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Clinical Perspectives

Smoking and asthma: never the twain *should* meet

Mark F. Sands, MD

Department of Internal Medicine, Division of Allergy, Immunology and Rheumatology, University at Buffalo School of Medicine and Biomedical Sciences, and the Veterans Administration Healthcare System of Western New York, Buffalo, New York

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Clinical Problem

The worldwide prevalence of smoking habituation and asthma is significant; hence, these conditions will coexist in many patients presenting to a primary or specialty care setting. Optimal management of the patient with asthma who smokes requires knowledge of epidemiology, pathophysiology, and treatment options tempered by compassion. The practitioner must be able to anticipate, recognize, and overcome barriers to tobacco cessation to improve the odds that intervention will result in smoking abstinence and improved lung health. This article briefly summarizes the literature on managing the patient with asthma who smokes, particularly in regard to tobacco cessation. Where possible, it focuses on the unique challenges within this population and underscores the need for more specific research.

Cigarette smoking (CS) results in more than 400,000 deaths annually in the United States (US) and almost 6 million worldwide.^{1,2} In 2010, the prevalence (in the US) of CS in adults was 19.3% (21.5% of men and 17.3% of women).^{3,4} Against this backdrop, asthma prevalence in the US as of 2009 was estimated at 8.2% (24.6 million persons) for all ages.^{3–5} There is a paucity of data on the prevalence of patients with asthma who smoke. A limited 2001 California population study by Eisner et al⁶ on smoking in the asthmatic population indicated that those with asthma smoke at the same rate as those without asthma.

The physiologic consequences of smoking to the patient with asthma are significant, albeit only partially understood, because active smokers are generally excluded from mechanistic and clinical asthma trials. Data support the contention that tobacco smoke is a risk factor for the development of asthma. Pietinalho et al⁷ summarized the linkage between smoking and asthma. Specifically, exposure to tobacco smoke in utero and early childhood results in a permanent decrease in lung function and an increased asthma risk for children. Adult exposure to passive smoke increases asthma risk, and active and passive smoking worsen asthma.

Patients with asthma who smoke have a higher risk of developing chronic obstructive pulmonary disease than patients with asthma who do not smoke. Lange et al,⁸ in a seminal 15-year study of lung function in adults with asthma, found additive effects on loss of lung function when comparing patients with asthma who smoked and did not smoke to patients without asthma. Stated differently, tobacco use and asthma caused an accelerated decrease in lung function in adults. When patients with asthma smoke, the rate of decrease exceeds that seen when either factor is taken separately. Polosa et al⁹ reported a clear association between smoking and the development (risk) of asthma in patients with allergic rhinitis.

For pediatrics, Burke et al¹⁰ performed a meta-analysis of more than 70 studies, establishing causality of pre- and postnatal exposure to passive smoke to asthma development. Specifically, they highlighted that passive tobacco smoke exposure in utero or during childhood has repeatedly been shown to increase the risk for development of asthma in early life. Passive smoking effects on adult asthma has been detailed in a recent review.¹¹ Specifically, the role of CS in developing new-onset asthma and exacerbating existing asthma is clarified.

Large population-based epidemiologic studies have provided compelling evidence that active smoking is a distinct risk factor for developing asthma. A British cohort of more than 5,000, active smokers manifested asthma or wheezing from 17 to 33 years of age, with an odds ratio (OR) of 4.42 compared with controls. Further, patients with asthma in childhood that was in remission were more likely to have a relapse by 33 years of age with active adult tobacco abuse.¹² The use of at least 300 cigarettes annually resulted in an OR of 3.9 for developing asthma compared with nonsmoking controls.¹³ CS must be considered an independent risk factor for asthma.

Morbidity and mortality increase for the patient with asthma who smokes. Asthma symptoms and asthma-specific quality-of-life scores are adversely affected by CS.¹⁴ Worsening asthma control results in excess use of ambulatory and hospital resources in smoking vs nonsmoking patients with asthma.^{11,15} Moreover, a dose–response relation between CS and asthma exists. Longer CS duration (20 years) resulted in worsening in asthma severity and control plus higher frequencies exacerbation and death from asthma.¹⁶

Reprints: Mark F. Sands, MD, VA Western New York Healthcare System, 3495 Bailey Avenue, Buffalo, NY 14215; E-mail: mark.sands@va.gov.

