



Overview of Tobacco Cessation

By Steven Waller, PhD; Gina Forster, PhD

Tobacco usage has been associated with several major health care problems, including cardiovascular diseases, nonmalignant respiratory diseases and lung and other cancers. In 2005, the lifetime use rate for tobacco was nearly 30 percent for the population aged 12 or older.¹ The majority (90 percent) of adult tobacco users report initiating tobacco use prior to the age of 18, with the transition from experimentation to daily use occurring around age 14.²⁻⁶ The costs of continued tobacco use also are considerable. Tobacco-related health problems are estimated to be approximately \$96 billion (US\$) in direct costs and an additional \$97 billion (US\$) in indirect costs such as loss of productivity.⁷ Up to 14 percent of Medicaid expenditures are directed to tobacco-related illnesses.⁷ Further, half of all long-term tobacco users are likely to die from tobacco-related diseases.⁸

Interestingly, nearly 44 percent of tobacco users report recent attempts to stop using tobacco products.⁹ Most were unsuccessful and attempted without professional assistance. Research has shown health professional intervention, even casual intervention, can enhance the likelihood of successful smoking cessation.¹⁰ Unfortunately, health care

professionals often avoid the most basic of intervention strategies, and instead emphasize primarily the health benefits of not using tobacco products.

Recently, a panel of scientists and health care providers convened by the U.S. Department of Health and Human Services and The Agency for Healthcare Research and Quality (AHRQ) reviewed the current medical literature relating to tobacco use and cessation and published *Treating Tobacco Use and Dependence: 2008 Update* through the National Library of Medicine Web site.¹⁰ The panel report represents a thorough analysis and review of the research relating to tobacco use and cessation. More than 8,700 research articles were critically reviewed with 300 used in the primary meta-analysis of the project, and an additional 600 studies were used in the consensus work. From this comprehensive review, the authors developed conclusions and recommendations rated Evidence Strength A, B, or C (ES-A, ES-B, or ES-C, respectively). Findings assigned ES-A were based on well-designed randomized clinical studies and presented consistent findings and recommendations. Those findings and recommendations rated ES-B were based on studies lacking in design consistency, were

not directly relevant to tobacco use and cessation or had minor technical flaws. Findings and recommendations rated as ES-C were reached by the authors through consensus but lacked adequate or randomized controlled studies. This paper will attempt to summarize the salient findings of this significant report as well as other complementary reports.

The key findings of the panel were summarized into ten guideline recommendations that can be generalized into four essential points:¹⁰

1. Tobacco use is characterized by intense addiction that may require repeated attempts at cessation. However, effective treatments for cessation of tobacco (nicotine) addiction exist;
2. All clinicians must evaluate tobacco use status at every visit and encourage continued abstinence to the non-user or former user and to encourage cessation steps to the current user;
3. Current users willing to quit should be provided support and treatments in tobacco cessation and those not willing to quit should be provided directed interventions to encourage them to quit; and
4. Treatment of tobacco use should include counseling in addition to pharmacological treatments. Counseling and pharmacological interventions are effective separately but are more effective when combined.

The first essential point restates what is obvious to most health care providers and systems; tobacco users are addicted to nicotine and successful abstinence, especially sustained abstinence, is sometimes difficult to achieve. This is particularly pertinent to adolescent tobacco users, who report subjective measures of dependence and strong cravings during withdrawal,^{2,11,12} and appear to be more sensitive to the addictive properties of nicotine when compared to adults.⁴ However, routine visits to primary care physicians offer important opportunities to initiate tobacco cessation intervention in all age groups, and the AHRQ Panel found strong evidence successful interventions were both practical and possible.¹⁰

The second and third points of the AHRQ panel's findings and recommendation are perhaps the most important. Societal pressures to quit tobacco usage are increasingly evident. The opportunity to build on these pressures means health care providers at all levels must take the time to evaluate tobacco use during each patient visit. Current statistics suggest fewer than 50 percent of health care visits include some type of tobacco use assessment with fewer than one in seven tobacco users offered any assistance in

tobacco cessation.¹³ This is a missed opportunity to assist tobacco users in achieving cessation. Further, pediatric populations represent a critical but challenging target for tobacco cessation. Surveys of pediatricians and family physicians cite that children under the age of 15 often are not asked about their tobacco use.^{3,5} These health professionals report that the barriers to establishing the extent of tobacco use of patients under the age of 18 include patient false self-report to prevent parental knowledge of a tobacco habit or the physician's fear that tobacco counseling would anger parents.^{3,5} For all tobacco users, interventions by health care providers or systems as brief as three minutes in length can be beneficial.^{3,5,6} However, there is a positive relationship between the frequency and intensity of interventions and success.¹⁰ Even long-term users unwilling to quit tobacco use may respond to repeated approaches.

