nonsmokers. Tobacco is the single most important source of preventable diseases and premature death in the United States. The 2006 Surgeon General's report estimates that exposure to environmental tobacco smoke led to the deaths of greater than 3,000 adult nonsmokers from lung cancer, 46,000 from heart disease, and an estimated 430 newborns from sudden infant death syndrome in 2005. Exposure of nonsmokers to secondhand smoke may increase the risk of cardiovascular disease by 25 – 30% and lung cancer by 20 – 30%. Secondhand smoke can also aggravate asthma, bronchitis, and pneumonia, as well as impair blood circulation.[10] As evidence of the harmful effects of secondhand smoke continues to grow, many states and countries outside the United States have enacted smoke-free workplace laws banning smoking in offices, restaurants, and/or bars.

ADDICTION TO NICOTINE

All widely marketed cigarettes deliver enough nicotine to establish and maintain dependence on nicotine. The nicotine concentration in one cigarette ranges from 1- to 12-mg.[11] Nicotine yield is a measure of the amount of nicotine in the smoke that a smoker inhales; a smoker will absorb anywhere from 1.23-mg to 3.4-mg per cigarette, depending on the type of cigarette.[12,13] A typical smoker who smokes a pack a day (20 cigarettes) will absorb approximately 20- to 60-mg of nicotine daily. Nicotine is widely distributed throughout the body and increases a smoker's heart rate, blood pressure, and respiratory rate. When tobacco smoke reaches the lungs, the enormous surface area of the airways, as well as the rate of absorption of nicotine at physiologic pH (7.4), facilitates the transfer of nicotine into the lungs.[14] Nicotine then enters the circulation, where it is quickly distributed to body tissues. Nicotine takes 10 to 19 seconds to pass through the blood-brain-barrier into the brain. This rapid delivery to and effect on the brain provides behavioral reinforcement for smoking.[15] Concentrations then fall rapidly because of uptake by peripheral tissues and elimination of nicotine from the body. Nicotine levels in the brain decline between cigarettes, providing an opportunity for positive reinforcement of the pleasurable effects of smoking. Over time, increased amounts of nicotine are required to maintain the stimulating effects.[16]

Important to nicotine addiction are the nicotinic acetylcholine receptors, which are found throughout the brain.[16] Nicotine's neurochemical effects involve multiple neurochemical pathways and the release of numerous neurotransmitters, including acetylcholine, dopamine, and norepinephrine.[17] A 1988 report from the Surgeon General concluded that cigarettes are addicting, that nicotine is the drug in cigarettes that causes addiction, and that the pharmacologic and behavioral aspects of nicotine addiction are similar to those seen in heroin and cocaine addiction.[14] Some experts consider nicotine to be more addicting than alcohol, cocaine, or heroin.[16]

Inhalation of nicotine via cigarette smoking appears to be the most addictive method of administration. Oral ingestion results in low concentrations of nicotine because of extensive breakdown in the gastrointestinal tract.[15] Compared with smoking, the slow release of nicotine from transdermal patches produces little or no behavioral reinforcement and much lower peak concentrations.[16]

BENEFITS OF SMOKING CESSATION

According to the 1964 Surgeon General's report, an ex-smoker's risk of dying from a smoking-related disease decreases with each year of abstinence.[18] This evidence encouraged more than 30 million people in the United States to quit smoking in the years following this report. Data collected by the Centers for Disease Control and Prevention (CDC) revealed that from 1965 to 1990, the number of Americans who smoked cigarettes decreased from 42.4% to 25.5%; however, the percentage of women who smoked increased over this period.[19] By 1991, although approximately 44 million Americans had quit smoking, the decline was four times greater in men than in women. The prevalence of smoking in the United States has continued to decline since 1990; from 24.1% in 1998 to 20.6% in 2008. However, current smoking rates have remained relatively constant over the past 5 years.[2] Since 2002, the percentage of former smokers is greater than the number of current smokers in the United States.[2] A landmark trial by Doll and colleagues evaluated the health effects of quitting smoking at different ages.[20] Quitting at ages 30, 40, 50, and 60 resulted in 10, 9, 6, and 3 years of life gained, respectively. Those who quit before age 35 add 10 years of life and have a life expectancy similar to that of men who have never smoked. Continuing smokers lose an average of 10 years of life expectancy, but quitting at any age will reduce the risk of death from smoking.

Smoking cessation aids have never been as widely available as they are today. The benefits of smoking cessation are well documented and include the reduction of health risks for the smoker, lower medical costs, and an increase in healthy behaviors.[18] Nonetheless, smoking cessation is difficult as smokers often crave the effects of nicotine. Symptoms of nicotine withdrawal include difficulty concentrating, nervousness, headaches, weight gain, decreased heart rate, insomnia, irritability, and depression. These symptoms are most evident during the initial period and may resolve within a month. Many smokers fail in their attempts to quit due to severe withdrawal symptoms.

SMOKING CESSATION STRATEGIES

In 1996, the Agency for Health Care Policy and Research and the CDC reviewed the existing literature on smoking cessation and developed guidelines for the delivery of effective interventions for practicing clinicians, smoking cessation specialists, and health care administrators and insurers.[21] These guidelines were updated in 2000 to reflect significant changes in this area.[22] These guidelines were updated a second time in 2008, encompassing current research and treatments available through 2007.[23] The 2000 smoking cessation guidelines recommended that all clinicians strongly advise their patients to quit smoking at every intervention. The 2008 smoking cessation guidelines have expanded this recommendation to include that clinicians offer effective tobacco dependence counseling and medication treatments to smokers and for health systems and insurers to make these treatments

available to patients. The major findings and recommendations include the following:[23]

1. Tobacco dependence is a chronic disease that often requires repeated interventions and multiple attempts to quit. Effective treatments are available that can significantly increase rates of long-term abstinence.
2. It is essential that clinicians and health care delivery systems consistently identify and document tobacco use status and treat every tobacco user seen in a health care setting.
3. Tobacco dependence treatments are effective across a broad range of populations. Clinicians should encourage every patient willing to make a quit attempt to use the counseling methods and medications recommended in the current guideline.
4. Brief tobacco dependence treatment is effective. Clinicians should offer every patient who uses tobacco at least the brief treatments shown to be effective in the current guideline.
5. Individual, group, and telephone counseling are effective, and their effectiveness increases with treatment intensity. Two components of counseling are especially effective, and clinicians should use these when counseling patients making a quit attempt:
   - Practical counseling (problem solving/skills training)
   - Social support delivered as part of treatment
6. Numerous effective medications are available for tobacco dependence. Clinicians should encourage their use by all patients attempting to quit smoking, except when medically contraindicated or with specific populations for which there is not enough evidence of effectiveness (i.e., pregnant women, smokeless tobacco users, light smokers, and adolescents).
   - Seven first-line medications (5 nicotine and 2 non-nicotine) reliably increase long-term smoking abstinence rates:
     – Bupropion sustained release (SR)
     – Nicotine gum
     – Nicotine inhaler
     – Nicotine lozenge
     – Nicotine nasal spray
     – Nicotine patch
     – Varenicline
   - Clinicians also should consider the use of certain combinations of medications identified as effective in the current guideline.
7. Counseling and medication are effective when used by themselves for treating tobacco dependence. The combination of counseling and medication is more effective than either alone. Thus, clinicians should encourage all individuals making a quit attempt to use both counseling and medication.
8. Telephone quitline counseling is effective with diverse populations and has a broad reach. Therefore, both clinicians and health care delivery systems should ensure patient access to quitlines and promote quitline use.
9. If a tobacco user currently is unwilling to make a quit attempt, clinicians should use the motivational treatments shown in the current guideline to be effective in increasing future quit attempts.
10. Tobacco dependence treatments are both clinically effective and highly cost-effective relative to interventions for other clinical disorders. Providing coverage for these treatments increases quit rates. Insurers and purchasers should ensure that all insurance plans include the counseling and medication identified as effective in the current guideline as covered benefits.