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Cigarette smoking creates a complex problem for management. In addition to providing a distinct proinflammatory and irritant stimulus to the airway, by virtue of a neutrophil-rich injury, standard treatment is undermined. Specifically, patients with asthma who smoke respond less to steroid treatment than patients with asthma who do not smoke.¹⁴ Early addition of long-acting β -agonists to inhaled corticosteroids is beneficial.^{17,18}

Tobacco smoke exposure (passive or active) is clearly associated with developing asthma or exaggerating its negative impact on the individual and society. What evidence supports cessation as being beneficial? Small, relevant studies support benefit within the asthmatic subpopulation of smokers. Steroid responsiveness is regained with smoking cessation.¹⁹ Symptom control and lung function improve with abstinence from smoking. Tonnesen et al²⁰ showed a dose–response relation between complete and partial abstinence and lung function in asthma. Airway hyperreactivity was improved at 6 and 12 months of abstinence from smoking.⁵

Strategies and Evidence

Despite years of smoking prevention programs at a societal level, smoking is prevalent, even in those with asthma; hence, the need for cessation strategies.⁶ Recent articles have provided an overview and specifics to assist the provider in achieving abstinence in patients.^{17,21} Sustained cessation (at 6 months to 1 year) in the overall population is low (<50%), and the success rate of quitting on the initial try is low. A sustained partnership between patient and provider is needed to succeed. Frustration (practitioner or patient) cannot be allowed to generate nihilism, which will almost certainly result in an undesired outcome. Similarly, the practitioner cannot afford the attitude that “tobacco has produced a self-inflicted injury” and thus validate avoidance of optimizing care and cessation efforts. Smoking is an addiction, not just a bad habit. Nicotine induces escalation of physical and psychological dependence through central and peripheral nervous system stimulation and tachyphylaxis.²¹

Evaluation

Efforts must start with the recognition of perceived barriers to cessation followed by a frank discussion of how they can be overcome. This process may begin with the “5 As” as previously described.^{17,21–24} Ask about tobacco use. Patients may be reticent to

volunteer that they smoke (embarrassment, guilt, enjoyment). If the physician does not ask, patients may rationalize that it is not important. Advise cessation. Clearly advising cessation establishes that the provider sees this as an individual priority. “If you quit smoking, your asthma may be better controlled in the short term, and your lungs will be healthier over many years. Your asthma medications should be more effective, and you might require less to control your disease.” Assess willingness to quit. Assist with cessation (behavioral and pharmacologic support) and arrange for follow-up (without this, relapse is very high). Counseling also should incorporate the “5 Rs.” These include *relevance* (quitting is personal) and a review of symptoms, lung function test data, rate of decline, etc. For *risks*, have the patient describe the consequences of smoking on health (dyspnea, worse asthma control, cancers, heart attack, stroke), including for those around the patient. For *rewards*, identify the benefits of cessation (improved health, savings on medication and tobacco, family health). For *roadblocks*, patients must contemplate why they anticipate cessation might be undermined (household smokers, depression, anxiety, substance abuse, prior failed attempts, withdrawal symptoms, weight gain). For *repetition*, use these elements to interact when there is a relapse or lack of primary motivation (for an algorithmic approach, see Fig 1). Moreover, patients must want to quit for themselves, not for others. If they do not wish to quit, or cannot contemplate a quit date, they will not quit. It is better to continue to advise and assess and indicate plans to discuss in future. Once ready, a frank discussion of nicotine withdrawal is important, not only to prepare the patient but also to explore pharmacologic support. Withdrawal symptoms can include dysphoria or depressed mood, insomnia, irritability, anxiety, restlessness, difficulty concentrating, and increased appetite and weight gain. Also, many smokers experience increased sputum production in the first few months, and reassurance is needed that this is transient and manageable.