The AHRQ panel recommends every patient at every visit be screened for tobacco use using a template of five steps, each step beginning with the letter A: Ask the patient about tobacco use; Advise strongly all users to quit; Assess willingness to quit; Assist with quitting; and Arrange followup.¹⁰ Patients can be grouped into three primary classifications: non-using patients, patients using tobacco and willing to quit and patients using tobacco resistant to quitting. Non-using patients should be encouraged to remain tobacco-free. Patients using tobacco should receive advice to quit, which should be followed by assessment of interest in quitting. Tobacco users interested in quitting should be provided or referred for counseling to assist in quitting, and, when appropriate, offered pharmacotherapy. A follow-up visit or contact should be scheduled. Tobacco users not interested in quitting should be provided motivational intervention directed at promoting quitting. Motivational intervention strategies should emphasize the relevance of quitting to the patient's personal health goals; the risks of not quitting, including acute, long-term, environmental, or secondhand consequences; and the rewards realized by quitting. Roadblocks that may prevent the patient from successfully quitting should be discussed in relation to the benefits of quitting. Following motivational intervention, reassessment of the user's willingness to quit should be repeated and, if willing, the patient should be provided assistance in quitting as described above. If the patient is still unwilling to quit tobacco following motivational intervention, then a follow-up intervention should be planned for the patient's next visit. Regardless of the course the patient has taken, it is important that tobacco use be screened or at every visit using this approach. A special consideration for cessation of tobacco use in adolescent populations is parental smoking appears to reduce the

motivation or readiness to quit tobacco use, whereas non-smoking parents with restrictive smoking policies are more likely to induce motivation and confidence to quit in their adolescent offspring.^{11,14} Therefore, parents' tobacco use and/or attitudes towards tobacco use represent an important target for health professionals to enhance adolescents' motivation to quit tobacco. The importance of screening each patient for tobacco use was rated ES-A for adults and ES-C for children and adolescents, indicating it was supported by the medical literature.¹⁰ In the AHRQ panel report, special mention was given to secondhand smoke and children. Clinicians are encouraged strongly to promote tobacco cessation among parents who smoke to protect the long-term health of the children in the household (ES-B).¹⁰

As summarized by point four of the AHRQ panel recommendations, successful tobacco use cessation is greatest when a combination of counseling and pharmacotherapy is used.¹⁰ The most effective counseling strategy for tobacco cessation can involve three types of counseling: practical counseling, intra-treatment counseling and extra-treatment counseling.¹⁰ Practical counseling emphasizing problem solving and skills training seems especially important to patient success. Practical counseling includes training in how to recognize situations where the risk of smoking will be high, developing coping skills to avoid or successfully navigate dangerous situations and sensitivity to the potential for relapse. Counseling in the symptoms associated with tobacco withdrawal the patient might expect during the first two to three weeks after quitting are also an important part of practical counseling.

Intra-treatment supportive counseling is the second form of counseling advocated by the AHRQ panel.¹⁰ Common elements of intra-treatment supportive interventions include direct and frequent encouragement of the patient to quit, the clear communication of caring and concern for the patient as a tobacco user attempting to quit, a willingness to listen to the concerns and fears of the patient attempting to quit and the celebration of the progress of the patient attempting to quit. Intra-treatment supportive counseling should include presentation of treatment options and their success rates. Much of the intra-treatment counseling process involves allowing the tobacco user the opportunity to discuss their personal reasons, fears and feelings about quitting. For those patients that have unsuccessfully tried to quit, the difficulties in the past that may have contributed to their failures should be discussed.

Extra-treatment supportive counseling includes those counseling services accessed by the tobacco user outside of the formal treatment process.¹⁰ Common extra-treatment

supportive counseling services accessed by users seeking to quit include self-help resources such as pamphlets, booklets and manuals, quit lines and help lines, stepped-care interventions such as 12-step programs and Internet-based resources. The value of extra-treatment supportive counseling in assisting a tobacco user in quitting is not as robust as practical and intra-treatment counseling. Self-help programs were found to be inconsistent in benefit, with greatest benefit associated with those self-help programs that actively engaged the user. However, these were still rated as marginally effective. Quit lines and/or help lines, stepped-care interventions and Internet-based resources were most effective when used in conjunction with practical and intra-treatment counseling. These programs differed from self-help programs in being tailored to the needs of the individual user seeking to quit. Health care providers or systems can be powerful resources directing tobacco users to specific resources.

