



Evidence-Based Best Practices

Smoking Cessation

November 2010

The material in this report discusses uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration. The following information is provided for educational purposes and not to endorse off-label use.

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INTRODUCTION

SCORxE

The South Carolina Medicaid Academic Detailing Program is officially identified as SCORxE which stands for South Carolina Offering Prescribing Excellence. This program is a collaborative effort between the South Carolina College of Pharmacy (SCCP) and the South Carolina Department of Health and Human Services (SCDHHS) to improve the healthcare of Medicaid beneficiaries diagnosed with mental health disorders, HIV/AIDS, or cancer. The goal is to promote individualized care while maintaining excellence in quality, evidenced-based, cost-effective drug therapy.

The core of the Academic Detailing program involves clinical educators meeting face-to-face with clinicians to provide unbiased clinical information that will assist in prescribing decisions. SCORxE aims to create connectivity and build professional relationships with clinicians in order to encourage best practices. While cost-effectiveness is taken into consideration for best practices, the primary goal of this initiative is to improve the quality of care for South Carolina (SC) Medicaid patients.

SCORxE Best Practices Report Development Process

A group of primary care physicians, pharmacists, and other healthcare professionals was created to develop an evidence-based best practices report to focus on promoting smoking cessation in primary care. ***The May 2008 Treating Tobacco Use and Dependence: 2008 Update. Clinical Practice Guideline. U.S. Department of Health and Human Services Public Health Service (hereby referred to as PHS Guideline) was the group's primary source of information. Most of the evidence is based on studies of cigarette smoking. In many cases, the PHS Guideline panel believes the results can be generalized to all tobacco users.*** This report includes additional recommendations from a review of primary literature published since the PHS Guideline was issued. Modifications were made to the PHS Guideline as necessary for the SCORxE project.

SCORxE Smoking Cessation Best Practices Report

The SCORxE smoking cessation best practices offers providers with balanced, evidence-based clinical information to assist in making optimal treatment decisions about medication and psychosocial and behavioral therapy. Treatment options recommended throughout this document are based on available data derived from various sources. The following symbols, found in parentheses following statements, indicate the level of evidence for the statements as shown below:

- (Level A) - Multiple well-designed randomized clinical trials, directly relevant to the statement, yielded a consistent pattern of findings.
- (Level B) - Some evidence from randomized clinical trials supported the statement, but the scientific support was not optimal. For instance, few randomized trials existed, the trials that did exist were somewhat inconsistent, or the trials were not directly relevant to the statement.
- (Level C) - Reserved for important clinical situations in which the PHS Guideline panel achieved consensus on the statement in the absence of relevant randomized controlled trials.

The information contained in this report is intended to supplement the knowledge of clinicians regarding best practices and drug therapy to promote smoking cessation in primary care patients. This information is advisory only and is not intended to replace sound clinical judgment, nor should it be regarded as a substitute for individualized diagnosis and treatment. Special considerations are needed when treating some populations such as adolescents, the elderly, pregnant or breast-feeding women, and patients with certain medical conditions (e.g., cardiac disease, liver and renal impairment).

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KEY MESSAGES FOR PROMOTING SMOKING CESSATION

- Question and document tobacco use at every visit.
- Understand the challenge to quit and expect relapse.
- Identify readiness to quit to best tailor approach to patient.
- Treatment is effective and multiple options allow for individualized interventions.

SMOKING CESSATION AT-A-GLANCE

- Tobacco use is the number one cause of preventable morbidity and mortality in the U.S.
- Tobacco dependence is an addiction that is hard to kick; it is a chronic disease that often requires repeated intervention and multiple attempts to quit.
- Smoking cessation is one of the most cost-effective preventive care services. Clinically effective treatments exist that can significantly increase rates of long-term abstinence.
- Consistent identification and documentation of smoking status and treatment of all tobacco users seen in healthcare are essential.
- Two key questions: “Do you smoke?” and “Do you want to quit?” are important starting points for counseling patients about smoking cessation during the clinical encounter.
- A physician’s advice to patients to quit smoking increases overall abstinence rates; even brief counseling lasting less than 3 minutes is effective.
- Pediatric visits offer important opportunities to ask and advise parents and caregivers about tobacco use to effectively increase abstinence among adults who smoke.
- Individual, group and telephone counseling are effective and their effectiveness increases with treatment intensity. Three types of counseling are particularly effective:
 - Practical counseling (problem-solving/skills training);
 - Social support delivered as part of treatment; and
 - Motivational interviewing or motivational enhancement based approaches, primarily effective at increasing future quit attempts in smokers currently unwilling to quit.
- Advising smokers to provide a smokefree home and car for family and others in their care is important to minimize health risks associated with secondhand smoke.
- Proactive telephone quitlines (e.g., S.C. Tobacco Quitline 1-800-QUIT-NOW) provide patients easy access to support and can effectively augment office-based treatment and counseling.
- Counseling and medications are each effective as monotherapy; however, the combination is more effective than either treatment alone.
- Several medications are effective for tobacco dependence and should be considered unless contraindicated or in populations for which evidence of safety and/or efficacy is insufficient (i.e., pregnancy, smokeless tobacco users, light smokers, adolescents).
 - First-line medications that increase long-term abstinence rates:
 - ✓ Nicotine gum
 - ✓ Nicotine inhaler
 - ✓ Nicotine lozenge
 - ✓ Nicotine nasal spray
 - ✓ Nicotine patch
 - ✓ Bupropion SR
 - ✓ Varenicline
 - Certain combinations of medications may also be considered.

SMOKING TRENDS AND RELATED HEALTH ISSUES

Smoking Prevalence

In 2008, one out of 5 adults in the U.S. were current smokers.¹ Older smokers make up a large percentage of all adult smokers in the U.S. with 41% being age 45 or older.^{2,3} Men (23.1%) were more likely to be smokers than women (18.3%).¹ South Carolina reported similar smoking rates of about 20% with slightly more men (21.6%) than women (18.7%) who were smokers. Smoking was reported in 20.1% of Hispanics, 19.2% of Caucasians, and 18.5% of African Americans.⁴ Eleven percent of women in the U.S. reported smoking during pregnancy in 2004.⁵ Smoking rates in patients with psychiatric disorders are almost double that of the general population.⁶

Light smoking (defined here as anyone who smokes less than 10 cigarettes per day, including individuals who may not smoke daily and those who smoke low-tar/low nicotine cigarettes) is on the rise, possibly due to smoking restrictions and higher costs. Approximately 25.4% of U.S. adult smokers reported smoking 10 or fewer cigarettes per day and 11.6% reported smoking 5 or fewer cigarettes per day in an analysis of 1991 - 1993 data from the National Household Survey on Drug Abuse (NHSDA).⁷ Cigarette sales have been declining over the past decade, but sale of cigars increased 15.3% in 2005, and 'little cigars' hit an all-time high in 2006.² In South Carolina a pack of cigarettes cost on average \$5.40 (including the 2009 federal tax increase and the South Carolina tax increase effective July 1, 2010).⁸ A pack/day smoker spends around \$1,971 on cigarettes each year. In 2005, 4% of adult men reported smokeless tobacco use (chewing tobacco, snuff, moist snuff, betel quid), whereas less than 1% of women reported use of smokeless tobacco. Use of smokeless tobacco has been rising among children and adolescents.²

Smoking is also prevalent among children and adolescents. In 2006, an estimated 3.3 million U.S. adolescents (12 – 17 years old) reported tobacco use within the past month and 2.6 million were current cigarette smokers.² In the U.S., the prevalence of teenage smoking (defined as having smoked at least once in the last 30 days) has declined from a peak of 36.5% in 2002 to 22% in 2007.⁹ South Carolina recorded a high school youth smoking prevalence of 21.8% in 2009, a 3% increase from 2007 that did not reach statistical significance.^{10,11} Several reasons may influence whether young people experiment with tobacco or become regular users, including: social and parental norms, advertising, movies and popular media, peer influence, parental smoking, weight control, and curiosity. Among current adult smokers, 90% reported trying their first cigarette before age 21.² Evidence shows that people who do not smoke before the age of 20 are significantly less likely to take up the habit as an adult.⁹

Tobacco-Related Risks and Health Consequences

Tobacco use is the number one cause of preventable morbidity and mortality in the U.S.¹ Smoking is a risk factor for 7 of the 14 major causes of death for older adults over 65 years old. Smoking can be linked to hypertension/cardiovascular disease, cancer, stroke/cerebrovascular disease, chronic obstructive pulmonary disease (COPD), diabetes, arteriosclerosis, ulcers, and cataracts. Bronchitis, shortness of breath, coughing, colds, loss of stamina, pneumonia, and osteoporosis are also more prevalent among smokers.³ Acutely, smoking promotes platelet aggregation and coagulation activity which increases the risk of thrombus formation. Smoking promotes plaque development in the vasculature while upregulating proteinases, which weaken the arterial walls. Smoking also increases oxidative stress, leading to increased levels of oxidized LDL-cholesterol; and, in turn, long-term smoking promotes atherosclerosis.¹²

Hospitalized smokers have impaired bone and wound healing and are more likely to experience interference with their recovery and overall health. Racial and ethnic minorities experience higher mortality rates influenced by tobacco exposure in a number of diseases (e.g., cancer and cardiovascular disease among African Americans; and infant deaths among African Americans, American Indians, or Alaskan natives).²

Despite lower use, light smokers are still at risk for developing smoking-related diseases. In Norway, an increased risk of death from ischemic heart disease and other tobacco-related causes for both men and women who smoked 1 to 4 cigarettes per day was found in a large longitudinal study (N=42,722). A Finnish cohort study found similar results and reported increased cardiovascular morbidity and mortality among men reporting to be 'occasional smokers'.²

Cardiovascular/Peripheral Artery Disease (PAD): The risk for acute myocardial infarction is nearly three-fold greater in current smokers versus never smokers.¹² Smokers with cardiac disease are more likely to have a second heart attack if they continue to smoke;² this exceeds the risk attributed to diabetes (OR 2.37), hypertension (OR 1.9) and abdominal obesity (OR 1.6). Even at the lowest levels of exposure (one cigarette per day), cigarette smoking is associated with an increased risk for cardiovascular disease.¹² Smoking is also associated with increased levels of carboxyhemoglobin which leads to tissue hypoxemia. This can inhibit tissue healing, especially in those with PAD.