Therapy

Nonpharmacologic care

Behavioral therapy (health professional counseling, group therapy, and help lines) has been shown to improve outcomes in smoking cessation when combined with pharmacologic interventions.^{25,26} It is the author's practice to offer patients the option of formal cessation classes or support at scheduled outpatient visits.

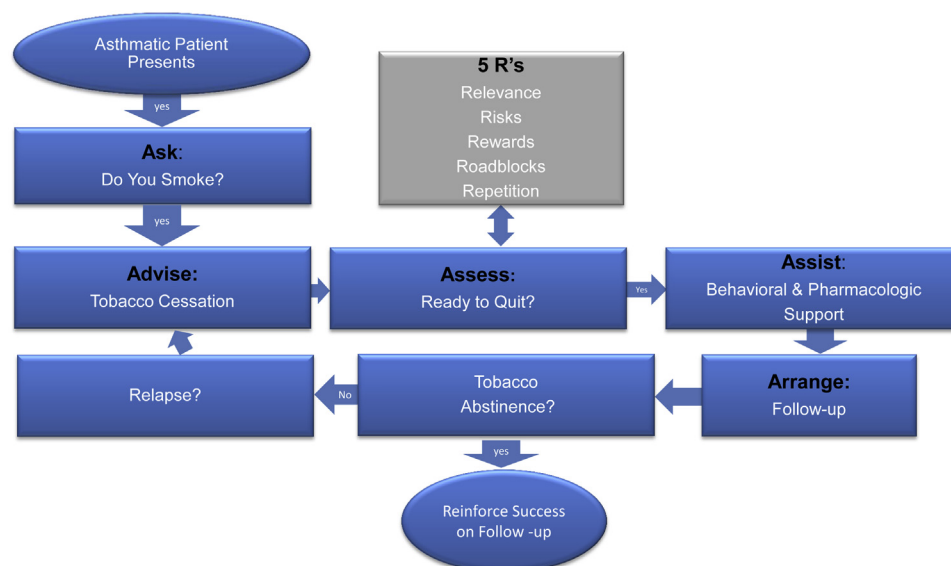


Figure 1. An algorithmic approach to smoking cessation incorporating the 5 As and the 5 Rs. Adapted from Fiore²⁴ and Polosa et al.¹⁷

Pharmacologic care

Recent reviews have compared and contrasted pharmacologic support for cessation.^{21,22} Nicotine replacement therapy (NRT) is extensively used as a first-line approach and is available without prescription. Quit rates with NRT are approximately doubled compared with placebo, without increasing relapse rates. NRT is available in multiple forms, including patch, gum, lozenge, nasal spray, inhaler, and recently the electronic cigarette (e-cigarette), which is not regulated by the US Food and Drug Administration (FDA) and discussed separately. Patient preference may dictate which are used. The patch has a slow release, and use of a rapid-release formulation, such as nicotine gum, in combination, may stave off immediate cravings. Combination of slow- and immediate-release NRT improves quit rates compared with either alone. Side effect profiles with nicotine replacement are well described and deserve brief comment. Cardiac effects, including a mild increase in heart rate, are usually minimal, but it is not recommended in the context of acute cardiovascular presentations. It may be used with chronic disease. Patients with asthma should not use nicotine inhalers or nasal sprays because these can trigger bronchospasm.²² The FDA pregnancy category is C for gum and lozenge, but D for spray, inhaler, and patch. (*FDA definitions—category C: animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks; category D: there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience of studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks*).²⁷ Recommended duration of use varies from 3 to 6 months depending on the product.

Other first-line products include bupropion and varenicline.^{21,22} The mechanism underlying bupropion's efficacy in smoking cessation is presumptive. It inhibits non-adrenergic or dopaminergic neuronal uptake, and with increases in norepinephrine, nicotine withdrawal symptoms are blunted. Similarly, dopamine increases are believed to weaken cravings to smoke. It should be started 1 week before cessation. As with NRT, the quit rate is doubled vs placebo for non-hospitalized patients. Abstinence rates at 2 years are approximately 40%. In the face of prior relapse, use for at least 3 months may be prudent. Serious adverse events have included seizure and suicide. It is important to monitor (and discontinue) even in previously mentally healthy patients for any suicidal ideation, hostility, agitation, or depression. For patients with existing neuropsychiatric disease, collaboration with mental health or neurology providers may provide the necessary support to determine whether this is a good option. Bipolar disorder contraindicates its use because it may trigger a manic event. It may be used concurrently with NRT.