NICOTINE REPLACEMENT THERAPY

Nicotine replacement therapy (NRT) may reduce nicotine withdrawal symptoms, lessening cravings for cigarettes by partially replacing the nicotine that would be obtained from tobacco use. Once nicotine is absorbed into the body, it is thought to stimulate nicotinic receptors in the brain causing release of dopamine.[17] Numerous product formulations containing nicotine are available, including gum, patches, lozenges, nasal spray, and inhaler. Compliance and behavioral modification are critical in smoking cessation and the form of NRT depends largely on the preference of the patient. It is important to address ease of use,

social acceptance, and tolerance throughout the quitting process. Cessation plans are often modified to include numerous methods fitting a variety of individual patient circumstances.

The FDA's approval of nicotine gum in 1984 for prescription use only was the first NRT on the U.S. market. In 1996, the gum was approved for over-the-counter (OTC) sales. Because some people could not tolerate the taste and use the proper "chew and park" method with the gum, transdermal nicotine patches became available in 1991 and 1992 by prescription only, with subsequent OTC status in 1996. The nicotine nasal spray and nicotine inhaler were approved in 1996 and 1997, respectively, and became available by prescription only. The nicotine lozenges were approved for OTC sales in 2002.[24]

All of the NRT products (i.e., gum, patches, nasal spray, lozenges, and inhaler) appear to be equally effective. A recent analysis of multiple studies concluded that all forms of NRT can increase the chance of successfully quitting smoking and increase the quit rate by 50 – 70%.[25] The treatment effect of all formulations of NRT was found to be independent of other treatments such as counseling or behavioral modification.[25]

Nicotine Polacrilex Gum

Nicotine gum is available in the United States as Nicorette® and as various generic products. Nicotine, which is bound to an ion-exchange resin base, is slowly released when the gum is chewed. The gum is available in 2- and 4-mg doses, and bicarbonate is added to facilitate absorption by creating an alkaline (basic) pH in the mouth. Acidic beverages such as coffee, juice, wine, or soft drinks interfere with the buccal (lining of the mouth) absorption of nicotine, so patients should be counseled to avoid eating or drinking for 15 minutes before and while chewing nicotine gum.[26] The amount of nicotine absorbed from the gum is lower than that obtained from smoking; however, buccal administration of NRT enables patients to control the amount and timing of use based on their own need. The freedom to titrate to personal need or combat an immediate craving with a quick response agent is a benefit over the transdermal patch. Further, for those with oral cravings, gum provides substantial oral activity during behavioral modification.

The initial dosage of nicotine polacrilex gum should be individualized based on the patient's nicotine dependence. Dosage is determined by the number of cigarettes smoked daily (Table 1) or by the Fagerstrom Tolerance Questionnaire (FTQ).[27] The FTQ, which has been used in many trials to measure nicotine dependence, has a scoring range of 0 to 11 points (0 is minimum dependence and 11 is maximum dependence).[28] Highly dependent smokers (FTQ score of ≥ 7 or ≥ 25 cigarettes a day) should receive the 4-mg dose initially. Other patients should begin treatment with the 2-mg dose.

Table 1. Nicotine Polacrilex Gum

Cigarettes Smoked Daily	Weeks 1 to 6	Weeks 7 to 9	Weeks 10 to 12
Less than 25[a]	1 piece of 2-mg strength every 1 to 2 hours	1 piece of 2-mg strength every 2 to 4 hours	1 piece of 2-mg strength every 4 to 8 hours
Equal to or more than 25[b]	1 piece of 4-mg strength every 1 to 2 hours	1 piece of 4-mg strength every 2 to 4 hours	1 piece of 4-mg strength every 4 to 8 hours

[a] For the 2-mg gum, patients should not chew more than 30 pieces a day if under a physician's supervision or more than 24 pieces a day if not under a physician's supervision.

[b] For the 4-mg gum, patients should not chew more than 24 pieces a day.

Adapted from reference 27.

For a patient who is unable to stop smoking within the first 4 weeks of therapy, the likelihood of quitting on that attempt is low, and the gum should be discontinued.

Patient Information

As with all NRTs, patients should stop smoking before starting to chew the gum. Patients should be instructed in the "chew and park" method of administration of the nicotine gum to improve the effectiveness and decrease side effects related to the gum. Patients should chew each piece slowly several times (about 15 chews). They should notice a tingling sensation and either a peppery, minty, citrus, or cinnamon taste. They should then place the gum in the mouth between the cheek and gums for several minutes until the tingling sensation is gone. The above steps should be repeated until the tingling sensation ceases to return. Each piece of gum should last approximately 20 to 30 minutes. After 1 to 2 months, patients should gradually begin reducing the amount of nicotine gum they use. Reducing the gum use over time will help prevent nicotine withdrawal symptoms. Using nicotine gum for more than three months is discouraged, and it should not be used for more than six months without consulting a health care provider.[27]

Adverse Reactions

Although approximately 25% of users have reported adverse reactions, most were very minor and of short duration. Adverse reactions that resulted in the discontinuation of therapy included headache, indigestion, mouth irritation, mouth ulcers, and nausea. Gastrointestinal effects are a result of swallowing nicotine released from the gum. If these occur, patients should be instructed to chew less vigorously, chew for shorter periods of time, and to limit the amount swallowed. Nicotine gum does not have any adverse effects on cardiovascular conditions. The gum may stick to dental work such as dentures, crowns, bridges, and fillings. Safety of the simultaneous use of the nicotine gum and cigarette smoking was evaluated, with no evidence of increased adverse reactions.[29]

Clinical Efficacy

Many trials have been completed comparing the nicotine gum to placebo gum in order to determine whether the nicotine gum is effective in smokers. In one trial, the effectiveness of the nicotine gum in combination with a behavior modification program was evaluated in 322 smokers.[30] The behavior modification program consisted of 12 group sessions over 6 weeks, with each session lasting 60 to 80 minutes. Smokers were classified into high-dependent and moderate-to-low-dependent groups based on their FTQ score. The high-dependent group (FTQ range 7 to 11; average 7) was treated with either 2-mg or 4-mg of nicotine gum, while the moderate-to-low group (FTQ range 4 to 6; average 5) was treated with 2-mg of nicotine gum or placebo gum. Throughout the 2-year follow-up, the 4-mg dose produced higher quit rates in highly dependent smokers than the 2-mg dose. Among the moderate-to-low group, those smokers receiving 2-mg of nicotine gum were two times more likely to remain smoke-free than those smokers that received the placebo gum. A second similar trial also found that the quit rates for the 4-mg dose were significantly better than those for the 2-mg dose in highly dependent smokers.[31] In the moderately dependent group, the 2-mg nicotine gum approximately doubled the quit rate compared to placebo gum.

These studies, as well as additional trials that have been completed, demonstrate that nicotine gum is effective in achieving and maintaining abstinence and that a dose-dependent response is seen. The 4-mg gum is more effective than the 2-mg gum in highly nicotine dependent smokers. Counseling is a useful adjunct to NRT.

Transdermal Nicotine Patch

When using the transdermal nicotine patches, nicotine is absorbed into the bloodstream following application of the patch to intact skin for either 16 or 24 hours. The patches are used as a temporary aid to smoking cessation and as a way to decrease nicotine withdrawal symptoms. Patches are the only long-acting nicotine replacement products available; however, treatment beyond three months is not routinely recommended.