Practical and intra-treatment counseling were both regarded by the AHRQ panel as being important components in tobacco cessation programs, separately earning an ES-A classification.¹⁰ The AHRQ panel expressed consensus support for the combined benefits of practical and intra-treatment counseling, but the absence of rigorous studies resulted in the combined counseling strategy being rated as ES-B.¹⁰ The Evidence Strength for extra-treatment supportive counseling was assessed by the AHRQ Panel as ES-B, with greatest strength associated with the individualized extra-treatment supportive counseling programs.¹⁰ Department of Health and Human Services guidelines recommend that counseling interventions that are effective with adult tobacco users should be considered for use with children and adolescent users, but the content should be modified to be developmentally appropriate.¹⁰

The AHRQ panel found strong evidence for the combined effects of counseling and directed medications on the ability of an adult tobacco user to successfully quit (ES-A).¹⁰ The panel recommended the combined approach be the practice standard and that counseling or medications used separately only for tobacco users when it is not feasible to do both, or the user will not use both. Medications directed at tobacco cessation may not be appropriate for use in every patient, especially where there are no studies showing effectiveness in certain populations, such as pregnant women, smokeless tobacco users or light smokers.

There are seven medications considered first line pharmacotherapies for tobacco cessation: bupropion, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch and varenicline.^{1,10,15} With the exception of

the nicotine lozenge, the use of each medication was found by the AHRQ panel to have a beneficial use in tobacco cessation for adults with an ES-A.¹⁰ The nicotine lozenge has not been as extensively studied and was assigned a classification of ES-B.¹⁰ The use of these medications in pediatric nicotine-dependent populations has been less extensively studied as compared to adult populations, but recent reports suggest bupropion or nicotine replacement in the form of gum or patches can be safe and mildly efficacious for adolescents.^{4,6} There are fewer studies assessing the benefits of bupropion in tobacco cessation in adolescents, and results are mixed.¹⁰ However, the FDA does not label any of the seven first-line medications for individuals under 18 years of age, the efficacy of nicotine replacement therapy in adolescence is still controversial and the potential for misuse is problematic.^{4,6,16,17,18} There is no evidence that nicotine replacement therapy or bupropion used for treating nicotine addiction are harmful to adolescents, but the AHRQ panel does not recommend nicotine replacement or bupropion for treating children or adolescent tobacco use due to the lack of strong evidence that these medications are effective in promoting long-term smoking abstinence among adolescent populations.¹⁰ If these medications are considered, several factors should be taken into account before prescribing to adolescents, such as degree of dependence, motivation to quit, frequency of tobacco use and body weight.¹⁸

Bupropion has two potential mechanisms of action in tobacco cessation. The primary mechanism of action for bupropion is thought to be related to inhibition of the neurotransmitter dopamine's reuptake processes reducing the rewarding and addictive effects of nicotine. A second mechanism of action may be related to mild nicotine blocking action that antagonizes central actions of nicotine, including presumably those related to addiction. Bupropion is available in a variety of release forms with bupropion sustained release (SR) being the most commonly studied form in tobacco cessation. Bupropion SR use is associated with a doubling of cessation rates in nicotine-dependent adults compared to placebo, and it is effective in promoting cessation from smokeless tobacco. However, bupropion SR and nicotine combination therapy was not found to be significantly better than bupropion alone in both adolescent and adult populations.⁶

Bupropion's most common adverse effects include insomnia and dry mouth.¹⁵ There are reports of headache, nausea, tremor, rash and anxiety associated with bupropion usage, but these are unusual. When used for depression, bupropion has been associated with seizure development, but this has

not been observed when used for tobacco cessation.¹⁹ Patients using bupropion and nicotine replacement therapy using the patch should be monitored for development of hypertension.¹ Bupropion has a black box warning for increased risk of suicidality in children adolescents and young adults when used for major depression. The FDA classifies bupropion as pregnancy Category C.