Pulmonary: COPD is an inflammatory disease that is predominantly found in patients with a history of cigarette smoking. According to the World Health Organization (WHO), 80 million people worldwide have moderate-to-severe COPD; in 2005, the disease was associated with 3 million deaths worldwide.¹³

Cancer: Smoking and secondhand smoke are 2 of the risk factors for developing various cancers, including lung cancer, one of the leading causes of death in both men and women. There are approximately 129,000 deaths from lung cancer and 35,000 other cancer deaths attributed to smoking each year.¹⁴

Diabetes Mellitus: Smoking is associated with reduced insulin sensitivity and lower glucose utilization. The risk of developing type 2 diabetes increases with heavy smokeless tobacco use and doubles with heavy smoking (one pack per day).¹⁵

Chronic Kidney Disease (CKD): Cigarette smoking increases the risk and progression of chronic kidney disease, estimated to affect more than 11% of the U.S. population.¹⁶

HIV-Positive Smokers: Compared with HIV-positive nonsmokers, HIV-positive smokers are at increased risk of several opportunistic infections and spontaneous pneumothorax and have higher mortality rates.²

Pregnancy and Breastfeeding: Smoking has been linked to infertility. Smoking also carries serious risks and health consequences for pregnant women and their fetuses: stillbirths, spontaneous abortions, ectopic pregnancy, fetal growth restriction, premature labor and delivery, low birthweight (an estimated 20% of low birthweights could be prevented by eliminating smoking during pregnancy), placental abruption, placenta insufficiency, and thrombotic complications. In addition to secondhand smoke, children of women who smoke during breastfeeding are exposed to nicotine secreted in breast milk. Smoking also reduces breast milk production.^{2,17,18}

Children Exposed In Utero: In utero exposure to smoking increases the risk of: sudden infant death syndrome (SIDS); respiratory infections; asthma; middle ear disease; orofacial clefts; craniosynostosis; clubfoot; attention deficit disorder; other cognitive, emotional and behavioral problems; and some childhood cancers.^{2,17,18}

Secondhand Smoke: Secondhand smoke causes immediate and long-term adverse health effects in children and adults. In Scotland, the number of hospital admissions for acute coronary syndrome decreased by 17% after smoking was banned from public places. Two-thirds of the decrease involved non-smokers.¹⁹ Other studies involving smaller towns have shown even larger reductions in hospital admissions.²⁰ Exposure to secondhand smoke is associated with low birthweight, sudden infant death syndrome, asthma and other respiratory problems in children.²¹ Children are exposed to higher levels of secondhand smoke than adults; they are primarily exposed in their home environment. More than 30% of children in the U.S. are currently exposed to secondhand smoke at home.^{22,20}

Other Tobacco Product Forms: Regardless of the tobacco product form used, there are health risks. Smokeless tobacco is not a safe alternative to smoking and carries serious health risks, including: identifiable oral lesions, teeth abrasion, gingival recession, periodontal bone loss, leukoplakia, and oral and pancreatic cancer. In addition, there is no evidence that smokeless tobacco products are an effective aid to quit smoking. Noncigarette smoking tobacco products (cigars, pipes, cigarillos, bidis, loose tobacco, and water pipes

[hookahs, narghile]) have been associated with: coronary heart disease; COPD; periodontitis; and cancers of the oral cavity, esophagus, larynx, lungs, and stomach.²

Nicotine Addiction

Smoking is an addiction that is hard to kick. The addiction is due to a combination of pharmacologic, behavioral, psychological, social and environmental factors. Although nicotine has been considered the primary cause of addiction in cigarettes and other forms of tobaccos, other ingredients may also play a role.^{23,24,25} Nicotine dependence is related to both its positive and negative reinforcing effects.²⁶ Nicotine stimulates dopaminergic neurons in the mesolimbic pathway (particularly in the nucleus accumbens of the brain) to release dopamine, which produces a pleasure effect. Because nicotine from cigarette smoke is absorbed by the pulmonary venous system rather than the systemic venous system, it quickly reaches the brain.²⁵ Rapid delivery to the brain provides almost immediate positive reinforcement, facilitating the particularly addictive nature of smoking cigarettes. The negative reinforcement comes from symptoms of withdrawal that are alleviated with continued nicotine use. Newer research suggests that monoamine oxidase (MAO) enzyme inhibition may also play a role in the addictive potential of tobacco.²³ MAO-A and MAO-B are catabolizing enzymes that break down monoamines such as dopamine, noradrenaline, and serotonin. Inhibiting the degradation of these monoamines contributes to increased dopaminergic tone and the reward pathway associated with tobacco use. This change is likely caused by some ingredient in tobacco smoke other than nicotine, because nicotine itself does not dramatically alter MAO levels.²⁴

With regular smoking, specific moods, situations, or environmental factors (i.e., cues) become associated with the rewarding effects of nicotine. This association between cues, anticipated effects of nicotine, and resulting urge to use nicotine, constitute a form of conditioning. Cues associated with nicotine withdrawal can worsen withdrawal through a direct effect on the brain's reward system, thus maintaining the urge to smoke and triggering relapse.²⁴

Benefits of Smoking Cessation

The best proven method for reducing harm in patients who smoke is complete cessation.

Short-Term: The short-term benefits of smoking cessation include a decrease in the frequency of respiratory problems, fewer sick days, improvement in children's asthma and a general feeling of well-being.²⁷ Smoking cessation initially increases the forced expiratory volume in one second (FEV₁) in patients with mild to moderate COPD and eventually the rate of decline reverts to the age-related decline seen with never smokers. However, the deficit in predicted FEV₁ is never fully recovered and airway inflammation persists in ex-smokers with COPD. Compared to COPD patients who continue to smoke, those who quit have a decreased risk for hospitalizations due to COPD exacerbation and decreased mortality.¹³

Long-Term: There are definite long-term benefits as well. Smoking cessation will lower the risk for coronary heart disease, stroke, COPD, lung cancer, oral cancers and bladder cancer. Smoking cessation decreases the risk of developing cancer of the cervix, pancreas and kidneys.²⁷ Cardiovascular mortality risk decreases substantially within 2 years following smoking cessation. Cardiac patients can reduce their risk of death by at least one-third if they quit smoking after a heart attack or cardiac surgery.²⁸ Smoking cessation at age 35 can add up to 8.5 years of life for men compared to those who continue to smoke. Older smokers experience similar benefits to younger ex-smokers when they quit smoking.^{2,3} Even smokers who quit at age 65 can add an additional 2 years to their life expectancy.²⁹

Smoking Cessation-Related Weight Gain

Concerns and fears about weight gain, especially among women and adolescents, can motivate individuals to start smoking or continue smoking. Most smokers gain weight when they quit smoking. Weight gain is usually less than 10 pounds, but may be as much as 30 pounds in up to 10% of ex-smokers.^{2,30} Weight gain that follows smoking cessation is considered a modest health risk compared with those risks associated with smoking. Populations at highest risk for major weight gain are heavy smokers (smoking more than 25 cigarettes per day), African Americans, and people under age 55. Also, women tend to gain slightly more weight compared to men. This weight gain appears to be caused by both increased calorie intake and

decreased metabolism. Individuals who resume smoking at pre-cessation levels will usually lose some or all of the weight gained during the quit attempt.²

For smokers with weight concerns, bupropion SR or nicotine replacement treatment (NRT) (in particular, nicotine gum and nicotine lozenge) may be the best selections since they have been shown to delay weight gain after quitting (Level B).² The clinician should acknowledge that quitting smoking is often followed by weight gain. Additionally, the clinician should:

- note that the health risks of weight gain are small when compared to the risks of continued smoking;
- recommend physical activities and a healthy diet to control weight; and
- offer to help the patient address weight gain (either personally or via referral) once the patient has successfully quit smoking.

Smoking Cessation Rate/Relapse Rates

Tobacco dependence is a chronic disorder in which patients have periods of relapse and remission. Most smokers make several attempts before they are successful at quitting, with surveyed smokers reporting an average of 4 to 7 attempts.^{31,32,33} A 2006 Gallup Poll assessed quit attempts in 195 current smokers and reported an average of 4.1 quit attempts. The same survey revealed that former smokers reported an average of 6.1 quit attempts.³² The relapsing nature of the condition requires ongoing rather than just acute care. While most of the research has focused on treatment and assessment of cigarette smokers, intervention should occur for all tobacco users.²

Most smokers who try to quit smoking still make unaided quit attempts; only 4 to 7% are successful.² The evidence is compelling that a physician's advice to patients to quit smoking, even with an intervention lasting less than 3 minutes, increases overall abstinence rates by 1-3% (Level A).^{2,34} At least 70% of smokers see their physician at least once a year, 70% of smokers want to quit, and almost two-thirds of smokers who relapse want to try quitting again in thirty days.² Therefore, it is strategic that physicians actively promote smoking cessation to give patients their best chance at success, particularly since smokers cite a physician's advice to quit as an important motivator for attempting to stop smoking.²

Few smokers get specific help with quitting, with only 39% of smokers reporting that their clinician discussed either medications or counseling strategies to quit. Although the rate of tobacco dependence interventions has increased in insured patient populations, there is a clear need for additional improvement in various populations. For example, only a quarter to a third of Medicaid patients, pregnant women, and adolescents are offered counseling. Some racial and ethnic minorities (e.g., African Americans, Hispanics, American Indians, Alaska Natives, Asians) are less likely to receive advice to stop smoking or use tobacco dependence treatment.²

Adolescents vastly underestimate the addictive potential of nicotine, thinking they can quit at any time. However, the rate of failed adolescent quit attempts is greater than that of adult smokers; only about 4% of smokers aged 12 to 19 successfully quit each year. Young people are very interested in quitting; 82% of 11 to 19 year-olds are interested in quitting, and 77% have seriously attempted to quit in the past year. They usually make spontaneous unplanned attempts and choose unassisted quit methods despite evidence that young people enrolled in a tobacco cessation program are 2 times more likely to quit.^{2,9}

Older smokers are more tobacco dependent, have better psychological functioning, and poorer physical functioning compared to younger smokers.³ They do not appear to have a reduced desire to quit.^{2,3} Older smokers are more likely to use multiple medications; smoking can alter drug metabolism and complicate treatment.³ Smokers over the age of 65 are less likely to receive tobacco dependence treatment, despite the established efficacy of smoking cessation treatments in this older age group, and their expanded benefits through Medicare for tobacco dependence treatment, for both counseling and prescription medications.²

Light smokers often have difficulty quitting even though they are motivated. Light smokers are also less likely to receive tobacco cessation intervention than heavier smokers.²

TREATMENT OPTIONS FOR SMOKING CESSATION

Treatment with either counseling or medication for smoking cessation is effective at improving abstinence rates (Level A). However, the combination of counseling and medication is more effective for achieving abstinence than either medication or counseling alone (Level A). Medication is not recommended when contraindicated or in special populations or conditions where evidence of safety and/or efficacy is insufficient (i.e., pregnancy, adolescence, smokeless tobacco users, or light smokers).²

BEHAVIORAL AND PSYCHOSOCIAL INTERVENTIONS

There are several behavioral and psychosocial interventions for smoking cessation. The effective interventions are usually based on established theories of human behavior. The most commonly used interventions are detailed below. A summary of these interventions and how to use them during the clinical encounter is provided in Table 1.