The FDA approved four transdermal nicotine

patches in 1991 and 1992. Two of these were given OTC status in 1996: Nicotrol® and NicoDerm CQ®. Other OTC nicotine patch products followed (ProStep® in 1998 and Habitrol® in 1999). The Nicotrol® brand patch is no longer available in the United States and the Prostep® brand was discontinued as a prescription item in 1999 and previously sold as a store-brand OTC product.[32] Habitrol® is manufactured by Novartis Consumer Health and labeled as the Nicotine Transdermal System. It is distributed to various retailers (CVS, Rite Aid, etc.) and marketed under their store names.[33]

A summary of the different products available is provided in Table 2.[34,35,36]

Patient Information

Both the generic nicotine patch and NicoDerm CQ® are available as a 3-step program. Following a lag time of 1 to 2 hours, nicotine concentrations in the blood increase to peak levels between 6 and 12 hours and then decrease gradually.[35,36] Patients should be instructed to stop smoking when starting the patch and to apply it to a clean, dry, non-hairy (unshaven) area on the trunk or arm. The patch should be pressed firmly on the skin for 10 seconds, and patients should then wash their hands. After 24 hours, the patch should be removed. If left on longer, the patch may cause skin irritation and will lose strength. For consistent absorption, a different body site in the same general area should be chosen for the next patch. Patients should be advised that showering or bathing should not affect the patch and that they can engage in their normal activities, but that heating pads should not be applied over the patch. Patients should discard the patch by folding it in half with the adhesive parts together. Used patches may contain residual nicotine, which is poisonous, so they should be discarded away from pets and children.[35,36] Patients should also be instructed <u>not</u> to cut their patches in half to save money because this may cause a loss of nicotine from the edges of the patch and could impact the effectiveness of the product.

Adverse Reactions

During clinical trials, approximately 35 to 50% of participants reported experiencing adverse effects, including local skin reactions.[35,36] Reported

Table 2. Nicotine Transdermal Systems

Product	Product Description	Dosage
Nicotine Transdermal System, manufactured by Novartis Consumer Health for various retailers (Ahold, Albertson's, BJ's, Brooks, CVS, Duane Reed, Eckerd, Kroger, Longs, Medicine Shoppe, Meijer, Publix, Rite Aid, Safeway, Walgreens, and Wal-Mart); also manufactured by Watson *NicoDerm CQ®*, manufactured by GlaxoSmithKline	Nicotine Transdermal System Step 1: 21-mg/day Step 2: 14-mg/day Step 3: 7-mg/day Absorbed in 24 hours Each step contains either 7 or 14 patches per box.	Greater than 10 cigarettes smoked daily: Begin with Step 1. Use the 21-mg patch for 4 weeks, then the 14-mg patch for 2 weeks, followed by the 7-mg patch for 2 weeks. 10 or less cigarettes smoked daily: Do not begin with Step 1. Begin with Step 2, the 14-mg patch, for 6 weeks, followed by the 7-mg patch for 2 weeks. Completing the full program will increase the chances of quitting successfully. Discontinue at the end of 8 weeks. Patients who have cardiovascular disease, weigh less than 100 pounds, or smoke less than half a pack of cigarettes daily should be started on the 14-mg patch.

Adapted from references 34, 35 and 36.

reactions included redness, itching, rash, or burning at the application site. Local irritation was also reported after patch removal in approximately 20% of patients. Gastrointestinal side effects included diarrhea, heart burn, and dry mouth. Additional uncommon adverse events were joint pain, muscle pain, sweating, drowsiness, and abnormal dreams. Sleep disturbances, such as insomnia and vivid dreams, can be minimized by removing the patch before bedtime and replacing the patch in the morning providing a patch-free period of time.[35,36]

Clinical Efficacy

A large number of clinical trials have been performed using transdermal NRT, making it the most widely studied smoking cessation therapy currently available. Several trials have been conducted examining the effectiveness of the 3-step NicoDerm CQ® dosing regimen of 21-mg, 14-mg, and 7-mg.[37,38,39] Overall, the nicotine patch has been shown to approximately double the quit rate when compared to placebo.

One study attempted to predict which type of smoker benefited the most from using a transdermal patch.[40] The trial examined 1,686 patients recruited from 19 general physician practices and evaluated continuous smoking cessation from 8 to 52 weeks. Results demonstrated that nicotine patches were more effective for smokers with moderate nicotine dependence than in mildly or highly dependent smokers. In addition, younger smokers (24 to 49 years old) had better success rates than older smokers (50 to 65 years). Early abstinence from smoking was the strongest predictor of continued smoking cessation.

Nicotine Nasal Spray

Another method of nicotine delivery is by nasal spray, which is marketed in the United States by Pfizer, Inc. as Nicotrol NS®. This system consists of a hand-driven pump spray with anagueous (water-based) nicotine solution.[41] Each 10-mL spray bottle contains 100-mg of nicotine in an inactive base solution, and each actuation delivers 0.5-mg of nicotine. One dose is 2 sprays, 1 in each nostril, for a total of 1-mg.[41] Patients should be started at 1 to 2 doses per hour. The recommended minimum dose is 8 doses per day (16 sprays), up to a maximum daily dose of 40-mg (80 sprays) depending on prior tobacco use. Administering less than 8 doses per day is unlikely to result in effective nicotine levels and patients should not use greater than five doses per hour. The maximum recommended duration is three months.[41]

Following the administration of 2 sprays of Nicotrol NS®, approximately half of the nicotine dose is absorbed.[41] Nicotine concentrations in the blood rise rapidly after a 1-mg dose and reach maximum concentrations within 4 to 15 minutes. Due to the rapid absorption of nicotine, the nasal spray most closely mimics that of cigarette smoking. The use of nasal vasoconstrictors, such as nasal decongestants, will delay the absorption of nicotine into the circulation from the nasal spray.[41]

Patient Information

Patients should be instructed to stop smoking when starting this form of NRT and not to sniff, swallow, or inhale through the nose, but rather to tilt their head back and breathe normally as the spray is being administered.[41] Patients may blow their nose before administering the nasal spray. They should use 1 to 2 doses (1 dose equals 2 sprays) per hour and should be treated with Nicotrol NS® for 8 weeks, after which the spray should be tapered and discontinued over 4 to 6 weeks. Patients may increase the duration between doses or use one spray at a time instead of two sprays. The safety of using this product for greater than 6 months has not been established.[41]

Adverse Reactions

Adverse drug reactions reported with the nicotine nasal spray are primarily local and include nasal or throat irritation, sneezing, runny nose, watery eyes, and coughing. These symptoms were reported in nearly every patient on at least 1 occasion.[42] The frequency of local irritation declined with continued use, but was still experienced by 81% of patients after 3 weeks of therapy. Other less common adverse events reported by the manufacturer include chest tightness, numbness in the limbs, constipation, and stomatitis (mouth sores).[41]

Clinical Efficacy

The effectiveness of the nicotine nasal spray has been studied in several trials. One study examined the efficacy of the nicotine nasal spray in 255 smokers who were given either the nicotine nasal spray or placebo for up to six months.[43] Smoking abstinence rates were more than doubled for the nasal spray compared to placebo at 6 and 12 months. Adverse effects included local throat and nose irritation, coughing, sneezing, runny nose or eyes, heart palpitations, nausea, and a feeling of being high. The authors concluded that nicotine nasal spray is a safe and efficacious treatment for smoking cessation.

In a second trial, abstinence rates at 12 months were similar to those in the previous trial.[44] Abstinence rates for the active drug group compared with the placebo group were 26% and 10%. A third trial evaluated the efficacy of nicotine nasal spray for smoking cessation after the quit date at three months and then two years.[45] Abstinence rates were improved with the nicotine nasal spray for up to six months, but not at the 1- and 2-year follow-up visits.

