

CLINICAL REVIEW

Smoking and Asthma

Megan Stapleton, PharmD, Amanda Howard-Thompson, PharmD, BCPS,
Christa George, PharmD, BCPS, CDE, Robert M. Hoover, MD,
and Timothy H. Self, PharmD

Background: The purpose of this review is to describe the current understanding of the prevalence and adverse effects of cigarette smoking and secondhand smoke (SHS) in asthmatics in terms of patient outcomes and response to inhaled corticosteroids.

Methods: We searched the English biomedical literature via PubMed, Embase, and Scopus using the terms “smoking and asthma,” “secondhand smoke and asthma,” “environmental tobacco smoke and asthma,” and “smoking/secondhand smoke and corticosteroids.” We also reviewed reference lists of identified articles for relevant citations.

Results: In asthmatic patients who smoke, disease control is poorer than in asthmatic nonsmokers. Of all forms of SHS, maternal exposure seems to have the largest impact on asthma by increasing the frequency and severity of the disease and decreasing lung function. Asthmatic children exposed to multiple household smokers face an increased risk for respiratory illness-related absences from school, and these effects persist during adolescence but weaken during adulthood. Airway mucosal permeability is increased in smokers, which could lead to increased clearance of inhaled corticosteroids from the airways. Smokers also have decreased histone deacetylase activity, which is necessary for corticosteroids to fully suppress cytokine production, and can lead to corticosteroid resistance.

Conclusions: Cigarette smoking and SHS in asthmatics lead to detrimental effects in patient outcomes and effectiveness of steroid therapy. (J Am Board Fam Med 2011;24:313–322.)

Keywords: Asthma, Inhaled Corticosteroid Resistance, Secondhand Smoke, Smoking

Asthma is an inflammatory airway disease that involves both airway inflammation and impaired airflow, and it affects 22 million Americans. Airway inflammation in asthma involves a very complex interaction of cells, mediators, cytokines, and chemokines. Immune and nonimmunologic environmental factors are important triggers of asthma, including cigarette smoking and secondhand smoke (SHS).¹ Approximately 25% to 35% of individuals with asthma are current smokers.² It is well-docu-

mented that smoking or exposure to SHS among asthmatics increase asthma-related morbidity and disease severity.¹ Prolonged exposure to tobacco smoke in patients with asthma contributes to a decline in lung function: approximately 18% in forced expiratory volume in 1 second (FEV₁) over 10 years.³ Asthmatic patients who smoke share features similar to those found in the early stages of emphysema.⁴ Key mechanisms of the detrimental effects of smoking in patients with asthma are listed in Table 1.

The purpose of this review is to assess the recent (1994–2009) literature on this subject and relate current evidence regarding the prevalence of smoking and SHS exposure among asthmatics and their negative effects on patient outcomes. In addition, the effects of smoking and SHS on response to inhaled corticosteroids are summarized. The foundation of this review article started as grand rounds and was found to be of considerable importance because of the breadth of evidence and lack of

This article was externally peer reviewed.

Submitted 2 August 2010; revised 23 November 2010; accepted 7 December 2010.

From the Department of Clinical Pharmacy, Texas Tech University Health Science Center, Dallas (MS); and the Departments of Clinical Pharmacy (AH-T, CG, THS) and Family Medicine (AH-T, RMH), University of Tennessee Health Science Center, Memphis.

Funding: none.

Conflict of interest: none declared.

Corresponding author: Amanda Howard-Thompson, PharmD, Departments of Clinical Pharmacy, University of Tennessee Health Science Center, 1301 Primacy Parkway, Memphis, TN 38119 (E-mail: amhoward@uthsc.edu).

Table 1. Examples of Mechanisms of Smoking and Airway Damage in Asthma

Mechanisms	References
Toxin direct to the bronchial epithelium, causing oxidative damage	5
Release of proinflammatory mediators and increased epithelial permeability	6
Proinflammatory mediators and cytokines involved	
Interleukin-8	7–9, 10
Lipopolysaccharides	11
Leukotriene B4	7, 10
Prostaglandin E ₂	12
Angiopoietin-2	13
Eotaxin-1	14

literature discussing it in family medicine journals. Family medicine physicians are not only the primary health professionals involved in patients' general health care, but they also have the luxury of seeing the family as a whole, making them the ideal candidates to counsel and discuss the effects of primary smoking and SHS exposure on their asthmatic patient population.

Methods

We searched the English biomedical literature via PubMed, Embase, and Scopus using the terms "smoking and asthma," "secondhand smoke and asthma," "environmental tobacco smoke and asthma," and "smoking/secondhand smoke and corticosteroids." We also reviewed reference lists of identified articles for relevant citations.

Risk of Asthma Development from Primary Smoking

The risk of developing asthma was significantly higher among current smokers and among ex-smokers compared with those who have never smoked (adjusted odds ratio [OR], 1.33 and 1.49, respectively) in an investigation by Piipari et al.¹⁵ Their results support the hypothesis that smoking causes asthma in adulthood. In addition, they found that women may be more susceptible to the adverse effects of smoking. It is debated whether smoking induces the development of asthma in adolescents. In a prospective cohort study including 2609 children with no lifetime history of asthma, Gilliland et al¹⁶ discovered that children who were nonsmokers without any history of allergy at study entry and who became regular smokers later in life were 5.2

times more likely to develop asthma; however, among those with a history of allergy there was little evidence of increased risk.