The starting dose for bupropion SR is 150 mg PO once daily for three days and then increased to 150 mg PO twice daily for seven to 12 weeks.¹⁵ Doses should be separated by at least eight hours and the last daily dose taken in early evening to avoid sleep disruption. To optimize benefits, bupropion SR should be used approximately one to two weeks before tobacco cessation to allow steady state levels to be established in the central nervous system.¹⁰

Nicotine replacement therapy is available as gum, inhalers, lozenges, nasal sprays and transdermally (patch). Three forms – gums, lozenges, and patches – are available without prescription and appear as effective as the prescription inhaler and nasal spray.¹⁵ All nicotine replacement therapies deliver a controlled dose of nicotine to sustain the addiction to nicotine and prevent nicotine withdrawal symptoms, a fact of which the patient should be informed. The dose of nicotine achieved by nicotine replacement therapy is generally lower than achieved by tobacco use. The nicotine replacement therapy user can reduce the nicotine dosage gradually to reduce or end the addiction to nicotine.

All nicotine replacement therapies doubled tobacco cessation rates in adults after about six months of therapy.^{10,15} Nicotine is FDA Pregnancy Classification D. All nicotine replacement therapies should be used with caution during the first two weeks post-myocardial infarction, in patients with serious arrhythmias and in patients with unstable angina.¹⁰ Although all forms of nicotine replacement therapies decreased weight gain associated with tobacco cessation, use of gum and lozenge delivery forms were related to the lowest levels of weight gain.¹⁰

Gum, lozenges and inhalers are all considered oral delivery forms of nicotine¹⁰. However, nicotine absorption is actually a buccal (gum and lozenge) or oropharynx (inhaler) absorption process as first pass biotransformation limits bioavailability to below clinically effective levels. Gum and lozenges are available in 2 mg and 4 mg doses, with the higher dose often initially recommended for patients using the equivalent of more than 25 cigarettes per day.¹⁰ Gum should be chewed slowly until soft and the base flavor of the gum (mint or pepper) appears, and then it should be

positioned for buccal drug absorption for about 30 minutes. Lozenges, also available in 2 mg and 4 mg doses, should be allowed to dissolve slowly in the mouth. Lozenges provide more nicotine than gum because of complete dissolution of the lozenge delivery form.^{10,15} Acidic foods and beverages may interfere with buccal nicotine absorption, so eating or drinking (other than water) should be avoided 15 minutes before and during oral nicotine replacement therapy. Inhalers provide 4 mg doses and are inefficient at delivering nicotine when ambient room temperature is below 40 degrees Fahrenheit.¹⁰ Patients should be advised during cold weather to keep the inhaler system in an inside pocket or other warm area. Patients using oral nicotine replacement therapies should be encouraged to use the products on a fixed schedule initially (up to several months), as some users have been reported to underuse the products achieving suboptimal benefits. Adverse reactions with oral delivery forms are generally mild. Nicotine gum use may produce transient jaw and mouth soreness, hiccups and dyspepsia. Nicotine lozenges use may produce nausea, hiccups and heartburn, and the 4 mg lozenge may produce headaches and coughing. Nicotine inhaler use may produce local irritation of the mouth and throat, coughing and rhinitis. For all three oral delivery systems, these adverse effects diminished with continued use.¹⁰

Nasal nicotine spray provides the fastest onset of nicotine action of all nicotine delivery forms except smoking.^{10,15} The faster onset of nicotine action can be valuable for patients needing faster relief from nicotine withdrawal symptoms. Users of nasal nicotine spray should tilt their heads slightly back during drug delivery and to avoid sniffing, swallowing or inhaling through the nose during delivery to minimize nasal irritation.¹ The AHRQ panel noted that nasal nicotine was associated with dependency and that some patients will use the drug longer than recommended.¹⁰ In the only trial of nasal spray in adolescent smokers to date, the poor adherence due to adverse effects such as nasal irritation and the lack of efficacy suggest nasal spray may not be an effective pharmacotherapy for this population.¹⁷

Nicotine nasal sprays provide 0.5 mg per spray with typical dosing of one to two sprays each nostril every hour.¹ Because of the higher blood levels achieved by nasal nicotine sprays, nicotine nasal spray should be used only after cessation of tobacco products to avoid nicotine toxicity. Following an eight- to 12-week period of hourly dosing, the patient should be encouraged to begin tapering slowly with complete nicotine cessation achieved over a six-week period.