Nicotine Inhaler

Another addition to the available treatments is the nicotine inhaler (marketed as the Nicotrol® inhaler), which is indicated for the relief of withdrawal symptoms and satisfies the "hand-to-mouth" habit that many smokers must overcome.[46] The Nicotrol® inhaler system consists of a plastic mouthpiece into which a cartridge containing a porous plug impregnated with 10-mg of nicotine is inserted. Menthol, an inactive ingredient, is added to reduce the irritant effects of nicotine.[46]

Most of the nicotine released from the inhaler is deposited in the mouth, where buccal (lining of the mouth) absorption occurs. Intensive inhalation (80 breaths over 20 minutes) releases an average of 4-mg of nicotine per cartridge with about 50% (2-mg) of this amount slowly absorbed into the bloodstream. Peak concentrations are reached within 15 minutes after inhalation ends. A single inhaler achieves approximately one third of the nicotine concentration achieved with cigarette smoking.[46]

Patient Information

Patients should be instructed to stop smoking completely when they begin using the Nicotrol® inhaler.[46] The initial dosage is individualized. Patients should self-titrate to the level of nicotine they require, usually between 6 and 16 cartridges per day. Best results were seen with frequent continuous puffing for 20 minutes. Patients should be instructed to press the cartridge firmly into the bottom of the mouthpiece until the seal breaks and to inhale with shallow, intensive puffing. After 20 minutes of puffing, the nicotine in the cartridge is used up, and the cartridge should be safely discarded out of the reach of animals and children. Patients may use the inhaler for less than 20 minutes and then reuse the cartridge until they have puffed for a total of 20 minutes. The mouthpiece should be cleaned regularly with soap and water. It is recommended that the inhaler be used for 3 months, after which patients should be gradually weaned from it over 6 to 12 weeks. The safety and efficacy of continued use for greater than six months have not been established.[46]

Adverse Reactions

Local throat irritation was reported by 40% of the patients in clinical trials.[46] Most side effects were mild and declined with continued use. Coughing was seen in one-third and inflammation of the nasal passages was seen in one-fourth of the patients receiving the nicotine inhaler. Heart burn and headache were also reported.[46]

Clinical Efficacy

The nicotine inhaler has demonstrated effectiveness in decreasing cravings and other withdrawal symptoms. Several trials have compared the nicotine inhaler to placebo. One trial evaluated 286 volunteer smokers who used the nicotine inhaler for 3 months and then tapered their use over 3 months.[47] The nicotine inhaler more than doubled the quit rate at 12 months. Treatment was well tolerated, and no serious adverse effects were noted.

Other studies have shown similar results. In a trial of 247 patients, the efficacy and safety of the nicotine inhaler were assessed.[48] After one year of follow-up, abstinence rates for the treatment group compared with the placebo group were

approximately double. Further, the inhaler group had fewer withdrawal symptoms than the placebo group. Adverse effects reported more frequently in patients using the inhaler were cough and mouth or throat irritation.

Nicotine Lozenge

The nicotine lozenge was approved by the FDA for OTC use in 2002 and is marketed as the Commit® lozenge in 2-mg and 4-mg strengths. A generic product is also available. Like the gum, the lozenge contains nicotine polacrilex, a resin complex of nicotine and polacrilin. The lozenge is available in original, mint, cherry, or cappuccino flavors and is sugar free. Compared with nicotine gum, the lozenges deliver approximately 25% more nicotine since they dissolve completely and no nicotine is retained in the product as is the case with the gum.[49] Buffering agents are added to the lozenges to increase the pH and the buccal (lining of the mouth) absorption of nicotine. Peak concentrations of nicotine are achieved in 30 to 60 minutes.[49]

Unlike other nicotine replacement products, the lozenges are dosed based on "time to first cigarette" (TTFC), which is used as an estimate of nicotine dependence on the assumption that the sooner the first cigarette is smoked, the higher the patient's dependence on nicotine.[50] If the first cigarette is smoked within 30 minutes of awakening, the 4-mg strength should be used. If the TTFC is more than 30 minutes after waking, the 2-mg strength should be used. Lozenges should be placed in the mouth and allowed to dissolve completely over 20 to 30 minutes. As the lozenge dissolves, a tingling sensation may be felt in the mouth. To achieve the best quit rates, the lozenge should be used on a scheduled basis rather than as needed. Patients should use one lozenge every 1 to 2 hours for the first 6 weeks, then taper to one lozenge every 2 to 4 hours for weeks 7 to 9, then one lozenge every 4 to 8 hours for weeks 10 to 12. Patients should use at least 9 lozenges per day for the first 6 weeks.[51]

Patient Information

To decrease the possibility of gastrointestinal side effects, the lozenges should not be chewed or swallowed, and patients should rotate the lozenge to different areas of the mouth occasionally to decrease the potential for irritation of the lining of the mouth. Acidic beverages such as wine, soda, and coffee may affect the absorption of nicotine, so patients should be instructed not to eat or drink for 15 minutes before or while using the lozenge.[49]

Adverse Reactions

The most common adverse events reported with the lozenge were gastrointestinal. In clinical trials, heartburn, hiccups, and nausea were found to be more common in both the 2-mg and the 4-mg groups. Cough was found to be more frequent in the 4-mg group only.[52] Flatulence, headache, and sore throat were also reported.

Clinical Efficacy

The nicotine lozenge was studied in a large trial of almost 2,000 smokers who were assigned a lozenge strength of 2- or 4-mg based on their TTFC.[52] Patients in each of the groups were randomized to either active treatment or placebo. Follow-up was performed at 2, 4, 6, 12, 24, and 52 weeks after beginning the study. At 52 weeks, the abstinence rate for the 2-mg lozenge group was 17.9% versus 9.6% for the placebo group, showing that the 2-mg lozenge doubles the quit rate compared to placebo. For the highly dependent smokers assigned to receive the 4-mg lozenge, the 52-week abstinence rate was 14.9% for the active treatment group and 6.2% for the placebo group, showing that the 4-mg lozenge more than doubled the quit rate compared to placebo.

NON-NICOTINE REPLACEMENT STRATEGIES

Bupropion Sustained-Release

Many of nicotine's effects on the central nervous system mimic those of an antidepressant. Bupropion hydrochloride has been available in the United States since 1989, first as an immediate-release product (Wellbutrin®), then as a sustained-release product (Wellbutrin SR®). In 1997, a second sustained-release product (Zyban SR®) was introduced for the management of smoking cessation, and a generic product was released in 2004. Bupropion inhibits the uptake of

norepinephrine, serotonin, and dopamine in the brain. The exact mechanism by which bupropion aids in smoking cessation is not known; however, the effect is not related to the antidepressant effect.[53,54]

Bupropion is rapidly absorbed from the gastrointestinal tract.[53] The recommended dose for smoking cessation is 150-mg of the sustained-release product once a day for 3 days, then twice per day for 7 to 12 weeks or longer, with or without NRT.[53] Daily doses should be taken at least 8 hours apart to decrease the risk of seizures by avoiding a high peak concentration of bupropion or its metabolites. Bupropion should be avoided in patients who have a history of, or a predisposition to, seizures. Bupropion should be used cautiously in patients with hepatic cirrhosis, and the dose in these patients should not exceed 150-mg every other day. The manufacturer suggests advising patients to stop smoking during the second week of treatment since one week is needed to reach steady-state blood concentrations. If a patient has not made significant progress toward quitting smoking by week seven, the attempt is not likely to be successful, and therapy should be discontinued. The usual treatment course is 7 to 12 weeks, and the manufacturer recommends that patients receive counseling and support throughout treatment.[53]