The Transtheoretical Model (TTM) of Behavior Change

Changing behavior, especially an addictive behavior like smoking, takes time. The Transtheoretical Model (TTM) of behavior change developed by Prochaska and DiClemente identifies 5 stages an individual passes through in order to change an established behavior.³⁵ Smoking cessation, based on TTM, progresses through 5 stages (Table 1):

- Precontemplation: Does not want to quit
- Contemplation: Might quit 1-6 months from now
- Preparation: Actively planning to quit
- Action: Actively quitting
- Maintenance: Maintaining abstinence after 6 months

Tobacco use and dependence is a chronic disorder in which patients have periods of relapse and remission. Two additional stages in the TTM provide a complete picture of the smoking cessation process:

- Relapse: Smoking after quit date (leads to recycling through 2 or more stages)
- Termination: Quitting considered permanent

Only a minority of smokers achieve permanent abstinence on the first try. It often takes 4 to 7 quit attempts before a patient 'permanently' abstains from tobacco use, so relapse should not discourage the clinician or the tobacco user from future quit attempts. Relapses usually occur early in the quitting process but can also occur months or years after the quit date.² It is often part of the learning process and enables patients to modify factors leading to breakdowns and more successfully complete future quit attempts. While evidence for the effectiveness of stage-based interventions in changing smoking behavior is limited, TTM offers a guide for talking about change from a practical perspective.³⁶ It is appropriate to consider stage-based interventions to promote tobacco use cessation until better defined studies show otherwise.

Motivation is important throughout the TTM progression and impacts readiness to change, which is a combination of perceived importance of the problem and confidence in ability to change. Understanding the role of personal motivation and readiness to change helps providers address the diverse needs of tobacco users and promote successful cessation.³⁶ There is new research that shows that not all smokers go through all the stages of TTM described above. For patients highly motivated to quit smoking, skipping the preparation stage and moving directly to action and an immediate quit date may be the most appropriate 'stage-selective' intervention. Unplanned quit attempts have been shown to have a greater chance of success than those planned in advance. The odds of success with unplanned quit attempt have been shown to be 2-2.6 times higher than those planned in advance.^{37,38}

Practical Strategies to Increase Smoking Cessation: The 5 A's Approach

The 5 A's is an approach for treating tobacco use and dependence in the clinical setting recommended by the National Cancer Institute and the American Medical Association (see Table 1). Components of the 5 A's include:

- **Ask** about tobacco use,
- **Advise** to quit,
- **Assess** willingness to make a quit attempt,
- **Assist** in quit attempt, and
- **Arrange** follow-up.

It is important to implement all 5 components, with assistance and follow-up actions chosen based on patient's smoking status (current, former, never); readiness to change (willing/unwilling to quit); and length of abstinence (recent quitter/long-term abstinence) (See Tables 1 – 4.). The early stages of the smoking cessation algorithm involve non-drug, behavioral interventions. Clinicians should consistently identify and document tobacco use at every visit because tobacco dependence is a chronic, relapsing condition that requires monitoring. The addition of a 'sixth vital sign' for tobacco use status (i.e., current, former, never), chart sticker reminders, or computer prompts in electronic medical systems are all viable options to ensure that tobacco status identification takes place at every visit (Level A).² ICD-9 diagnostic codes are available to add tobacco use disorder and tobacco use disorder/in remission to the patient's problem list.

Modifications of the 5 A's have been adopted by various professional organizations to fit their practice needs. For example, the South Carolina Department of Health and Environmental Control (SC DHEC) and the American Academy of Pediatrics (AAP) promote the 2 A's + R (Ask, Advise, Refer); the American Academy of Family Physicians (AAFP) uses the 2 A's Cessation Model (*Ask about tobacco use* and *Act on that information*); and the American Dental Hygienists' Association suggests the 3 A's (Ask, Advise, Assist).

Brief Motivational Interviewing Treatment

Most patients want to quit smoking, but feel they cannot achieve and sustain abstinence. Motivational interviewing is a technique whereby clinicians focus on the patient's desire to quit smoking, by developing an awareness of the discordance between knowledge and behavior, and then supporting patient's self-efficacy in achieving that desire.³⁹ There are 4 principles of motivational interviewing (Table 5):

- Express empathy,
- Develop discrepancy,
- Roll with resistance, and
- Support self-efficacy.

When the patient is ready to quit smoking, practical counseling that focuses on problem solving/skills training (e.g., build on past success, avoid triggers, limit/abstain from alcohol, stress management) and offering support and encouragement during patient-provider interactions are especially effective.²

Intensity of Behavioral Interventions

One intervention lasting less than 3 minutes increases overall tobacco abstinence rates. All tobacco users should be offered this minimal intervention, even in the absence of more intensive interventions (Level A). Longer person-to-person interactions and multiple sessions that can be provided by more than one provider type (i.e., physician and non-physician) have greater impact (Level A).^{2,34} Two or more sessions significantly increase abstinence rates; 4 or more interventions are especially effective (Level A); and 8 or more sessions up to a total of 90 minutes contact time (number of sessions multiplied by session length) have the greatest impact on abstinence rates.² When offered in addition to pharmacotherapy, 2 to 3 counseling sessions provide additional benefits versus no counseling or only one session; the incremental benefit of more intensive counseling in combination with pharmacotherapy is unclear.^{2,40,41}

For more intensive interventions, proactive telephone quitlines (e.g., S.C. Tobacco Quitline 1-800-QUIT-NOW that offer specialist-delivered counseling), group counseling and individual counseling are all effective tobacco use treatment approaches (Level A).^{2,40,41,42} No one approach appears to be any better than another, and using multiple approaches for smoking cessation interventions increases abstinence rates (Level A).² It is unknown if the increase in quit rates may be the result of more personal contact time and treatment intensity versus different intervention and provider types.²

Gradual Reduction Prior to Quitting versus ‘Cold Turkey’

Abrupt abstinence (i.e., cold turkey with or without medication) may result in better quit rates than gradual reduction of smoking prior to quitting (e.g., ‘cut down’ or cigarette fading) in patients who quit on their own – they are almost twice as likely to succeed and less likely to relapse. In structured cessation programs, ‘cut down’ has been shown to be at least as effective as abrupt abstinence. It seems likely that the increased success rate on the part of smokers who choose to quit cold turkey is due to increased motivation.³⁸

Patient Tailoring

Tailored interventions using biomedical tests to provide personalized risk awareness, questionnaires (see *Assessment of Nicotine Addiction* below), and clinical interviews do not appear to improve quit rates any more than non-tailored interventions. Two possible exceptions are spirometry results explained in terms of ‘lung age’ and the value of nicotine gum or lozenge for high nicotine dependence.^{2,43} There is insufficient evidence to support the use of stepped care, another form of tailoring that initiates treatment with low-intensity interventions and reserves more intense treatment for relapse.²

Both print and interactive, web-based materials tailored for individual smokers are more effective than untailored self-help materials (e.g., pamphlets, reactive hotlines). Although the overall effect is small, the use of patient-tailored self-help materials may help people quit (Level B) and become a means of support for tobacco users who attempt to quit on their own or with minimal personal contact with a health professional.^{2,44} While they do not show an additional benefit when used with advice or medication treatment, that is looking at the short-term value of the materials and perhaps underestimating the long-term effect of having access to help with future quit attempts.⁴⁴

Assessment of Nicotine Addiction

There are several rating scales currently used in measuring nicotine dependence in smokers. The most well known scale is the Fagerstrom Tolerance Questionnaire (FTQ) and its 6-item, revised version, the Fagerstrom Test for Nicotine Dependence (FTND). More recent scales include the Heaviness of Smoking Index (HSI), the Cigarette Dependence Scale (CDS), and the Nicotine Dependence Syndrome Scale (NDSS).^{45,46} All of the scales appear to have good test-retest reliability and at least adequate internal validity. The FTND has been extensively studied and is probably the scale used most often. The HSI is a scale that consists of 2 questions from the FTND regarding time to first cigarette and number of cigarettes per day. It has not been quite as extensively studied. It appears to have good test-retest reliability and adequate internal validity as well.⁴⁷ The CDS is either 5 or 12 items long and it has been shown to have more internal validity than both FTND and HSI.^{48,49} The NDSS is the longest scale (19 items) and appears to have the highest internal validity.⁴⁵

In regards to comparative predictive validity, results are mixed. One study found that all scales with the exception of NDSS adequately predicted smoking abstinence after 8-day follow-up, with CDS being the best. However, after 31 days, only HSI, FTND, and one NDSS subscale were found to be significant predictors. It is important to note that, in the latter result, the difference was small (possibly due to the small sample size) and the author postulated that those results may not be clinically significant. A second study found that the 12 question version of CDS better predicted self-efficacy in quitters after 8-day follow-up.⁴⁹

A valid questionnaire to measure addiction to cigarettes could be useful to guide treatment decisions and predict abstinence. However, nicotine dependence is only one factor in succeeding at a quit attempt; other variables such as cognitive, affective and environmental factors probably play a larger role in sustaining abstinence beyond the first few days to weeks of smoking cessation.^{50,51} Thus, except for eliciting information relevant to the selection of the appropriate dosage strength of NRT products, the clinical utility of existing nicotine dependence rating scales is limited.

MEDICATIONS

First-Line Medications

NRTs, bupropion SR, and varenicline are first-line medications that are effective for smoking cessation and are approved by the FDA for this use (Level A).^{2,52} Table 6 summarizes standard recommendations on dosing, administration instructions, and duration of treatment.

NRTs deliver nicotine to replace, at least partially, the nicotine obtained from cigarettes and to reduce the severity of nicotine withdrawal symptoms. Nicotine replacement by any delivery system approximately doubles the odds of long-term abstinence (Level A).² Currently, 5 forms of nicotine delivery are available: gum, lozenge, inhaler, nasal spray and patch. All NRTs appear to be equally efficacious, so patient preference and ease of use usually determines the choice of nicotine replacement modality. The nicotine patch is associated with the best adherence rate, although it does not treat acute cravings. Other NRTs may be used on a fixed schedule, or *ad libitum* to address acute cravings. Fixed schedules may be more beneficial than *ad libitum* use as patients often do not use enough NRTs *ad libitum* to obtain optimal effects.²

Nicotine Gum

Nicotine gum is available in 2 and 4 mg strengths, and is packaged with important instructions on correct usage, including chewing (Table 5). The 4 mg gum is more effective than the 2 mg gum in highly dependent smokers (Level A).^{2,53} Regular course (6-14 weeks) increases the likelihood of long-term abstinence by 1.5 times; long-term (> 14 weeks) nicotine gum use approximately doubles the likelihood of long-term abstinence compared to placebo treatment (Level A).²

Nicotine Inhaler

Nicotine inhaled through the mouthpiece is absorbed buccally rather than through the lungs.²

Nicotine Lozenge

The nicotine lozenge is available in 2 mg and 4 mg strengths. The 4 mg lozenge is more effective than the 2 mg lozenge in highly dependent smokers (Level A).^{2,53,54}

Nicotine Nasal Spray

The nicotine nasal spray produces higher peak nicotine levels than other NRTs and has the highest dependence potential.²

Nicotine Patch

The starting dose is based on the level of nicotine dependence: highly dependent smokers start with the 21 mg patch; less dependent smokers start with the 14 mg patch.² Wearing the nicotine patch during waking hours (16 hours duration) is as effective as wearing it for 24 hours (Level A).⁵³ The standard course of treatment lasts 8 weeks (range of 6 to 14 weeks). High-dose (> 25 mg) nicotine patch does not appear to yield additional benefits compared to usual dose (14–25 mg) (Level A).² Of note, 21 mg is the highest strength currently available in the U.S.