Varenicline is a partial agonist ($\alpha_4 \beta_2$ subunit) for the nicotinic acetylcholine receptor in the central nervous system. It may work through a combination of stimulation of the nicotinic receptor (decreases withdrawal symptoms) and blocking the physiologic nicotine effects from smoking, thus blunting the "reward" effect of nicotine use. Varenicline has not been studied extensively in combination with NRT, and no clear additive effect has been observed.²⁸ The OR (vs placebo) for quitting is 3.0. The OR of tobacco abstinence at 6 months is 2.27. However, it does not appear superior for sustained abstinence (vs NRT) at 1 year.²⁹ It was found to be superior to bupropion in some randomized trials involving thousands of patients at 3 to 6 months.³⁰ Varenicline, like bupropion, should be started 1 week before cessation and is FDA category C in pregnancy. Particular concern exists over increasing suicide risk. Moore et al³¹ described increased suicidality for varenicline vs bupropion from 1998 through 2010. This difference has not been supported by subsequent randomized trials. Nevertheless, caution

seems prudent until a definitive answer is available, because data are conflicting. Even in the absence of a psychiatric history, monitoring, as in bupropion, is wise. The Federal Aviation Administration has prohibited its use in pilots and air traffic controllers. Cardiac safety also is not fully elucidated.

Electronic cigarettes bear mention because their use has become widespread in the USA and Europe.³² They have been marketed with the implication that they are "safer than cigarettes and can aid in tobacco reduction/cessation." Objective data on this are limited, especially in patients with asthma. Furthermore, e-cigarettes are not regulated by the FDA and vary as to device, nicotine delivery, and vapor characteristics. As a result, controlled prospective data are minimal. A recent, small ($n = 18$) retrospective study of e-cigarettes in patients with asthma who smoked showed benefit in the Asthma Control Questionnaire score and decreased airway hyperreactivity.³³ Because safety and efficacy remain unclear, recommendation for use of unregulated e-cigarettes as a routine part of the NRT armamentarium is an area of uncertainty.

Summary

Combined pharmacologic and behavioral interventions are superior to either alone, particularly as the severity of tobacco use increases. NRT, with counseling, is a reasonable first step, often combining a patch with quick-release agent such as gum. Bupropion has similar efficacy to NRT, but has some contraindications in neuropsychiatric disease states. It may be combined effectively with NRT. Varenicline may have superior efficacy to NRT or bupropion, but safety issues, particularly in higher-risk cardiovascular or neuropsychiatric patients, is an area of uncertainty. Moreover, the use of support plus a pharmacologic intervention will at least double, if not triple, the likelihood of quitting, and up to 40% may sustain abstinence at 2 years. Relapse rates between years 1 and 5 of cessation are well established, and run at 35% to 40%, with evidence that varenicline (rather than bupropion) for extended periods may improve outcomes.³⁴ Providers should prepare for, and recognize, risk factors for relapse, including a high degree of nicotine dependence, alcohol dependency, depression, brief prior cessation attempts, and early-onset smoking. If relapse occurs, counseling and intervention should be made and restart the process when the patient is receptive (Fig 1).¹⁷

Conclusion

There is a growing recognition that patients with asthma who smoke are a unique subpopulation, and areas of uncertainty persist regarding optimal asthma management for these individuals, including best techniques for smoking cessation. This article underscores the need for more investigation into the pathophysiology and management of the patient with asthma who smokes. Providers who care for those with asthma should recognize the potential to improve short- and long-term asthma outcomes with smoking interventional measures and then apply proven methods to achieve cessation. As a medical community, we must continue to expand our knowledge to better meet this challenge.

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