Patient Information

Patients should be counseled that bupropion is part of a plan to help them stop smoking and is not appropriate for everyone. Patients with a history of seizures or an eating disorder should not take this medication.[53] All patients should be observed for agitation, hostility, depression, and suicide-related activities and should be instructed to discontinue the drug and contact a healthcare provider if any of these occur.[53] Patients should be advised that the active ingredient in Zyban® and Wellbutrin® is the same, so these medications should not be taken together and the sustained-release tablets should not be crushed or broken. To avoid insomnia, the second daily dose of bupropion should be taken several hours prior to bedtime.[53]

Adverse Effects

The use of immediate-release bupropion has been limited by concerns about a high incidence of seizures associated with higher doses.[53] The seizure risk is dose-dependent, so doses greater than 300-mg/day of the sustained-release product should not be used for smoking cessation. Episodes of depression and suicide attempts have been reported in patients taking bupropion for smoking cessation and a black box warning regarding this effect has been added to the package insert. The most common adverse effects leading to discontinuation of the drug include tremor and skin rash; however, agitation and insomnia have been documented in patients taking the drug for depression. Dry mouth is also a common side effect. Decreasing the dose to 150-mg/day may provide similar clinical efficacy and better tolerability in cases where 300-mg/day cannot be tolerated because of adverse effects.[55]

Clinical Efficacy

Bupropion was studied in 615 patients in a 7-week trial.[56] Those patients who were enrolled were assigned to one of four different regimens: sustained-release bupropion at a dose of 50-mg twice daily, 150-mg every morning, 150-mg every day for 3 days and then 150-mg twice daily, or placebo. Patients set a target quit date one week after the start of their medication regimen and treatment continued for 7 weeks. Patients who received 300-mg of bupropion per day had a significantly better quit rate than those who received 100-mg or 150-mg per day. Bupropion 150-mg and 300-mg per day were found to be more effective than placebo at both 6 months and 12 months.

For the first week after the quit date, no differences in withdrawal symptoms were found among the four treatment groups. A total of 37 patients stopped treatment early because of adverse events such as tremor, headaches, rash, and itching. Those patients on the higher doses experienced less weight gain. In general, bupropion was well-tolerated. The most commonly reported side effects were insomnia, headache, and dry mouth.[56]

In a second study, four different treatment regimens were evaluated: 300-mg of bupropion per day, the Habitrol® nicotine patches (21-mg/day for weeks 2 through 7, 14-mg/day for week 8, and 7-mg/day for week 9), the combination of Habitrol®

plus bupropion, and placebo.[57] At 12 months, 15.6% of the patients taking placebo had quit smoking, compared with 16.4% of the patients on the Habitrol® patch, 30.3% of the patients on bupropion, and 35.5% of the patients randomized to the combination of the Habitrol® patch and bupropion.

An analysis evaluating 31 trials of bupropion used as single therapy for smoking cessation found that bupropion doubled the odds of quitting smoking compared with placebo.[54] The 2008 smoking cessation guidelines agree that bupropion sustained release approximately doubles the chance of quitting smoking for five months or longer.[23]

Varenicline

Varenicline (Chantix®) is the most recent addition to the available treatments for smoking cessation. Approved on May 11, 2006, and marketed by Pfizer, Inc., varenicline is a partial nicotine agonist which binds to the nicotine receptors in the brain.[58] Varenicline decreases craving and withdrawal symptoms similar to the nicotine replacement agents, but also blocks the reinforcing and reward behavior associated with smoking.[58,59]

To decrease the risk of nausea and insomnia, the dose should be gradually increased over one week. The dose on days 1 to 3 should be 0.5-mg daily, followed by 0.5-mg twice daily on days 4 to 7. The maintenance dose of 1-mg twice daily should be taken beginning on day 8 and continued through the end of treatment. The recommended length of treatment is 12 weeks; the dose does not need to be tapered before stopping the drug. In patients with kidney impairment (creatinine clearance less than 30-mL/min), the maximum dose should be 0.5-mg twice per day.[58]

Patient Information

Patients should be counseled to start taking varenicline one week before their actual quit date. Varenicline should be taken after a meal with a full glass of water, and therapy should last for 12 weeks. To avoid relapse, an additional 12 weeks can be considered for those patients who have successfully stopped smoking by week 12.[58]

Adverse Effects

The most common adverse events associated with the 1-mg twice daily dosing were nausea, sleep disturbances including insomnia and abnormal dreams, constipation, flatulence, and vomiting. Nausea, the most common adverse event seen with varenicline, is usually mild or moderate and transient; however, in some patients, nausea continued for several months. It is dose-dependent, so lowering the dose to 0.5-mg twice daily may be an option if the nausea is severe or if it continues.[58] There have been reports of agitation, depression, and suicide risk in patients taking varenicline for smoking cessation; therefore, a benefit-risk assessment must be completed.[60] A warning was recently added to the prescribing information for varenicline stating that depression, agitation, changes in behavior, suicidal ideation, and suicide have been reported in patients attempting to quit smoking while using varenicline. Prescribers should monitor for these effects and obtain a psychiatric history before using varenicline for smoking cessation.[58]

Clinical Efficacy

Two trials comparing varenicline with bupropion SR and placebo have been completed.[61,62] Participants were smokers who were 18 to 75 years old, smoked 10 or more cigarettes daily, had less than 3 months of abstinence from smoking in the previous year, and were motivated to quit smoking.

In the first trial, the abstinence rate for varenicline at 24 weeks (29.5%) was shown to be greater than for placebo (10.5%) and bupropion SR (20.7%). At 52 weeks, the abstinence rate for varenicline was higher than it was for placebo, but no longer greater than bupropion SR.[61] In the second trial, 23% of participants in the varenicline group continued to be abstinent at week 52 compared with 14.6% in the bupropion SR group and 10.3% in the placebo group. At 52 weeks, there was a 2.66 times greater chance of quitting with varenicline over placebo and a 1.77 times greater chance of quitting with varenicline over bupropion SR.[62]

An analysis of seven trials that evaluated varenicline for smoking cessation was completed.[63] They found that compared to placebo, patients taking varenicline had a 2.33 times greater chance

of quitting smoking and compared to bupropion SR, a 1.52 times greater chance of quitting smoking. They found that varenicline was well tolerated even if used longer than for the 12 weeks that are recommended. The 2008 smoking cessation guidelines evaluated the different dosing levels of varenicline.[23] For the 1-mg daily dose, the odds of quitting smoking double, while for the 2-mg daily dose, the odds of quitting smoking triple.

COMBINATION TREATMENT

Combination treatment with first-line agents for smoking cessation has been shown to be effective and may provide better cessation rates than first-line agents used alone.[23] Use of the nicotine patch long-term, meaning for greater than 14 weeks, plus another form of as needed NRT such as the gum or nasal spray, tripled the chance of quitting smoking. Other combination treatments including the nicotine patch plus the inhaler, and the nicotine patch plus bupropion SR, doubled to tripled the chance of quitting. The nicotine patch plus bupropion SR combination is FDA-approved for smoking cessation. The nicotine patch plus another form of NRT that provides immediate relief of cravings may offer patients better control of nicotine cravings and withdrawal symptoms, making the early phases of quitting less difficult.

OTHER SMOKING CESSATION THERAPIES

Aside from the first-line therapies including NRT products, bupropion, and varenicline, other agents endorsed by the 2008 smoking cessation guideline as second-line therapies include nortriptyline and clonidine.[23] These two second-line agents are available by prescription only and should be used with physician supervision. Additionally, many investigational agents are being studied for smoking cessation at this time.