Bupropion SR doubles long-term abstinence rates compared to placebo treatment (Level A).²

Bupropion SR was the first non-nicotine medication shown to be effective for smoking cessation. The FDA-approved and most commonly studied target dose is 150 mg BID,² although a lower dose of 150 mg daily does not appear to differ in efficacy.⁵⁵

Varenicline is a non-nicotine medication that is effective for smoking cessation. The FDA-approved target dose of varenicline is 1 mg BID. A lower dose of 0.5 mg BID is also effective, albeit slightly less so.² Preliminary evidence suggests that a self-regulated, flexible dosing strategy may also be effective.⁵⁶ The 0.5 mg BID dose of varenicline approximately doubles, and the 1 mg BID dose of varenicline approximately triples, the likelihood of long-term abstinence from tobacco compared to placebo treatment (Level A).² The higher dose (1 mg BID) is also associated with greater reductions in craving and withdrawal symptoms than the lower dose (0.5 mg BID).⁵⁷ Varenicline has demonstrated superior efficacy compared to monotherapy with bupropion or the nicotine patch. The recommended varenicline dose of 1 mg BID increases the odds of long-term abstinence by 1.5 times compared to bupropion SR (Level A) and by 1.3 times compared to NRT (Level B).^{2,57}

Second-Line Medications

Nortriptyline and clonidine are reserved as second-line medications. Both medications approximately double the odds of long-term abstinence compared to placebo treatment (Level A), but they have side effect profiles which limit their widespread use. Neither one is FDA-indicated for smoking cessation.^{2,55,58} Table 7 summarizes standard recommendations on dosing, administration instructions, and duration of treatment.

Medication Combinations

Certain medications can be effectively combined for smoking cessation treatment. Some combinations may yield higher abstinence rates; evidence also suggests that medication combinations may result in greater suppression of tobacco withdrawal symptoms than monotherapy (Tables 6 and 7). Factors to consider in selecting the optimal regimen includes patient preferences, previous smoking cessation attempts (e.g., number of attempts, withdrawal symptoms), current medical conditions, side effect profile, cost, and pharmacology. A combination currently not recommended is varenicline with NRT because of the nicotine antagonist properties of varenicline.

Compared to placebo, the following combinations significantly increase abstinence rates: nicotine patch + lozenge (Level B),⁵⁹ nicotine patch + inhaler, long-term nicotine patch + *ad libitum* NRT, nicotine patch + bupropion SR, and nicotine patch + nortriptyline (Level A).²

Compared to monotherapy, medication combinations increase the likelihood of long-term abstinence by 1.5 times.⁶⁰ Specific combinations found to be more effective than the patch alone include bupropion SR + nicotine patch and combination NRT formulations. Although bupropion SR + nicotine patch is the only FDA-approved combination, the benefits of adding bupropion SR to NRT are unclear, or perhaps small at best.^{2,55} Increasing evidence suggests that combining NRT formulations improves efficacy. Combination therapy with the nicotine patch and *ad libitum* nicotine gum or nicotine nasal spray nearly doubles the odds of quitting compared to the patch alone (Level A).² This type of NRT combination allows administration of both steady dosing (e.g., patch) and episodic dosing, which may help with episodic urges. Combination therapy with the nicotine patch and nicotine lozenge is also associated with a small but significant advantage over monotherapy (patch, lozenge, or bupropion) (Level B).⁵⁹ A triple combination consisting of the patch + bupropion SR + *ad libitum* inhaler has been found to more than double the long-term abstinence rates compared to the nicotine patch alone (Level B).⁶¹ Preliminary findings suggest that varenicline + bupropion SR may yield high abstinence rates, but double-blind, controlled studies are needed.⁶²

Initiation of Treatment

Smoking cessation medications such as varenicline, bupropion SR, clonidine and nortriptyline are initiated prior to the established quit date (Tables 6 and 7). NRTs are FDA-approved for post-quit use only, although recent research has investigated their use while smoking, either for smoking cessation in patients wanting to quit or smoking reduction in patients not willing to quit, but willing to reduce smoking.

In smokers willing to make a quit attempt, the use of the nicotine patch prior to quitting may increase long-term abstinence rates by 80% (Level B).^{2,53,63} Current smoking cessation guidelines await more research on this strategy before a recommendation is made.² If precessation smoking NRT is used clinically, patients should be advised to cease NRT use if they develop symptoms of nicotine toxicity (e.g., nausea, vomiting, dizziness).

In patients not willing to quit but willing to reduce smoking, the use of NRT approximately doubles the odds of long-term abstinence. Nicotine gum (for 6–12 months), nicotine inhaler (for 6–24 months), nicotine patch (for up to 6 months), or a combination of these NRTs are helpful for smoking reduction.^{2,64} Current smoking cessation guidelines do not recommend medication use as a standard intervention for smokers unwilling to quit due to insufficient evidence and concerns that this strategy may undermine interest in quitting.²

Duration of Treatment

The usual duration of therapy with smoking cessation medications is 8 to 12 weeks. For some patients, it may be helpful to continue medication treatment for periods longer than is usually recommended (e.g., smokers with persistent withdrawal symptoms during medication treatment; smokers with a history of relapsing

after medication discontinuation; or smokers interested in long-term therapy).² The FDA has approved the use of the nicotine inhaler, the nicotine nasal spray, bupropion SR, and varenicline for up to 6 months of use.

Additional research is needed on the optimal duration of treatment with NRTs. Extending treatment beyond 8 to 14 weeks does not improve long-term abstinence rates.^{2,53} More recent evidence suggests that 24 weeks of therapy may improve abstinence rates compared to 8 weeks of treatment, although this benefit does not appear to be sustained after treatment discontinuation (Level B).⁶⁵ Long-term use of gum may be more effective than a shorter course of gum therapy.^{2,66} The nicotine gum has been used safely and successfully for periods of 1 to 5 years. Combination treatment with long-term nicotine patch and *ad libitum* NRT is associated with the largest effect size on abstinence rates.²

Extended treatment with varenicline for an additional 12 weeks has been shown to significantly reduce relapse (risk ratio 1.18, 95% confidence interval 1.03 to 1.36) in patients who had successfully quit smoking with a short course of treatment.⁶⁶ It is unclear whether the benefit of a longer course of treatment with varenicline is maintained long-term after its discontinuation.⁵⁷

The benefits of extended bupropion SR treatment in patients who have successfully quit with a short course of treatment are unclear.^{2,66}

Relapse

Benefits of offering further pharmacotherapy to relapsed smokers are unclear; some evidence suggests it may yield small or no benefit while other evidence suggests that it may be of substantial benefit.^{2,53,55} The time interval between attempts may be an important factor. A second treatment with smoking cessation medications soon after relapse is associated with a low success rate while a longer gap may improve the success rate.^{53,55}

Treatment Discontinuation

Of the first-line smoking cessation medications, NRT is usually administered in a step-down dosing fashion (e.g., gum, lozenge, patch), or tapered at the end of treatment (e.g., inhaler, nasal spray). However, no difference in efficacy and tolerability has been shown between abrupt discontinuation versus gradual reduction of the nicotine patch.⁵³ No specific tapering recommendations are made for bupropion SR and varenicline.²

Second-line smoking cessation medications, especially clonidine, require gradual tapering before discontinuation. Abrupt discontinuation of clonidine can result in rebound hypertension, particularly in hypertensive patients, as well as in other symptoms such as nervousness, agitation, headache and tremor. Tapering of clonidine dosing over several days to one week is recommended.⁵⁸ Abrupt discontinuation of medications with anticholinergic side effects such as nortriptyline can cause cholinergic rebound. A gradual taper by 25 mg every 3-5 days is recommended.

Side Effects

Side effect profiles of smoking cessation medications vary. Tables 6 and 7 provide common side effects, cautions, warnings and administration instructions. NRTs have a well-established safety and tolerability profile; combination NRT products are also well tolerated with minimal side effects reported.^{2,53,60} Despite delivering nicotine, NRTs are associated with a decreased abuse potential because of the slower rate of nicotine absorption and lower overall nicotine plasma concentrations compared to tobacco products.⁶⁷ The slowest route for nicotine absorption is transdermal, followed by buccal, inhalation, and nasal spray.^{68,69} The transdermal, oral, and inhalation routes of NRTs also yield a lower brain-to-blood nicotine concentration ratio compared with cigarette smoke.²⁵

Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and NRT because of a higher incidence of treatment-emergent hypertension in patients treated with the combination.

Similar to other antidepressants, bupropion SR and nortriptyline bear a warning of potential increased suicidality when used in children and young adults. Reports of serious neuropsychiatric symptoms (including

behavioral changes, depressed mood, hostility, and suicidal thoughts) while taking varenicline and bupropion prompted the FDA to require a boxed warning be added to their package inserts. While some of the behavioral and mood changes may be associated with nicotine withdrawal, some occurred in people who continued to smoke while on the medication. In many cases, the neuropsychiatric symptoms began shortly after starting the medication and ended when the medication was discontinued. Some people continued to have symptoms after discontinuing the medication. In a few cases, the problems began after the medication was discontinued.^{55,70}

Numerous reports of serious injury linked to traffic accidents or falls have led 3 U.S. government departments to limit or ban the use of varenicline.⁵⁷ The Federal Aviation Administration has banned its use by airline pilots; the Department of Transportation has limited its use among truck drivers; and the Department of Defense has prohibited its use by aircraft and missile crews. While these reports suggest a possible link to serious events, further research is under way to better evaluate causality and magnitude of risk with varenicline use, particularly in vulnerable populations (e.g., patients with preexisting psychiatric conditions).