Transdermal nicotine, i.e., the nicotine patch, provides the slowest onset of nicotine action of all nicotine delivery

forms but provides the most stable blood levels for nicotine with continued use.^{1,10,15} As with any transdermal system, some patients will experience local skin reactions. Most are mild and self-limiting and can be treated using over-the-counter topical steroid creams, changing the brand of patch and by moving the patch to a new relatively hairless location each day.¹⁵ Patches are available in stepped 24-hour doses of 7, 14 and 21 mg.¹ Some nicotine patches are presented as 16-hour patches to be removed before bedtime. The higher dose forms are often preferred in patients with a history of higher tobacco use. Transdermal nicotine replacement therapy is sometimes associated with insomnia and vivid and strange dreams.^{1,10,15} Patients experiencing sleep problems should remove the patch before bedtime.

Though there are differences among brands of transdermal patches in dosing instructions, patients with histories of heavy tobacco use should begin therapy with the higher dose patch, patients with moderate use rates the middle dose patch and patients with light tobacco use rates the lower dose patch.^{1,10} Tobacco use should not overlap with the start of nicotine patch therapy to avoid nicotine toxicity. Following determination of the starting dose, the patch should be used for approximately seven weeks. At the end of seven weeks, patients using the 14 or 21 mg patches should step down to the lower dose (7 or 14 mg, respectively) for two weeks. Patients using the 14 mg patch should step down to the 7 mg patch for another two weeks. Patients using the 7 mg patches should be able to discontinue use of the patch with minimal adverse effects.

It should be noted that pregnant women seeking to stop tobacco use should be encouraged to do so without the use of medications (EL-A), as all the medications used for tobacco cessation are FDA Pregnancy Class C or D.¹⁰ However, nicotine replacement therapy generally produces lower nicotine blood levels than tobacco use and is probably safer for the mother and the fetus.^{1,10,15} If the alternative to nicotine replacement therapy is tobacco use and there is a reasonable expectation cessation can be achieved, then nicotine replacement therapy may be important option to consider for the pregnant tobacco user.

Varenicline is a mixed partial agonist/antagonist of nicotine receptors. The partial agonist properties of varenicline presumably stimulate the nicotine receptors adequately to relieve cravings and withdrawal symptoms, while the antagonist properties to nicotine receptors are adequate to reduce the reward or pleasurable effects of active tobacco use. Though a recent addition to tobacco cessation treatments, three studies have reported varenicline to be more effective than bupropion in promoting tobacco cessation in adults.¹⁰

Importantly, varenicline was shown in one study to be better at delaying tobacco use relapse than nicotine replacement therapies.^{10,15} As with other treatments, varenicline therapy should start approximately one week before the target quit date to achieve optimal blood levels.^{1,10} Varenicline is generally well-tolerated with common adverse reactions of nausea, sleep disturbances, vivid or strange dreams, headache, constipation and flatulence.^{10,15} Nausea can be reduced by taking the varenicline with food, and the sleep disturbances and vivid and strange dreams can be reduced by taking the last dose of the day during the early evening rather than at bedtime. Varenicline is excreted unchanged in the urine, and dosage should be reduced in patients with renal dysfunction. Sleep disturbances associated with varenicline may impair the ability of some patients to drive or operate heavy machinery.^{10,15} Pharmacovigilance of varenicline led the FDA to issue a warning of increased depressed mood, agitation, changes in behavior, suicidal ideation and suicide among patients using the product for tobacco cessation.¹⁵ The FDA recommends tobacco users being considered for varenicline treatment be carefully interviewed for any history of psychiatric illnesses prior to the start of therapy and carefully monitored for changes in mood or behavior during therapy.¹⁵ Varenicline is not approved for use in patients younger than 18 years of age.⁴

Varenicline dosing should start at 0.5 mg orally once daily for three days, stepped up to 0.5 mg orally twice daily for three days and then stepped up to 1 mg orally twice daily for eleven weeks.^{1,10,15} To reduce nausea, varenicline should be taken with food. Tobacco cessation should begin after approximately one week of varenicline therapy.^{10,15} Varenicline may be continued for an additional 12 weeks if necessary. Varenicline is excreted unchanged, and in patients with creatine clearance below 30, treatment effectiveness should be assessed at 0.5 mg orally once daily and if necessary, increased to 0.5 mg orally twice daily.