BEHAVIORAL TREATMENTS

Behavioral therapy has long been an option for those who seek treatment for nicotine addiction. Current research has examined the efficacy of self-help materials, individual and group counseling, personalized feedback, and telephone counseling including quitlines.[23] These types of counseling have all been shown to be effective for smoking cessation either alone or in combination with medications. The current smoking cessation guidelines also promote the use of brief interventions as a useful tool to improve quit rates. Brief interventions are less than 10 minutes in duration and should be offered at every clinician visit. For patients not yet ready to quit, brief interventions can increase the chance of quitting at a later time due to the continued advice to quit smoking. Due to their short duration, they can fit well in busy office practices and be completed by a variety of different healthcare providers.

The 5 A's is a model that can be used for brief counseling. This strategy is outlined in Table 3.

When evaluating intensive counseling for smoking cessation, session length and the number

Table 3. The 5 A's Model

Ask about tobacco use.	Ask about and document tobacco use at every visit for every patient.
Advise to quit.	Urge every tobacco user to quit in a clear, concise manner.
Assess willingness to make a quit attempt.	Determine if patient is willing to make a quit attempt at this time.
Assist in the quit attempt.	If the patient is willing to make a quit attempt, offer and provide medication or refer for additional treatment. If the patient is unwilling to make a quit attempt, provide motivation to increase future quit attempts.
Arrange follow-up.	If the patient is willing to make a quit attempt, arrange for follow-up within one week of quitting. If the patient is unwilling to make a quit attempt, address the issue again at the next visit.

of sessions provided impacted the chance of quitting smoking. Longer sessions and programs with 8 or more sessions overall showed better quit rates.[23]

A strategy that can be used to increase a patient's motivation to quit smoking is the 5 R's. The 5 R's include **R**elevance, **R**isks, **R**ewards, **R**oadblocks, and **R**epetition. Relevance involves making quitting smoking relevant to that individual by identifying specific reasons that the patient has for wanting to quit smoking. Risks includes identifying specific risks from smoking specific to that patient and Rewards includes identifying any benefits that may be gained from stopping smoking. Roadblocks involves identifying the barriers that individual has to stopping smoking. These could include fear and worry about withdrawal symptoms. Repetition involves repeating this intervention with the patient at every visit.

Table 4. Cost per Unit for Smoking Cessation Treatments

Treatment/Availability	Dosage	Cost per Unit[a]
Sustained-release bupropion (Zyban®)/Prescription	150-mg every morning for 3 days, then 150-mg twice daily (begin treatment 1 to 2 weeks before quitting)	150-mg, 60 tablets $174.05 (brand) $69.98 (generic)
Varenicline (Chantix®)/Prescription	0.5-mg every morning for 3 days, then 0.5-mg twice daily for 4 days, then 1-mg twice daily (begin treatment 1 week before quitting)	0.5-mg, 56 tablets $107.53 1-mg, 56 tablets $107.53
Nicotine gum (Nicorette®)/over-the-counter	For patients who smoke 1 to 24 cigarettes/day: 2-mg of gum (up to 24 pieces/day)	2-mg, 50 pieces $29.49
	For patients who smoke 25 or more cigarettes/day: 4-mg of gum (up to 24 pieces/day)	4-mg, 48 pieces $29.49
Nicotine inhaler (Nicotrol®)/Prescription	6 to 16 cartridges/day	4-mg, 168 actuations $148.12
Nicotine lozenge (Commit®)/over-the-counter	Time to first cigarette: Greater than 30 minutes: 2-mg lozenge Less than 30 minutes: 4-mg lozenge (up to 20 lozenges/day)	2-mg, 192 lozenges $78.10 4-mg, 192 lozenges $78.10
Nicotine nasal spray (Nicotrol NS®)/Prescription	8 to 40 inhalations/day	10-mL, 4 spray units $148.12
Nicotine transdermal patch (Novartis Consumer Health)/over-the-counter	7-mg for 24 hours 14-mg for 24 hours 21-mg for 24 hours	7-mg, 7 patches $17.63 14-mg, 7 patches $17.63 21-mg, 7 patches $17.63

[a] Prices are based on average wholesale price in 2009.

ECONOMICS OF SMOKING CESSATION

Between 2000 and 2004, smoking was associated with $96 billion annually in direct medical costs and $96.8 billion annually in lost wages and productivity from associated diseases and death.[1] Numerous cost-effectiveness studies have evaluated smoking cessation counseling with or without NRT, and a cost-benefit analysis has been completed for varenicline.[64] Fiscella and Franks determined the incremental cost-effectiveness of the transdermal patch taken in addition to smoking cessation counseling by a physician.[65] They found that the use of the patch produced one additional lifetime quitter at a cost of $7,332. Further studies may document the long-term savings from quitting smoking as offsetting this initial cost. Another study evaluated the impact of a pharmacist's smoking cessation consultation with the nicotine patch. The cost of the treatment was $351, with a $302 net benefit for employers for the first year an employee did not smoke and $1,483 for each year thereafter.[66]

Although the cost-effectiveness varies, any program that aids in smoking cessation, whether it includes the use of medications or not, could be cost-effective. The top three employee health priorities ranked by employers are smoking, high blood pressure, and obesity. Employers felt that they should take steps to help employees quit smoking and that the best way to do this is to offer smoke-free working environments. Employees; however, ranked smoking cessation benefits as desirable to help them quit. Table 4 describes the direct costs associated with the various effective smoking cessation treatments.

CONCLUSION

Smokers who wish to quit can turn to a wide range of smoking cessation aids, both prescription and nonprescription, to help them achieve their goal. More options than ever are available to smokers for assistance with quitting smoking and the research continues to grow. NRT in any form (gum, patch, lozenge, inhaler, nasal spray) has been shown to approximately double the chances of quitting successfully. Bupropion SR is an oral agent that does not contain nicotine, and varenicline is a novel agent that offers an additional treatment option for smoking cessation. Smoking should be considered a chronic disease, and all patients should be offered some form of assistance in quitting. A successful plan for smoking cessation requires both behavior modification counseling and effective drug treatments. ■

REFERENCES

1. Centers for Disease Control and Prevention. Smoking-attributable mortality, years of potential life lost, and productivity losses – United States, 2000 – 2004. *MMWR Morb Mortal Wkly Rep* 2008;57(45):1226-1228.
2. Centers for Disease Control and Prevention. Cigarette smoking among adults and trends in smoking cessation – United States, 2008. *MMWR Morb Mortal Wkly Rep* 2009;58(44):1227-1232.
3. Centers for Disease Control and Prevention. Cigarette use among high school students – United States, 1991 – 2007. *MMWR Morb Mortal Wkly Rep* 2008;57(25):689-691.
4. The American Nonsmokers' Rights Foundation. Available at: www.No-smoking.org. Accessed March 8, 2010.
5. U.S. Department of Health and Human Services. The health consequences of smoking: a report of the Surgeon General. Atlanta, Ga.: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2004. Available at: http://www.surgeongeneral.gov/library/smokingconsequences/. Accessed December 21, 2009.
6. Centers for Disease Control and Prevention. Fact sheet: health effects of cigarette smoking (updated August 2009). Available at: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/health_effects/index.htm. Accessed December 21, 2009.
7. McBride PE. The health consequences of smoking: cardiovascular diseases. *Med Clin North Am* 1992;76(2):333-353.
8. Bartecchi CE, MacKenzie TD, Schrier RW. The human costs of tobacco use. *N Engl J Med* 1994;330(13):907-912.
9. Jackson RD, Donepudi S, Mysiw WJ. Epidemiology of fracture risk in the Women's Health Initiative. *Curr Osteoporosis Rep* 2008; 6(4):155-161.
10. U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a reort of the Surgeon General. Atlanta, Ga.: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Disease Prevention and Health Promotion, Office on Smoking and Health, 2006. Available at: http://www.surgeongeneral.gov/lirary/secondhandsmoke/report/index.html. Accessed December 16, 2009.
11. Benowitz NL, Jacob P III, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther* 2006;80(6):703-714.
12. Federal Trade Commission Report. Tar, nicotine, and carbon monoxide of the smoke of 1,206 varieties of domestic cigarettes for the year 1994. July 15, 1997. Available at: http://www.erowid.org/plants/tobacco/tobacco_nic.shtml. Accessed December 14, 2009.
13. The Boston Globe. Cigarettes pack more nicotine. August 30, 2006. Available at: http://www.boston.com/yourlife/health/other/articles/2006/08/30/cigarettes_pack_more_nicotine/. Accessed December 12, 2009.