Interactions

Several drug interactions exist with smoking. The polycyclic aromatic hydrocarbons in tobacco smoke, but not nicotine, induce the hepatic cytochrome P450 (CYP) 1A2, thereby increasing the dosage requirement of several medications; important examples include caffeine, clozapine, fluvoxamine, olanzapine and theophylline. Upon smoking cessation, the dose of these medications should be decreased to minimize the risk of adverse effects associated with higher levels.^{2,71}

Smoking increases the risk of oral contraceptive-induced adverse cardiovascular events. Consider alternate form of contraception in women who continue to smoke, particularly in heavy smokers age 35 and older (contra-indication in select products).⁷¹

Insulin requirements may be affected by tobacco smoke or NRT products. Nicotine-induced vasoconstriction may reduce subcutaneous absorption of insulin; increased glucose concentration and decreased response to insulin may be associated with compounds in tobacco smoke or nicotine. Adjustments in insulin may be necessary when NRT is discontinued or upon smoking cessation if NRT is not used.^{2,71}

Bupropion and its metabolites inhibit CYP2D6 and can increase the concentration of medications metabolized by this enzyme (e.g., certain antipsychotics, type 1C antiarrhythmics, beta-blockers, and tricyclic antidepressants). Due to the extensive metabolism of bupropion, enzyme inducers (e.g., carbamazepine, phenobarbital, phenytoin) and inhibitors (e.g., cimetidine) may affect its plasma concentration. Bupropion can lower seizure threshold, thus it should be used cautiously with other medications that lower the seizure threshold.²

Considerations in Some Specific Populations

Language, culture, and medical comorbidity can influence tobacco use and treatment decisions. It is important to communicate in a language at an appropriate educational level of understanding while also considering what is culturally relevant and acceptable to the patient. Individual spiritual and health beliefs can influence the success of treatment in all populations. Potential drug interactions and changes in liver metabolism due to disease or medication must also be evaluated in the presence of comorbid medical conditions. Within any population, it is important to consider their specific needs and unique clinical issues when looking at the prevalence of tobacco use and choosing a tobacco dependence treatment.²

Older Smokers. Although many older smokers are more tobacco dependent compared to the general population, they want to quit and experience similar benefits to younger ex-smokers when they quit smoking.^{2,3} Smoking cessation treatments have been shown to be effective for older adults.²

Psychiatric Disorders (Including Substance Use Disorders). Treating tobacco dependence can be more complex in this patient population if a patient has more than one psychiatric diagnosis and takes multiple medications.² All smokers with psychiatric disorders should be offered tobacco dependence treatment; some clinicians may prefer to offer treatment once psychiatric symptoms are less severe since stopping smoking or nicotine withdrawal may exacerbate comorbid psychiatric disorders.^{2,72} Several studies concluded that

tobacco dependence treatment does not interfere with successful recovery by the patient from other substance abuse diagnoses. The treatment of alcohol dependence before addressing tobacco use was suggested by one study to improve patient response to alcohol dependence treatment. Smokers with psychiatric disorders tend to have lower abstinence rates than smokers without these conditions.²

Bupropion SR and nortriptyline, both effective in treating depression, have been shown to be effective at increasing long-term abstinence rates in smokers with a past history of depression.^{2,55,72} One study of depressed smokers comparing bupropion to NRT (i.e., nicotine transdermal patch) found bupropion to be more effective than placebo or NRT with regard to smoking cessation; it was especially effective for female smokers. Patients with depression are more likely to smoke and to have a more severe nicotine dependency. Patients with depression may use smoking to self-treat since nicotine has been shown to act as an antidepressant. Low confidence and self-esteem are strong predictors of a failed smoking cessation attempt among patients with depression.⁷²

Racial and Ethnic Minority Populations. Other than behavioral studies on smoking cessation, there is a lack of congruent smoking cessation pharmacotherapy research in American Indian/Alaska Native, Hispanic and other ethnic populations.^{73,74} African-Americans may have more difficulty quitting regardless of the number of cigarettes smoked per day if: they smoke within 30 minutes of awakening, smoke mentholated cigarettes, and have high salivary cotinine levels.^{73,75} Smoking cessation treatments have been shown to be effective across different racial and ethnic minorities.

Women. Women have not been well studied as a single gender.^{2,74} They are more likely than men to seek help in their quit attempts. Women face different stressors and barriers to quitting, such as: greater possibility of depression, more concerns about weight gain, and hormonal fluctuations. Research suggests that women benefit from the same interventions as do men, although the data are mixed on whether they benefit as much as men. Weight gain is slightly more compared to men when they quit smoking.²

Hospitalized Smokers. Smoking cessation treatments have been shown to be effective for hospitalized patients. Hospitalized patients may be more motivated to quit tobacco use, especially when a 'teachable moment' arises if hospitalized for a reason related to tobacco use. It is also 'convenient' that hospitals are now a smoke-free environment. Patients may be more likely to use intensive treatments to maintain their abstinence or in a future quit attempt at home if they have a positive experience with alleviation of their withdrawal symptoms while hospitalized and unable to smoke. The importance of post-hospitalization follow-up has been demonstrated by research. Fax referrals to a quitline may be an effective and efficient way for hospitals to refer patients for smoking cessation follow-up. The following actions are recommended for all hospitalized patients:²

- Ask patients on admission if they use tobacco and document tobacco use status.
- For current tobacco users, list tobacco use status on the admission problem list and as a discharge diagnosis.
- Use counseling and medications to help all tobacco users maintain abstinence and to treat withdrawal symptoms.
- Provide advice and assistance on how to quit during hospitalization and remain abstinent after discharge.
- Arrange for follow-up regarding smoking status. Supportive contact should be provided for at least a month after discharge.

Patients with Chronic Diseases. Smokers with cardiac disease, chronic kidney disease (CKD), lung disease, diabetes or cancer are ideal candidates for clinicians to encourage to quit smoking since these patients have a chronic disease that may have been caused or exacerbated by smoking and may improve if they quit. Smokers with Lung Disease (e.g., COPD and Asthma) may possibly have more success quitting when they receive a combination of psychosocial treatment and pharmacotherapy compared to no treatment or psychosocial interventions alone.⁷⁶

Cardiac patients may be more motivated to quit when they are hospitalized due to coronary heart disease; providers can boost quit rates at one year to 35-70% (compared with typical quit rates of 10-25% in primary care settings) when they provide smoking cessation interventions to cardiac patients while hospitalized due to coronary heart disease.⁷⁷ Trials of smoking cessation intervention in patients with cardiac disease are few. A 2008 meta-analysis found that psychosocial smoking cessation interventions (e.g., behavioral counseling, telephone support and self-help interventions) are effective in helping smokers with coronary heart disease to quit; however, treatment duration must be adequate and the authors recommended a minimum of one month. Patients with coronary heart disease who smoked were more likely to quit (OR 1.98 [95% CI 1.49 to 2.65]) when interventions included follow-up contacts after the initial period of one month.⁷⁸ A more recent meta-analysis of randomized controlled trials to determine the efficacy of behavioral therapy and pharmacotherapy for smoking cessation in cardiac patients found a significantly higher proportion of smoking abstinence than usual care (OR 1.97 [95% CI 1.37 to 2.85]) associated with behavioral treatment.⁷⁹ In this meta-analysis, 4 trials were included that examined smoking cessation pharmacotherapy in cardiac patients; one trial used nicotine gum, one used transdermal nicotine patch, and 2 used bupropion. Compared to placebo, drug treatments were more efficacious (pooled OR 1.72 [95% CI 1.15 to 2.57]) and safety data were similar.⁷⁹ Three clinical trials in smokers with stable coronary heart disease (excluding acute coronary syndrome) receiving NRT found no evidence of increased ischemia or adverse cardiovascular events when comparing nicotine patch to placebo. For patients recovering from ST-elevation myocardial infarction, the American College of Cardiology and the American Heart Association recommend beginning pharmacotherapy (including NRT) at time of hospital discharge in addition to counseling and formal cessation programs.⁷⁷

There are some smoking cessation medication considerations for patients with CKD. In general, no dosage adjustments are recommended for NRT. However, reduced doses are recommended for bupropion or varenicline used in smokers with CKD who are attempting to quit smoking. Bupropion's major metabolites accumulate in patients with CKD, and the clinical significance of this metabolite accumulation is unknown at this time. In addition, the hydroxybupropion metabolite is unlikely to be removed by dialysis.⁸⁰ A reduced frequency and/or dose is recommended when using bupropion in patients with moderate to severe renal impairment.⁸¹ In patients undergoing hemodialysis, a dose of 150 mg every 3 days has been suggested.⁸⁰ Dosage adjustments are recommended when using varenicline in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) due to a two-fold increase in varenicline blood levels. The dose can be titrated from 0.5 mg daily up to a maximum dose of 0.5 mg twice daily. (For patients undergoing hemodialysis, a maximum dose of 0.5 mg daily may be used if tolerated.⁸² More research is needed on safety, efficacy and optimal dosing.

Special Considerations

Light Smokers. It is important to identify light smokers, strongly urge them to quit, and provide counseling cessation interventions (Level B). There are few studies examining the effectiveness of tobacco use medications to sustain abstinence, and findings have been mixed.² A recent one year study of 260 subjects smoking 6 to 15 cigarettes per day comparing the impact of high versus low counseling intensity combined with bupropion or the nicotine patch found no data to suggest that lighter smokers have an easier time quitting than heavier smokers. Former heavy smokers appeared to be especially prone to relapse. The authors suggested that the same counseling methods found effective for heavier smokers should be considered for lighter smokers.⁷⁵ There is limited research to suggest that light smokers of mentholated cigarettes are not necessarily 'less addicted' and may have higher exposure to nicotine with each inhalation. This effect apparently happens because smokers attempt to enhance the cooling and local anesthetic effects of menthol by taking larger and deeper inhalations and holding their breaths for an extended duration.⁷³

Non-Cigarette Tobacco Users. It is important to identify smokeless tobacco users, strongly urge them to quit, and provide counseling cessation interventions (Level A).² Patients using non-cigarette forms of smoking tobacco should receive the same care (Level C). In particular, clinicians delivering dental care should provide brief counseling interventions to all smokeless tobacco users (Level A). A review of the literature has shown that dental health clinicians can increase abstinence rates in smokeless tobacco users by delivering brief advice in the context of oral hygiene feedback. Emerging evidence supports the efficacy of proactive quitlines; interactive, tailored web-based counseling; and self-help materials combined with telephone-based

counseling in increasing long-term abstinence in smokeless tobacco users.^{83,84,85} Bupropion SR and NRTs have not been shown to increase abstinence rates among smokeless tobacco users.² More recently, varenicline was shown to increase the odds of long-term abstinence in smokeless tobacco users compared to placebo (OR, 1.70 [1.12-2.58]); results of the study have not yet been published.⁸⁶

Children and Adolescents. It is important for clinicians to ask pediatric and adolescent patients about tobacco use and to strongly encourage abstinence among youth (Level C) as well as their parents. It is important for clinicians to intervene with adolescents in a respectful and confidential manner (e.g., interviewing adolescents without parents present). More than 79% of 11th graders (5000 students) surveyed report they would acknowledge their smoking if asked. Yet, less than half of adolescents report receiving assistance in quitting, and only 16% reported receiving follow-up. Asking adolescents about tobacco use and advising them to quit are effective entry points to provide effective intervention, such as motivational interventions.²