Poor Control of Asthma Because of Primary Smoking

Several investigators have found that asthmatic patients who smoke are more likely to have poorer disease control compared with asthmatic nonsmokers.^{17–20} A survey of 2269 asthmatic patients enrolled in a health maintenance organization showed that smoking was significantly and inversely related to long-term control of asthma (OR, 2.6; 95% CI, 2.0–3.4).¹⁷ McCoy et al¹⁸ showed that asthmatic smokers older than age 10 were more likely to experience an episode of poor asthma control versus asthmatic nonsmokers (OR, 1.785; 95% CI, 1.119–2.847). In 2007, a telephone survey of 11,962 asthmatic adults in the United States revealed that those who currently smoked reported more asthma attacks (OR, 1.2; 95% CI, 1.0–1.4) and more nocturnal asthma symptoms (OR, 2.0; 95% CI, 1.4–2.7) during the past 30 days than those who did not smoke.¹⁹ Chaudhuri et al²⁰ reported that asthmatic smokers had significantly higher scores overall (OR, 2.8; 95% CI, 1.7–3.4) and for each individual asthma symptom on the Juniper Asthma Control Questionnaire, indicating poorer disease control compared with asthmatic nonsmokers. The association between smoking and poor asthma control has also been reported in studies conducted in Canada, France, and Switzerland.^{21–23}

Secondhand Smoke Exposure

SHS is comprised of sidestream smoke (SS) and mainstream smoke (MS).^{24,25} MS is the portion exhaled by smokers and accounts for 15% of total SHS exposure. SS is the portion of SHS that is released from the burning tip of a cigarette and accounts for 85% of total SHS exposure. In addition, the particle size of SS is one-tenth the size of MS, increasing its ability to reach the most distal alveoli in the lung.²⁶ SHS is also referred to as passive smoking, environmental tobacco smoke, and involuntary smoking. To prevent confusion between these different descriptive terms, this review will use the term "secondhand smoke." Some of the irritant gases in SHS that can contribute to the development of airway disease are ammonia, nitrogen dioxide, sulfur dioxide, hydrogen cyanide, and acrolein.^{24,25}

Assessment of SHS Exposure

Accurately quantifying exposure to SHS is problematic because of the multiple variables involved. The number of cigarettes smoked, length of time that smoking occurs, ventilation properties of the building, and absorptive qualities of elements contained in the building all contribute to exposure.^{24,25} This evaluation of exposure is through the use of either biomarkers measured in the urine, saliva, blood, or hair; self-reported questionnaires; or home air monitors.^{24,27} The nicotine metabolite cotinine is the biomarker of choice because its half-life is much longer (17–24 hours) than nicotine (2–3 hours).^{28,29} However, children with asthma may have lower clearance rates of nicotine, resulting in higher systemic exposure; African-American children differ in their rate of absorption and metabolism of nicotine, which further enhances the problems with obtaining these measurements.^{30,31}

One study determined that the use of 2 simple questions worked as well as cotinine screening among inner-city children with asthma. These two questions asked whether the primary caregiver smoked and if people were allowed to smoke within the child's home. These questions helped investigators to identify children with asthma with the greatest exposure to SHS and could predict which children would have elevated cotinine levels up to 9 months later.³² Another study developed a questionnaire containing 3 simple questions relayed from the primary caregiver to define children at highest risk of SHS exposure: Do you smoke? Do others who are often around the child smoke? and, Do you or others smoke inside of the home? The questionnaire was validated using child hair cotinine concentrations.³³

Effects of SHS Exposure among Children with Asthma

Smoking, in general, is the number one leading cause of preventable death in the United States.³⁴ Unfortunately, this statistic does not differentiate between primary and SHS exposure. There were a few manuscripts published in the 1990s referring to SHS exposure as the third leading cause of death, but this was in relation to causing heart disease-related not asthma-related deaths.^{35–37} SHS exposure is associated with chronic obstructive pulmonary disease, asthma, respiratory tract infections, and other body system damage.^{1,38} SHS from parents who smoke is associated with increased prevalence

of asthma and respiratory symptoms among school children. SHS from parents' smoking habits also is associated with more severe disease among those children with established asthma.^{39–41} Even exposure to "light cigarette smoking" (≤ 10 cigarettes per day) can cause children who have asthma to experience nocturnal symptoms.⁴² Of all the forms of SHS, maternal exposure seems to have the largest impact on asthma by increasing the frequency and severity of the disease.¹ Maternal smoking, in general, has been found to cause an increase of wheezing illness, especially during the first year of life, and to decrease lung function in children up to 6 years of age.^{43–46} Table 2 summarizes in utero exposure to SHS that results in asthma.