14. U.S. Department of Health and Human Services. The health consequences of smoking: nicotine addiction. A report of the Surgeon General, 1988. Washington, D.C.: U.S. Government Printing Office; 1988. DHHS Publication CDC 88-8406.
15. Benowitz NL. Cigarette smoking and nicotine addiction. *Med Clin North Am* 1992;76(2):415-437.
16. Benowitz NL. Pharmacology of nicotine: addiction and therapeutics. *Annu Rev Pharmacol Toxicol* 1996;36:597-613.
17. Pomerleau OF. Nicotine and the central nervous system: biobehavioral effects of cigarette smoking. *Am J Med* 1992;93(supp 1A):2s-7s.
18. U.S. Department of Health and Human Services. The health benefits of smoking cessation: a report of the Surgeon General. 1990. Rockville, MD: U.S. Department of Health and Human Services; 1990. DHHS publication CDC 90-8416.
19. Centers for Disease Control and Prevention. Cigarette smoking among adults – United States, 1992, and changes in the definition of current cigarette smoking. *MMWR Morb Mortal Wkly Rep* 1994;43(19):342-346.
20. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004;26;328(7455):1519.
21. Fiore MC, Bailey WC, Cohen SJ, et al. Smoking Cessation: Information for Specialists. Rockville, MD: U.S. Department of Health and Human Services; 1996. AHCPR publication 96-0694.
22. Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; 2000.
23. Fiore MC, Jaen CR, Baker TB, et al. Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service; May 2008.
24. Drugs@FDA. Available at: http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/. Accessed March 8, 2010.
25. Stead LF, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev 2008, Issue 1. Art. No.: CD000146.
26. Henningfield JE, Radzius A, Cooper TM, Clayton RR. Drinking coffee and carbonated beverages blocks absorption of nicotine from nicotine polacrilex gum. *JAMA* 1990;264(12):1560-1564.
27. Nicorette® (nicotine) gum [package insert]. Pittsburgh, PA: GlaxoSmithKline Consumer; 2009.
28. Fagerstrom KO, Schneider NG. Measuring nicotine dependence: a review of the Fagerstrom Tolerance Questionnaire. *J Behav Med* 1989;12(2):159-182.
29. Murray RP, Bailey WC, Daniels K, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest* 1996;109(2):438-445.
30. Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerström KO. Nicotine gum, 2 and 4 mg, for nicotine dependence: a double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995;108(2):447-451.
31. Tønnesen O, Fryd V, Hansen M, et al. Effect of nicotine chewing gum in combination with group counseling on the cessation of smoking. *N Engl J Med* 1988;318(1):15-18.
32. FDA approves OTC ProStep nicotine patch [press release]. Dublin, Ireland, and Allegan, MI; January 4, 1999. Available at: http://www.pslgroup.com/dg/d8dae.htm. Accessed December 16, 2009.
33. Habitrol Web site. Retailers. Available at: http://www.habitrol.com/retailers.html. Accessed December 16, 2009.
34. NicoDerm CQ Web site. Dosing calculator. Available at: http://www.nicodermcq.com/Quit_Place_Dose.aspx#. Accessed December 16, 2009.
35. Habitrol® (nicotine) transdermal system [package insert]. East Hanover, NJ: Novartis; 2006.
36. NicoDerm CQ® (nicotine) transdermal system [package insert]. Pittsburgh, PA: GlaxoSmithKline Consumer; 2006.
37. Mankani SK, Garabrant DH, Homa DM. Effectiveness of nicotine patches in a workplace smoking cessation program: an 11-month follow-up study. *J Occup Environ Med* 1996;38(2):184-189.
38. Sønderskov J, Olsen J, Sabroe S, Meillier L, Overvad K. Nicotine patches in smoking cessation: a randomized trial among over-the-counter customers in Denmark. *Am J Epidemiol* 1997;145(4):309-318.
39. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. *BMJ* 1995;311(7001):363-366.
40. Yudkin PL, Jones L, Lancaster T, Fowler GH. Which smokers are helped to give up smoking using transdermal nicotine patches? Results from a randomized, double-blind, placebo-controlled trial. *Br J Gen Pract* 1996;46 (404):145-148.
41. Nicotrol NS® (nicotine nasal spray) [package insert]. New York, NY: Pfizer, Inc.; 2008.
42. Schneider NG, Lunell E, Olmstead RE, Fagerström KO. Clinical pharmacokinetics of nasal nicotine delivery: a review and comparison to other nicotine systems. *Clin Pharmacokinet* 1996;31(1):65-80.
43. Schneider NG, Olmstead R, Mody FV, et al. Efficacy of a nicotine nasal spray in smoking cessation: a placebo-controlled, double-blind trial. *Addiction* 1995;90(12):1671-1682.
44. Sutherland G, Stapleton JA, Russell MAH, et al. Randomised controlled trial of nasal nicotine spray in smoking cessation. *Lancet* 1992;340(8815):324-329.
45. Blöndal T, Franzon M, Westin A. A double-blind randomized trial of nicotine nasal spray as an aid in smoking cessation. *Eur Respir J* 1997;10(7):1585-1590.
46. Nicotrol® inhaler (nicotine) inhalation system [package insert]. New York, NY: Pfizer, Inc.; 2008.
47. Tønnesen P, Nørregaard J, Mikkelsen K, Jørgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;269(10):1268-1271.
48. Hjalmarson A, Nilsson F, Sjöström L, Wiklund O. The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997;157(15):1721-1728.
49. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tobacco Res* 2003;5(5):635-644.
50. Heatherton TF, Kozlowski LT, Frecker RC, Rickert W, Robinson J. Measuring the heaviness of smoking: using self-reported time to the first cigarette of the day and number of cigarettes smoked per day. *Br J Addict* 1989;84(7):791-800.
51. Commit lozenge Web site. Choose the right strength. Available at: http://www.commitlozenge.com/Quit_Place_ Dose.aspx. Accessed December 16, 2009.
52. Shiffman S, Dresler CM, Hajek P, Gilburt SJA, Targett DA, Strahs KR. Efficacy of a nicotine lozenge for smoking cessation. *Arch Intern Med* 2002;162(11):1267-1276.
53. Zyban® (bupropion hydrochloride) sustained-release tablets [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2009.
54. Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. Cochrane Database Syst Rev 2007; Issue 4. Art. No.: CD000031.
55. Swan GE, McAfee T, Curry SJ, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. *Arch Intern Med* 2003;163(19):2337-2344.
56. Hurt RD, Sachs DPL, Glover ED, et al. A comparison of sustained-release bupropion and placebo for smoking cessation. *N Engl J Med* 1997;337(17):1195-1202.