Modest evidence supports the use of counseling interventions to help adolescent smokers quit (Level B). Therefore, adolescent smokers should be provided with counseling interventions to aid them in quitting smoking.² There is not sufficient data yet to make specific counseling intervention recommendations.⁹ Counseling has been shown to almost double long-term abstinence rates compared to usual care (e.g., brief advice, self-help pamphlets, reading materials, a referral) or no treatment. Despite improved abstinence rates, absolute abstinence rates have remained low which suggests the need for improved counseling interventions for young people. Counseling intervention techniques studied have used in-person counseling, telephone calls, and group sessions that vary in intensity and content. A proactive quitline, using personalized motivational interviewing plus cognitive behavioral skills training counseling, was recently shown to be effective at increasing long-term abstinence rates in adolescent smokers.⁸⁷ Various counseling intervention strategies studied in adolescents show promising effects: establishing rapport, setting goals, promoting problem solving and skill training, preventing relapse; enhancing self-monitoring and coping skills (cognitive-behavioral strategies); addressing social influences that serve to promote or maintain smoking (social influence strategies); and clarifying desire for change and reducing ambivalence toward change (motivational strategies).² NRT has been shown to be safe in adolescents; however, there is little evidence that NRT or bupropion SR are effective in promoting long-term smoking abstinence in this age group.^{2,9}

Secondhand smoke is harmful to children. Cessation counseling delivered in pediatric settings has been shown to be effective in increasing cessation among parents who smoke. Therefore, to protect children from secondhand smoke, clinicians should ask parents about tobacco use and offer them cessation advice and assistance (Level B).² Some recent research suggests that giving parents information on the harms of secondhand smoke reduces childhood exposure to smoking and may reduce smoking rates in parents. In 2005, the American Medical Association adopted a policy statement in support of pediatricians addressing parental smoking since parental smokers often see their child's healthcare providers more often than their own. Child healthcare offices are thus in a key position to positively influence smoking parents who are willing to quit and motivate those who are unwilling to quit.⁸⁸ There is some evidence to support the delivery of tobacco use interventions to parents in pediatric clinics or during child hospitalizations to improve parents' quit rates and encourage parents to make quit attempts and stop smoking.²

Pregnant Women. A recent meta-analysis reported that about 24% of women were able to quit smoking during pregnancy when their smoking treatment intervention provided incentives. This finding may be related to the fact that smoking during pregnancy is strongly correlated with poverty, low levels of education, poor social support, depression and psychological illness.¹⁷ Clinicians should offer effective tobacco dependence interventions to pregnant women who smoke during their initial prenatal visit and throughout their pregnancy because quitting at any point in pregnancy can yield benefits. However, abstinence early in pregnancy will produce the greatest benefits to the woman and her fetus (Level B).^{2,89} Whenever possible, pregnant women who smoke should be offered person-to-person psychosocial interventions (exceeding the minimal advice to quit) because of the serious risk of smoking to the woman and her fetus (Level A). Recommendations on medication use during pregnancy are not available at this time due to safety concerns and limited and conflicting evidence of efficacy. Although NRT (i.e., nicotine) is likely less harmful than cigarette smoking during pregnancy, its potential for harm due to direct effects on the fetus is unresolved.^{2,17}

Post-Partum. There is a high smoking relapse rate for women during the post-partum period, even if they maintained total abstinence from tobacco for 6 or more months during their pregnancy.² Relapse rates within the first year after delivery ranging from 50% to 90% have been reported.⁸⁹ It may be helpful to continue to emphasize the relationship between maternal smoking and poor outcomes in infants and children. More research is needed on the prevention of postpartum relapse.² There are several strategies that may help prevent and manage post-partum relapse: focusing on health benefits of quitting for the patient, infant, and family members; continuing counseling and cessation skills building at the end of pregnancy and post-partum; providing congratulatory messages and reinforcing the patient's desire to be a good mother; and providing counseling and reassurance to women who relapse and encourage them to try again.⁸⁹

ALTERNATIVE TREATMENT METHODS

In addition to counseling and medications, there are alternative approaches to smoking cessation that have variable evidence for effectiveness. Aversive stimulation has not been shown to be beneficial, other than rapid smoking which is unproven but may help smokers quit.⁹⁰ The U.S. Public Health Service Guideline Panel does not recommend use of aversive smoking. Any value from acupuncture (including the more recent electrostimulation or laser acupuncture) or hypnosis seems to be based on patient expectation and not the effectiveness of the procedure itself, although a recent study does report positive results with hypnotherapy.² While incentives (e.g., bonuses, promotional items) and competitions do not enhance long-term cessation rates, they do improve recruitment rates and ultimately result in more quitters (Level A).⁹¹

HARM REDUCTION STRATEGIES

Several strategies referred to as “harm reduction” strategies may be promoted as an alternative to smoking cessation, particularly for patients unwilling to quit smoking. These strategies, purported to reduce tobacco-related morbidity, include smoking reduction, long-term use of medicinal NRTs, and use of tobacco products that claim to contain fewer carcinogens or lower levels of nicotine or tar than regular cigarettes.

In a systematic review of 25 studies, reduced tobacco consumption was associated with improvements in cardiovascular risk factors (e.g., decreased cholesterol, white blood cell count, hemoglobin, and pulse rate) as well as decreased asthma symptoms and nighttime use of rescue medications and inhaled corticosteroids. No reduction in myocardial infarctions (MI), hospitalizations for COPD exacerbations, and lung cancer were observed.⁹² In contrast, a recent study observed a decrease in mortality in each 5-cigarette reduction in persistent smokers after an acute MI.⁹³ The limited benefits of smoking reduction may be explained by the fact that smokers who reduce the daily quantity of cigarettes smoked tend to compensate by taking more frequent puffs or inhaling more deeply and longer to maintain a similar serum level of nicotine.

NRTs are safe and effective smoking cessation aids (see section on medications); they are much safer than smoking cigarettes. However, the use of NRT as a long-term replacement for cigarettes has not been adequately evaluated; thus the long-term health effects of nicotine exposure via NRT are not clear. Chewing nicotine gum has been associated with insulin resistance and hyperinsulinemia.⁹⁴ Nicotine is also associated with increased heart rate, elevated blood pressure, and coronary artery vasoconstriction. Unlike cigarette smoking, nicotine alone does not lower oxygen carrying capacity, activate coagulation or lead to arterial disease. To date, there is no evidence from animal studies or clinical trials that NRT causes cancer in humans.⁶⁷ A recent study suggests that patients with a genetic predisposition may be at risk of developing oral carcinoma when using NRTs due to a co-carcinogenic effect of nicotine in NRTs.⁹⁵ Thus, NRTs play a role in eliminating exposure to carcinogens found in cigarettes, but their long-term utilization may not be without risks.

Low-tar cigarettes have been suggested as an alternative to regular cigarettes. Potential benefits include a reduction in respiratory symptoms in patients with COPD, as well as cardiovascular risk. There is no evidence of lower risk of lung cancer or mortality benefits compared to regular cigarettes. Smokers switching to low-tar cigarettes tend to increase the number of cigarettes smoked daily, potentially negating any benefit seen.⁹⁶

An electronic cigarette, or e-cigarette, is a battery-powered device that provides inhaled doses of nicotine by way of a vaporized solution. It is promoted as an alternative to smoked tobacco products. The WHO does not consider e-cigarettes to be a legitimate smoking cessation aid, or a safe and effective NRT due to a lack of evidence. The FDA released a warning regarding e-cigarettes in 2009. The FDA's Division of Pharmaceutical Analysis tested the e-cigarettes and found diethylene glycol and nitrosamines, which are carcinogens and toxic chemicals. Concerns have also been raised over unreliable amounts of nicotine contained in e-cigarettes, as well as inconsistent amounts of nicotine delivered when using the device. The FDA is encouraging the utilization of the MedWatch program for any adverse events related to the e-cigarettes. The FDA has argued that e-cigarettes should be classified as drug delivery devices and subject to regulation under the Food, Drug, and Cosmetic Act (FDCA). However, e-cigarette manufacturers were granted an injunction rejecting the FDA's position; the FDA has since filed an appeal. Pending the court's decision, it remains unknown whether e-cigarettes will be classified as drug-delivery devices, or if they will ultimately fall under the FDA's new tobacco jurisdiction.⁹⁷

Table 1. SMOKING CESSATION AND PATIENT BEHAVIOR

5 A's Model for Treating Tobacco Use and Dependence – Physician's Actions	Stages of Change – Understanding Where the Patient Is in the Process of Change	Stage of Change Assessment – Physician action matchup
<p>Ask about tobacco use</p> <ul style="list-style-type: none"> Identify and document smoking status of every patient at every visit <p>Advise to quit</p> <ul style="list-style-type: none"> In a clear, strong and personalized manner urge every smoker to quit, "<i>It is important for you to quit and I can help.</i>" <p>Assess</p> <ul style="list-style-type: none"> For the current smoker ask, "<i>Are you willing to give quitting a try at this time?</i>" For the ex-smoker, ask how recently he/she quit and are there challenges to remaining abstinent Offer motivation and increase patient's confidence in ability to change <p>Assist</p> <ul style="list-style-type: none"> Negotiate a plan to quit and implement it with the patient For the patient willing to make a quit attempt, offer medication and/or provide or refer for counseling to help the patient quit For patients unwilling to quit at this time, provide motivational interventions designed to increase future quit attempts For the recent quitter and any with remaining challenges, provide relapse prevention <p>Arrange</p> <ul style="list-style-type: none"> All those receiving the previous A's should receive follow-up to review progress If a relapse occurs, review circumstances that caused relapse; review medication use and problems; provide or refer for counseling 	<p>Precontemplation</p> <ul style="list-style-type: none"> Not thinking about change May be resigned Denial Feeling of no control <p>Contemplation</p> <ul style="list-style-type: none"> Weighs pros/cons of smoking cessation <p>Preparation¹</p> <ul style="list-style-type: none"> Commits to change Forms a plan of action Experiments with small changes <p>¹ Highly motivated patients may skip preparation and go straight to action</p> <p>Action</p> <ul style="list-style-type: none"> Takes definitive action to stop smoking Implements plan to stop smoking <p>Maintenance (post quit)</p> <ul style="list-style-type: none"> Determined to maintain smoking cessation Incorporates changes as part of a new lifestyle <p>Relapse</p> <ul style="list-style-type: none"> May be discouraged by relapse but should be viewed as normal part of smoking cessation 	<p>Motivational intervention</p> <ul style="list-style-type: none"> Relevance, Risks, Rewards, Roadblocks, Repetition (5Rs) Express empathy, develop discrepancy, roll with resistance, support self-efficacy <p>STAR (Formulate a quit plan)</p> <ul style="list-style-type: none"> Set a quit date Tell family/friends and obtain support/understanding Anticipate challenges and withdrawal/problem solving Remove tobacco from environment <p>STARt</p> <ul style="list-style-type: none"> Begin medication^{1,2} Counseling (problem solving/skills training) and encouragement Follow-up within 1 week of quit date by office visit or phone 2nd follow-up within 1 month if possible Additional follow-ups as needed Offer the S.C. Tobacco Quitline 1-800-QUIT-NOW for telephone counseling <p>¹ Unless contraindicated or insufficient evidence (e.g., pregnancy, adolescence, light smokers, smokeless tobacco users)</p> <p>² Varenicline 1 week prior to and bupropion 1-2 weeks prior to abstinence; all other meds on quit date</p> <p>Follow-up</p> <ul style="list-style-type: none"> Offer congratulations and encourage recommitment to quit Assist with problems associated with quitting (e.g., weight gain, residual withdrawal symptoms) <p>Relapse</p> <ul style="list-style-type: none"> Remind patient relapse is common and part of the learning process Assess readiness for another quit attempt, and offer stage-appropriate assistance