The use of tobacco products is most often initiated in early adolescence and remains a significant health issue for all age groups. There are effective counseling and pharmacological treatment strategies to assist the tobacco user in transitioning to cessation. The first and perhaps the most important step in this process is for all health care providers to consistently and persistently screen patients from at least the age of 14 for tobacco use and to encourage tobacco users to quit. Once the willingness to quit has been established, a combination of counseling and medications can be used to assist in tobacco cessation therapy. Counseling at the practical, intra-treatment and extra-treatment levels should be employed by the health care provider and the patient to

navigate successfully the pitfalls of sustainable tobacco cessation. Medications such as bupropion SR, nicotine replacement therapies and varenicline can be used to promote a sustainable tobacco cessation in adults. Though counseling and medications are separately effective, approaches that employ counseling and medications may optimize results in both adolescent and adult tobacco users.

REFERENCES

- Dipro JT, Talbert RL, Yee GC, et al. *Pharmacotherapy: A Pathophysiology Approach*. 7th ed. New York, McGraw Hill, 2008, 1088-1094
- Woolf AD Smoking and nicotine addiction: a pediatric epidemic with sequelae in adulthood. *Curr Opin Pediatr* 1997; 9:470-477.
- Kaplan CP, Perez-Stable EJ, Fuentes-Afflick E, Gildengorin V, Millstein S, Juarez-Reyes M Smoking cessation counseling with young patients: the practices of family physicians and pediatricians. *Arch Pediatr Adolesc Med* 2004;158:83-90.
- Prokhorov AV, Winickoff JP, Ahluwalia JS, Ossip-Klein D, Tanski S, Lando HA, Moolchan ET, Muramoto M, Klein JD, Weitzman M, Ford KH Youth tobacco use: a global perspective for child health care clinicians. *Pediatrics* 2006;118:e890-903.
- Milne B, Towns S Do paediatricians provide brief intervention for adolescents who smoke? *J Paediatr Child Health* 2007;43:464-468.
- Rosen IM, Maurer DM Reducing tobacco use in adolescents. *Am Fam Physician* 2008;77:483-490.
- Centers for Disease Control and Prevention. *Best Practices for Comprehensive Tobacco Control Programs – 2007*. Atlanta, GA DHHS, CDC, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. 2007
- Doll R, et al. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ* 2004; 328: 1519.
- Centers for Disease Control and Prevention. Cigarette smoking among adults – United States. 2006 *MMWR* 2007. 56:1157-61.
- Fiore MC, Jaén CR, Baker TB, et al. *Treating tobacco use and dependence: 2008 update*. Clinical practice guideline. Rockville MD, US Department of Health and Human Services, Public Health Service, May 2008.
- Kleinjan M, Engels RC, van Leeuwe J, Brug J, van Zundert R, van den Eijnden RJ Mechanisms of adolescent smoking cessation: Roles of readiness to quit, nicotine dependence, and smoking of parents and peers. *Drug Alcohol Depend*. (2008)
- Smith AE, Cavallo DA, McFetridge A, Liss T, Krishnan-Sarin S Preliminary examination of tobacco withdrawal in adolescent smokers during smoking cessation treatment. *Nicotine Tob Res* 2008; 10:1253-1259.
- Lancaster T, Stead L, Silagy C and Sowden A. Effectiveness of interventions to help people stop smoking: Finding from the Cochrain Library. *BMJ* 2000; 321(7257):355-358.
- Hebert R What's new in nicotine & tobacco research? *Nicotine Tob Res* 2008;10:943-950.
- Treatment Guidelines. Drugs for Tobacco Dependence. *Treatment Guidelines from The Medical Letter* 2008; 6: 61-66.
- Camenga DR, Klein JD Adolescent smoking cessation. *Curr Opin Pediatr* 2004; 16:368-372.
- Rubinstein ML, Benowitz NL, Auerback GM, Moscicki AB A randomized trial of nicotine nasal spray in adolescent smokers. *Pediatrics* 2008;122:e595-600.
- Fiore MC, Bailey WC, Cohen SJ, et al. (2000) *Treating tobacco use and dependence: Clinical practice guidelines*. Rockville, MD: US Department of Health and Human Services.
- Hurt RD, Sachs DP, Glover ED, et al. A comparison of sustained release bupropion and placebo for smoking cessation. *NEJM* 1997;337:1195-1202.

Conflict of Interest Statements

Dr. Steven Waller declares a family member has a financial interest in Pfizer Pharmaceuticals. Dr. Gina Forster declares she was a recipient of a Lilly Educational Grant sponsoring the Sanford School of Medicine's Centennial Symposium held in the summer of 2008.