57. Jorenby DE, Leischow SJ, Nides MA, et al. A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *N Engl J Med* 1999;340(9):685-691.
58. Chantix® (varenicline) tablets [package insert]. New York, NY: Pfizer, Inc.; 2009.
59. Foulds J. The neurobiological basis for partial agonist treatment of nicotine dependence: varenicline. *Int J Clin Pract* 2006;60(5):571-576.
60. Cahill K, Stead L, Lancaster T. A preliminary benefit-risk assessment of varenicline in smoking cessation. *Drug Saf* 2009;32(2):119-135.
61. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an alpha-4 beta-2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. *JAMA* 2006;296(1):47-55.
62. Jorenby DE, Hays JT, Rigotti NA, et al, for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an alpha-4 beta-2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. *JAMA* 2006;296(1):56-63.
63. Cahill K, Stead LF, Lancaster L. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2008; Issue 3. Art. No.: CD006103.
64. Jackson KC II, Nahoopii R, Said Q, Dirani R, Brixner D. An employer-based cost-benefit analysis of a novel pharmacotherapy agent for smoking cessation. *J Occup Environ Med* 2007;49(4):453-460.
65. Fiscella K, Franks P. Cost-effectiveness of the transdermal nicotine patch as an adjunct to physicians' smoking cessation counseling. *JAMA* 1996;275(16):1247-1251.
66. McGhan WF, Smith MD. Pharmacoeconomic analysis of smoking-cessation interventions. *Am J Health-Syst Pharm* 1996;53(1):45-52.

VOLUME 15 NO. 2 SMOKING CESSATION UPDATE
SELF-ASSESSMENT QUESTIONS 1 — 20

1. Which one of the following is <u>not</u> a symptom of nicotine withdrawal?
   A. Restlessness
   B. Insomnia
   C. Decreased appetite
   D. Depression

2. Which one of the following is <u>false</u> regarding counseling for nicotine dependence?
   A. Counseling alone is an effective method for treating nicotine dependence.
   B. Telephone quitline counseling has not been shown to be effective for nicotine dependence.
   C. The combination of counseling plus medication is more effective than either alone.
   D. Both individual and group counseling are effective for treating nicotine dependence.

3. SJ is a 42-year-old female patient who is very concerned about feeling irritable and nervous if she quits smoking. Which one of the "5 R's" would this situation represent?
   A. Relevance
   B. Rewards
   C. Risks
   D. Roadblocks

4. Which one of the following is <u>not</u> a common side effect of the nicotine gum and lozenge?
   A. Skin rash
   B. Headache
   C. Nausea
   D. Indigestion

5. RJ smokes 1½ packs per day and would like to use the nicotine gum to quit smoking. Which one of the following statements is <u>true</u> regarding the nicotine gum?
   A. RJ should begin with the 2-mg strength and chew no more than 24 pieces per day.
   B. RJ should not use the gum for greater than 8 weeks.
   C. RJ should avoid eating or drinking for 15 minutes before and while chewing the gum.
   D. RJ should not use any other nicotine replacement products while he is using the gum.

6. The "5 A's" is an effective strategy to provide counseling for smoking cessation. Which one of the following is the first step for every patient when using this model?
   A. Advise
   B. Assess
   C. Arrange
   D. Ask

7. TS has previously used the nicotine patch in an attempt to quit smoking; however, he was not successful due to severe cravings. Which one of the following agents would be appropriate to add to the nicotine patch on his next quit attempt?
   A. Nortriptyline
   B. Nicotine inhaler
   C. Clonidine
   D. No agent should be added.

8. There are several methods to determine the correct dose of the nicotine replacement agents. Which one of the following agents is dosed based on the time to first cigarette (TTFC)?
   A. Nicotine gum
   B. Nicotine inhaler
   C. Nicotine lozenge
   D. Nicotine nasal spray

9. There are a large number of health consequences related to smoking. Which one of the following is <u>true</u> regarding the health risks due to smoking?
   A. Quitting smoking provides long-term health benefits, but no short-term benefits.
   B. There are clear health benefits to smoking cigarettes that contain lower amounts of tar and nicotine.
   C. Smoking harms almost every organ in the body and negatively affects general health.
   D. Quitting smoking after age 35 does not affect the lifespan or provide health benefits.

10. KH is a 51-year-old male who has smoked 1 pack per day for the past 23 years. He would like to use the nicotine patch to stop smoking. Which one of the following is <u>true</u> regarding the nicotine patch?
    A. The patch should be placed on the hips and legs.
    B. Insomnia and vivid dreams can occur when the patch is left on overnight.
    C. The patch should be placed on the same site each day to assure consistent absorption.
    D. The patch rarely causes skin irritation, redness or itching at the site of application.

11. ST would like to quit smoking, but would like to know what benefits will result from stopping smoking. Which one of the following is a documented benefit of smoking cessation?
    A. Decreased health care costs
    B. Decreased healthy behaviors
    C. Increased health care costs
    D. Increased health risks

12. **First-line agents for smoking cessation have been shown to at least double the quit rate when compared to placebo. Which one of the following is <u>not</u> considered to be a first-line agent for smoking cessation?**
    A. Bupropion SR
    B. Nicotine nasal spray
    C. Clonidine
    D. Varenicline

13. **Which one of the following is a contraindication for the use of bupropion SR for smoking cessation?**
    A. Depression
    B. Cirrhosis
    C. Decreased renal function
    D. History of seizures

14. **Which one of the following is <u>false</u> regarding the nicotine inhaler?**
    A. Each inhaler cartridge contains 10-mg of nicotine.
    B. Menthol is added to the cartridge to reduce the irritant effects of nicotine.
    C. The inhaler should be puffed continuously for 20 minutes.
    D. The inhaler simulates smoking, but does not satisfy the hand-to-mouth habit.

15. **Smoking increases the risk of cardiovascular disease, cancer and many other diseases. Which one of the following is <u>true</u> regarding the cardiovascular health risks of smoking?**
    A. Smoking 1 – 4 cigarettes per day does not cause an increase in the cardiovascular health risks associated with smoking.
    B. Smoking and using oral contraceptives greatly increases the risk of cardiovascular disease.
    C. Environmental tobacco smoke is not a significant cause of cardiovascular disease in nonsmokers.
    D. Smoking is not considered to be a major risk factor for coronary heart disease.

16. **Which one of the following statements is <u>true</u> regarding nicotine addiction?**
    A. Nicotine is slowly absorbed from the lungs into other body tissues.
    B. Oral ingestion of nicotine results in high blood levels of nicotine.
    C. Nicotine absorption across the blood-brain-barrier occurs in 10 – 19 seconds.
    D. Nicotine levels in the brain remain constant between cigarettes.

17. **TD has smoked 1 pack per day for the past 10 years. He would like to quit smoking, but states he enjoys smoking and needs something to do with his hands. Which one of the following nicotine replacement therapies would be a good choice for TD?**
    A. Nicotine gum
    B. Nicotine inhaler
    C. Nicotine patch
    D. Nicotine nasal spray

18. **RK was started on bupropion SR to help her stop smoking 4 weeks ago. She is having difficulty with insomnia since starting this medication and is considering discontinuing it. Which one of the following options would be the best choice to alleviate the insomnia in RK?**
    A. Discontinue bupropion SR.
    B. Reduce the dose of bupropion SR.
    C. Take the second daily dose at least 3 hours before bedtime.
    D. Take both daily doses in the morning.

19. **TH is concerned about stopping smoking "cold turkey". Which one of the following treatments for smoking cessation allows patients to continue smoking for the first week after starting the medication?**
    A. Nicotine nasal spray
    B. Varenicline
    C. Bupropion SR
    D. Varenicline and bupropion SR

20. **EJ is able to quit smoking for one month, but she relapses back to her previous smoking level of 1 pack per day due to stress. Which one of the following would be important for EJ to be successful on her next quit attempt?**
    A. Arrange a follow-up meeting within one week of her quit date.
    B. Tell EJ that quitting smoking can wait until her stress level declines.
    C. Recommend that EJ eat chocolate to manage stress.
    D. EJ is not ready to quit so will not be successful.