Table 2. ASSISTING SMOKERS WILLING TO QUIT WITH A PLAN

Assist the smoker by formulating a quit plan, deciding on the most appropriate medication unless counseling alone is the preferred option, and offering practical counseling and social support

- Identify reasons for quitting and benefits of quitting
- Help formulate a quit plan:
 - ✓ Set a quit date, ideally within 2 weeks
 - ✓ If unable to stop 'cold turkey' on quit date, plan to cut down on number of cigarettes or delay smoking each cigarette by 30 minutes
 - ✓ Tell family and friends and coworkers about quitting
 - ✓ Get rid of all tobacco products and strive for smokefree household by quit date
- Review past quit attempts:
 - ✓ What worked
 - ✓ What did not work
- Learn new skills and behaviors:
 - ✓ Reduce stress
 - ✓ Change routine
 - ✓ Replace smoking with low-calorie foods
- Anticipate challenges and nicotine withdrawal symptoms, especially the first few weeks:
 - ✓ Avoid triggers/alter routine
 - ✓ Avoid alcohol to maximize the chance of success
 - ✓ Be careful around other smokers; if at all possible, stay in nonsmoking areas
- Get support from family, friends, and coworkers
- Abstinence is the goal (i.e., not a puff after the quit date)
- Decide on medication (unless counseling alone is preferred or appropriate option) and encourage use
- Initiate nicotine replacement therapy (NRT), bupropion SR, or varenicline unless contraindicated

Arrange follow-up in person or through telephone contact

- Schedule first follow-up contact within first week of quitting; second follow-up within the first month; other follow-ups as indicated
- Recommend toll-free helpline for counseling offered through the S.C. Tobacco Quitline: 1-800-QUIT-NOW (1-800-784-8669)
- Option to provide other resources, including links to websites for free materials (e.g., The Tobacco Control Research Branch of the National Cancer Institute at: www.smokefree.gov)

Table 3. ASSISTING SMOKERS WHO RECENTLY QUIT

Ask and document smoking status at every visit

- Recent quitters are at high risk for relapse. While there does not appear to be any particular behavioral strategy of counseling that decreases the likelihood of relapse, encouragement and ongoing support is valuable

Assess relapse potential

- Ask how long ago the patient quit. Most relapses occur within the first two weeks of quitting
- Ask about urges to smoke or challenges to remain abstinent

Assist with encouragement to stay abstinent

- Offer patient the opportunity to discuss:
 - ✓ Benefits that he/she may derive from smoking cessation
 - ✓ Any successes in quitting (e.g., duration of abstinence, reduction in withdrawal)
 - ✓ Challenges to remaining abstinent (e.g., depression, weight gain, significant stressors)
 - ✓ Medication effectiveness and adherence

Arrange follow-up

Table 4. ASSISTING SMOKERS UNWILLING OR UNDECIDED TO QUIT AT THIS TIME

<p>Assist with motivational interventions designed to enhance motivation to quit</p> <ul style="list-style-type: none"> • Relevance <ul style="list-style-type: none"> ✓ Encourage the patient to identify, in his/her own words, why quitting is personally relevant • Risks <ul style="list-style-type: none"> ✓ Ask the patient to identify potential negative consequences of smoking then highlight risks most relevant to the patient ✓ Explain that smoking low-tar/low-nicotine cigarettes or use of other forms of tobacco (e.g., cigars, pipes, smokeless tobacco) will not eliminate these risks • Rewards <ul style="list-style-type: none"> ✓ Ask the patient to identify potential benefits (e.g., money saved [\$1,971 per year for 1 pack/day smoker]) then highlight benefits most relevant to the patient • Roadblocks <ul style="list-style-type: none"> ✓ Ask the patient to identify barriers then offer problem-solving counseling and/or medication that could address barriers (e.g., depression) • Repetition <ul style="list-style-type: none"> ✓ Repeat motivational interventions at every visit and tell smokers that most people make repeated quit attempts before they are successful <p>Arrange to repeat on subsequent visits</p>

Table 5. MOTIVATIONAL INTERVIEWING STRATEGIES

<p>Express empathy</p>	<ul style="list-style-type: none"> • Use open-ended questions to explore: <ul style="list-style-type: none"> ✓ The importance of addressing smoking or other tobacco use (e.g., <i>“How important do you think it is for you to quit smoking?”</i>) ✓ Concerns and benefits of quitting (e.g., <i>“What might happen if you quit?”</i>) • Use reflective listening to seek shared understanding: <ul style="list-style-type: none"> ✓ Reflect words or meaning (e.g., <i>“So you think smoking helps you to maintain your weight.”</i>) ✓ Summarize (e.g., <i>“What I have heard so far is that smoking is something you enjoy. On the other hand, your boyfriend hates your smoking, and you are worried you might develop a serious disease.”</i>) • Normalize feelings and concerns (e.g., <i>“Many people worry about managing without cigarettes.”</i>) • Support the patient’s autonomy and right to choose or reject change (e.g., <i>“I hear you saying you are not ready to quit smoking right now. I’m here to help you when you are ready.”</i>)
<p>Develop discrepancy</p>	<ul style="list-style-type: none"> • Highlight the discrepancy between the patient’s present behavior and expressed priorities, values, and goals - weigh pros and cons: <ul style="list-style-type: none"> ✓ <i>“It sounds like you are very devoted to your family. How do you think your smoking is affecting your children?”</i> • Reinforce and support “change talk” and “commitment” language: <ul style="list-style-type: none"> ✓ <i>“So, you realize how smoking is affecting your breathing and making it hard to keep up with your kids.”</i> ✓ <i>“It’s great that you are going to quit when you get through this busy time at work.”</i> • Build and deepen commitment to change: <ul style="list-style-type: none"> ✓ <i>“There are effective treatments that will ease the pain of quitting, including counseling and many medication options.”</i> ✓ <i>“We would like to help you avoid a stroke like the one your father had.”</i>
<p>Roll with resistance</p>	<ul style="list-style-type: none"> • Back off and use reflection when the patient expresses resistance: <ul style="list-style-type: none"> ✓ <i>“Sounds like you are feeling pressured about your smoking.”</i> • Express empathy: <ul style="list-style-type: none"> ✓ <i>“You are worried about how you would manage withdrawal symptoms.”</i> • Ask permission to provide information: <ul style="list-style-type: none"> ✓ <i>“Would you like to hear about some strategies that can help you address that concern when you quit?”</i>
<p>Support self-efficacy</p>	<ul style="list-style-type: none"> • Help the patient to identify and build on past successes: <ul style="list-style-type: none"> ✓ <i>“So you were fairly successful the last time you tried to quit.”</i> • Offer options for achievable small steps toward change: <ul style="list-style-type: none"> ✓ Call the S.C. Tobacco Quitline (1-800-QUIT-NOW) for advice and information ✓ Read about quitting benefits and strategies ✓ Change smoking patterns (e.g., no smoking in the home) ✓ Share his or her ideas about quitting strategies

Table 6. FIRST-LINE MEDICATION GUIDELINES FOR SMOKING CESSATION

Medications* [Brand Examples]	Dosage	Duration	OR (95% CI) [#]	Daily Cost [†] [~ Pack]
Nicotine Gum (i) [Nicorette [®]] 2 mg, 4 mg OTC	2 mg: < 25 cigarettes/day 4 mg: ≥ 25 cigarettes/day Weeks 1-6: 1 piece q 1-2 h – Minimum: 9 pieces/day – Maximum: 24 pieces/day Weeks 7-9: 1 piece q 2-4 h Weeks 10-12: 1 piece q 4-8 h	Up to 12 weeks	1.5 (1.2-1.7)	\$3.51 - \$3.69 (9 pieces) [~ ¾ pack]
Nicotine Lozenge (i) [Nicorette [®]] 2 mg, 4 mg OTC	2 mg: 1st cigarette > 30 min after waking 4 mg: 1st cigarette ≤ 30 min after waking Weeks 1-6: 1 lozenge q 1-2 h – Minimum: 9 lozenges/day – Maximum: 20 lozenges/day Weeks 7-9: 1 lozenge q 2-4 h Weeks 10-12: 1 lozenge q 4-8 h	Up to 12 weeks	2 mg: 2.0 (1.4-2.8) (iii) 4 mg: 2.8 (1.9-4.0) (iii)	\$3.78 - \$3.96 (9 pieces) [~ ¾ pack]
Nicotine Patch, 24-hour (i) [Nicoderm CQ [®]] 7 mg, 14 mg, 21 mg OTC	If > 10 cigarettes/day: (ii) 21 mg/day x 4-6 weeks; 14 mg x 2 weeks; 7 mg x 2 weeks If ≤ 10 cigarettes/day: (ii) 14 mg/day x 6 weeks; 7 mg/day x 2 weeks	8 - 10 weeks	1.9 (1.7-2.2) PATCH plus: + bupropion HCl SR 2.5 (1.9-3.4) (iii) + ad lib gum or spray 3.6 (2.5-5.2) (iii,iv) + lozenge 2.3 (1.5-3.6) (iii,iv) + inhaler 2.2 (1.3-3.6) (iii,iv)	\$2.70 - \$3.13 (1 patch) [~ ½ pack]
Nicotine Nasal Spray (i) [Nicotrol NS [®]] (4 bottles/package) 200 sprays/10 ml bottle 0.5 mg/metered spray Rx	1 dose = 2 sprays (one spray in each nostril) Start with 1-2 doses/hour (Maximum: 5 doses/hour) – Minimum: 8 doses/day – Maximum: 40 doses/day Taper at end suggested	12 weeks; up to 6 months in selected patients	2.3 (1.7-3.0)	\$4.39 (8 doses) [~ ¾ pack]
Nicotine Inhaler (i) [Nicotrol [®]] (168 cartridges/package) 10 mg/cartridge Rx	10 mg cartridge (delivers 4 mg) ~ 20 minutes of active puffing – Minimum: 6 cartridges/day – Maximum: 16 cartridges/day Taper at end suggested	12 weeks; up to 6 months in selected patients	2.1 (1.5-2.9)	\$7.72 (6 cartridges) [~1.5 packs]
Bupropion HCl SR [Zyban [®]] 150 mg SR tablet Rx	Start 1-2 weeks before quit date Days 1-3: 150 mg q AM Day 4 until end: 150 mg BID (v) – Maximum: 300 mg/day	7 - 12 weeks; up to 6 months in selected patients	2.0 (1.8-2.2)	\$2.28 (2 tablets, generic) [~ ½ pack]
Varenicline [Chantix [®]] 0.5 mg, 1 mg tablet Rx	Start 1 week before quit date Days 1-3: 0.5 mg q AM Days 4-7: 0.5 mg BID Day 8 until end: 1 mg BID (vi)	12 weeks; up to 6 months in selected patients	3.1 (2.5-3.8) (vi)	\$5.62 (Two 1 mg tablets) [~ 1 pack]

* FDA approved in adults only; [#] OR = Estimated odds ratio for treatment versus placebo (95% Confidence Interval); [†] Daily drug cost and daily approximate cigarette pack equivalent [~ Pack] based on September 2010 average South Carolina retail costs; [‡] Breastfeeding recommendations are not provided due to limited/lack of human data. FDA pregnancy ratings: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

(i) FDA approved for post-quit use only; (ii) Preliminary evidence suggests that starting nicotine patch 2 weeks prior to quit date versus starting on quit date increases abstinence rates (OR 1.8 [1.2-2.7]); (iii) Based on 3 or fewer studies; (iv) Combination not FDA approved; (v) A lower dose of 150 mg daily does not appear to differ in efficacy; (vi) A lower dose of 0.5 mg BID (OR = 2.1 [1.5 – 3]) is effective but less so than 1 mg BID.

FIRST-LINE MEDICATION GUIDELINES FOR SMOKING CESSATION (CONTINUED)

	Administration Instructions	Cautions (<i>Pregnancy</i> [†])	Side Effects / Comments
Nicotine Gum	<ul style="list-style-type: none"> Chew gum slowly until tingles (~ 15-30 chews), then park between cheek and gum Resume chewing when tingle fades Repeat “chew-park” process until tingle is gone/does not return (~ 30 minutes) No food or beverages except water 15 minutes before or during use 	<ul style="list-style-type: none"> Caution in patients with recent myocardial infarction (within 2 weeks), serious arrhythmias, unstable angina Caution with dentures, dental caps, partial bridges, temporomandibular joint disease <i>FDA: C; Briggs: Compatible - maternal benefit >> embryo/fetal risk</i> 	<ul style="list-style-type: none"> Mouth soreness; jaw ache Hiccups Dyspepsia Gastrointestinal disturbances: <ul style="list-style-type: none"> Associated with improper use and swallowing large amounts of nicotine
Nicotine Lozenge	<ul style="list-style-type: none"> Dissolve slowly in mouth (~ 20-30 minutes); may notice warm tingling sensation Occasionally move to other side of mouth Do not chew or swallow No food or beverages except water 15 minutes before or during use 	<ul style="list-style-type: none"> Caution in patients with recent myocardial infarction (within 2 weeks), serious arrhythmias, unstable angina <i>FDA: C; Briggs: Not available</i> 	<ul style="list-style-type: none"> Nausea; hiccups; heartburn; indigestion 4 mg: Cough (< 10%) and headaches (< 10%)
Nicotine Patch, 24-hour	<ul style="list-style-type: none"> Apply patch to clean, hairless, dry skin on trunk or upper limbs Rotate application sites If sleep disturbances, remove patch at bedtime Do not cut patch 	<ul style="list-style-type: none"> Caution in patients with recent myocardial infarction (within 2 weeks), serious arrhythmias, unstable angina Avoid in patients with severe eczema or psoriasis Remove metal containing patches (e.g., tan-colored) prior to MRI <i>FDA: D; Briggs: Compatible - maternal benefit >> embryo/fetal risk</i> 	<ul style="list-style-type: none"> Insomnia Local skin reaction (50%): <ul style="list-style-type: none"> Usually mild Rarely leads to discontinuation Rotate application site to minimize
Nicotine Nasal Spray	<ul style="list-style-type: none"> Prime pump before 1st use or if not used for > 24 hours Shake nasal spray before using Deliver with head tilted slightly back Avoid sniffing, inhaling or swallowing 	<ul style="list-style-type: none"> Caution in patients with recent myocardial infarction (within 2 weeks), serious arrhythmias, unstable angina Avoid in patients with severe reactive airway disease and chronic nasal disorders Wait 5 minutes before driving Highest dependence potential <i>FDA: D; Briggs: Compatible - maternal benefit >> embryo/fetal risk</i> 	<ul style="list-style-type: none"> Nasal irritation (94%), nasal congestion Smell and taste alterations
Nicotine Inhaler	<ul style="list-style-type: none"> Inhale into back of throat or puff in short breaths; do not inhale into lungs Open cartridge retains potency for 24 hours Use inhaler at room temperature No food or beverages except water 15 minutes before or during use 	<ul style="list-style-type: none"> Caution in patients with recent myocardial infarction (within 2 weeks), serious arrhythmias, unstable angina Caution in patients with severe bronchospastic disease <i>FDA: D; Briggs: Compatible - maternal benefit >> embryo/fetal risk</i> 	<ul style="list-style-type: none"> Mouth and throat irritation (40%) Cough (32%) Rhinitis (23%)
Bupropion HCl SR	<ul style="list-style-type: none"> Take 2nd dose in afternoon to reduce insomnia Allow at least 8 hours between doses 	<ul style="list-style-type: none"> Contraindicated in patients with history of seizure or eating disorders Monitor blood pressure when combined with nicotine replacement therapy Monitor for changes in mood, behavior, psychiatric symptoms, and suicidal ideation <i>FDA: C; Briggs: Human data suggest low risk</i> 	<ul style="list-style-type: none"> Insomnia (35-40%) Dry mouth (10%) Seizures (rare) reported in smoking cessation trials
Varenicline	<ul style="list-style-type: none"> Take after eating (with a full glass of water) to reduce nausea Take 2nd dose at supper to reduce insomnia 	<ul style="list-style-type: none"> Caution in patients with significant renal impairment, serious psychiatric illness Caution driving/operating machinery Monitor for changes in mood, behavior, psychiatric symptoms, and suicidal ideation <i>FDA: C; Briggs: No human data - animal data suggest low risk</i> 	<ul style="list-style-type: none"> Nausea (up to 30%) <ul style="list-style-type: none"> Dose related May diminish over time Reduced with initial titration Insomnia; abnormal, vivid, strange dreams Rare serious skin/allergic reactions

References: Briggs, Gerald G., Roger K. Freeman, and Sumner J. Yaffe. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008. Print; Fiore MC, Jaén CR, Baker TB, et al. *Clinical Practice Guideline. Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008, Accessed October 21, 2009; Stead LF, Perera R, Bullen C, et al. Nicotine replacement therapy for smoking cessation. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub3; Piper ME, Smith SS, Schlam TR, et al. A randomized, placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. *Arch Gen Psychiatry* 2009;66:1253-1262; Rx for Change: Clinician – Assisted Tobacco Cessation. *Pharmacologic product guide: FDA-approved medications*. Copyright©1999-2010. The Regents of the University of California. Updated April 12, 2010. **For complete prescribing information, please refer to the manufacturers’ package inserts.**

Table 7. SECOND-LINE MEDICATION GUIDELINES FOR SMOKING CESSATION

Medications* [Brand Examples]	Dosage	Duration	OR (95% CI) [#]	Daily Cost [†] [~ Pack]
Clonidine [Catapres [®] , Catapres-TTS [®]] PO: 0.1 mg, 0.2 mg, 0.3 mg tablet Transdermal System - once weekly patch: 0.1 mg/day, for 1 week 0.2 mg/day, for 1 week Rx	Start ≤ 3 days before quit date <ul style="list-style-type: none"> Initial: <ul style="list-style-type: none"> PO: 0.1 mg BID Transdermal: 0.1 mg/day Titration: <ul style="list-style-type: none"> 0.1 mg/day per week if needed Range: <ul style="list-style-type: none"> PO: 0.15-0.75 mg/day Transdermal: 0.1-0.2 mg/day 	3 - 10 weeks; taper at end	2.1 (1.2-3.7) (i)	\$0.56 (0.3 mg tablet, generic) [~1/10 pack] \$5.42 (0.2 mg patch, generic) [~1 pack]
Nortriptyline [Pamelor [®]] 10 mg, 25 mg, 75 mg capsule 10 mg/ 5 ml Rx	Start 10-28 days before quit date <ul style="list-style-type: none"> Initial: 25 mg/day Titration: increase gradually Target: 75-100 mg/day 	3 months; up to 6 months; taper at end	1.8 (1.3-2.6)	\$0.85 (75 mg capsule, generic) [~1/6 pack]
		PATCH plus: + nortriptyline 2.3 (1.3-4.2) (i)*		

* Not FDA approved for smoking cessation; [#] OR = Estimated odds ratio for treatment versus placebo (95% Confidence Interval); [†] Daily drug cost and daily approximate cigarette pack equivalent [~ Pack] based on September 2010 average South Carolina retail costs).

(i) Based on 3 or fewer studies.

SECOND-LINE MEDICATION GUIDELINES FOR SMOKING CESSATION (CONTINUED)

Administration Instructions	Cautions (Pregnancy)*	Side Effects / Comments
Clonidine <ul style="list-style-type: none"> Apply patch to clean, hairless intact skin on trunk every 7 days Rotate application sites Leave patch in place even when bathing or swimming 	<ul style="list-style-type: none"> Caution in elderly Caution driving or operating machinery Monitor blood pressure Avoid abrupt discontinuation <ul style="list-style-type: none"> taper over 2-4 days to avoid rebound hypertension, agitation, confusion, and/or tremor FDA: C; Briggs: Limited human data - animal data suggest risk 	<ul style="list-style-type: none"> Dry mouth (40%) Drowsiness (33%) Dizziness (16%) Sedation (10%) Constipation (10%) Localized skin reaction to patch Prominent side effects limit its usefulness
Nortriptyline <ul style="list-style-type: none"> May take in divided doses or as a single dose at bedtime to minimize sedation 	<ul style="list-style-type: none"> Caution in patients with cardiovascular disease Caution driving or operating machinery Consider risk of overdose carefully before prescribing FDA: C; Briggs: human data suggest low risk 	<ul style="list-style-type: none"> Dry mouth (64-78%) Lightheadedness (49%) Tremor (23%) Blurred vision (16%) Urinary retention Sedation Low smoking cessation doses may be better tolerated than higher doses used in depression

* Breastfeeding recommendations: clonidine – limited human data, probably compatible; nortriptyline – limited human data, potential toxicity. FDA pregnancy ratings: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk; X, contraindicated in pregnancy.

References: Briggs, Gerald G., Roger K. Freeman, and Sumner J. Yaffe. *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*. Philadelphia, PA: Lippincott, Williams & Wilkins, 2008. Print; Fiore MC, Jaén CR, Baker TB, et al. *Clinical Practice Guideline. Treating Tobacco Use and Dependence: 2008 Update*. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. May 2008, Accessed October 21, 2009; Hughes JR, Stead LF, Lancaster T. Antidepressants for smoking cessation. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD000031. DOI: 10.1002/14651858.CD000031.pub3; *Drug Information Handbook for Psychiatry*. Fuller MA, Sajatovic M, editors. Hudson, OH, Lexi-Comp, 2007; *Clinical Handbook of Psychotropic Drugs*. Bezchlibnyk-Butler KZ, Jeffries JJ, editors. Toronto, ON, Hogrefe & Huber, 2006. **For complete prescribing information, please refer to the manufacturers' package inserts.**

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