To date, there have not been any studies focusing directly on the effect of paternal SHS. However, one study observed the effects of SHS on asthma symptoms and medications in children and found that about 82% of the SHS exposure was via the father.⁵⁸ SHS exposure occurred during the postnatal period and the determination of worsening of symptoms was through a subjective questionnaire and not actual laboratory measurements. Symptoms among the group with high SHS exposure were worse than those among the group with low to moderate SHS exposure, which was significant ($P = .0024$).

Epidemiologic evidence linking asthma and cigarette consumption, provided by the United States National Health Interview Study and the American Lung Association, supports the contributing role of SHS in the epidemic of childhood asthma.⁵⁹ Severity of asthma has been correlated to levels of SHS exposure. Morkjaroenpong et al⁴² found that children who were exposed to higher levels of SHS were 3 times as likely to be in the mild persistent

Table 2. In Utero Exposure to Secondhand Smoke, Resulting in Asthma

Results of Exposure	References
Offspring are 1.8 times more likely to develop asthma and a lifetime history of wheezing	47, 48
Children diagnosed with early-onset asthma have more persistent deficits in lung function	49
Other effects	50–57
Significant reductions in forced expiratory flow	
Suppression of alveolarization, functional residual capacity, and tidal flow volume	

category (26.8% vs 15.9%; OR, 3.4; 95% CI, 1.3–8.8) and twice as likely to be in the moderate to severe persistent category (54.9% vs 47.6%; OR, 2.3; 95% CI, 1–5.1) compared with those with lower levels of SHS (from “light” smoking [≤ 10 cigarettes/day]). Other investigators have also reported poor control of asthma in children because of SHS.^{60–62}

The data from children exposed to SHS who report to the emergency department are conflicting. After the implementation of a smoke-free law in Kentucky, the state once known to have the highest smoking rates in the United States, it was reported that emergency department visits because of asthma declined by 22%, suggesting a possible relationship between SHS exposure and asthma.⁶³ The prevalence of smoking and nicotine addiction was high among parents of children who are brought to the emergency department because of asthma or bronchiolitis in one study,⁶⁴ but, in another, SHS was found to have a weak association with acute asthma severity.⁶⁵

Counseling about the detrimental effects of SHS in the emergency department may have a *positive* impact on the smoking habits of caregivers when they are around their children by educating them about the possibility of smoking as a trigger to their child’s asthma, but more investigations are needed to verify. A study investigating the amount of SHS exposure after 20 minutes of asthma education in the emergency department found that there was a statistically significant decrease in the number of emergency department visits and hospitalizations because of asthma over a period of 1 year among children whose SHS exposure had decreased.⁶⁶ The measurement of SHS exposure in this study was via a telephone survey and not cotinine levels. Table 3 lists effects of SHS on children with asthma.

Effects of SHS Exposure on Adult Patients with Asthma

LeSon and Gershwin⁷⁷ assessed risk factors for young adult asthmatics who required intubation. Patients aged 20 to 34 years who were admitted during a 10-year period were evaluated. Among 550 hospital admissions, 34 required intubation. Although several risk factors were identified, such as psychosocial problems, prior intubation, and respiratory infection, active smoking or exposure to SHS were also important risk factors for intubation

Table 3. Effects of Secondhand Smoke (SHS) on Children with Asthma

Effects	References
Maternal exposure seems to be the most significant of SHS exposure, which may be because of the child’s close proximity to the mother	30, 67–69
The association between parental SHS exposure and asthma becomes less strong after adolescence into adulthood, which may be because the child is spending less time at home	70
Asthmatic children exposed to multiple household smokers face a 4.5-fold increase risk for respiratory illness related absences from school	71
Perinatal deficits in lung function are persistent and may increase during adolescence in the presence of parental SHS	72, 73
SHS is associated with increased asthma severity and is more likely to be diagnosed as moderate to severe asthma	42, 74
SHS is associated with worsening of lung function as evidence of decline in peak expiratory flow, and increase in symptoms and bronchodilator use in asthmatic children exposed to SHS	42, 58, 75
Household smoking increases the frequency of asthma attacks, number of visits to an emergency department, and risk of intubation	76

(OR 7.1; 95% CI, 5.1–9.9). Ebbert et al⁷⁸ studied a possible association between respiratory tract diseases (including asthma) and SHS exposure among flight attendants who had never smoked. These flight attendants had worked during the time when smoking was still allowed on airplanes. Of 15,000 mailed questionnaires, 2053 (14%) were returned. After excluding respondents with a history of smoking and one with a history of pulmonary disease before the age of 18 years, 1007 respondents remained for analysis. The great majority (>85%) of the flight attendants were women and white, and the mean age was 54 years. Asthma was reported in 13.6%, nasal allergies in 13.4%, and sinusitis in 43.4% of respondents. Jindal et al⁷⁹ compared asthma morbidity in 100 adults exposed to SHS (via a spouse and other close contacts) versus 100 adults who were not exposed during the preceding 12 months. The number of emergency department visits, other exacerbations, missed work, and corticosteroid requirement were greater in the group that was exposed to SHS ($P < .01$).

Resistance to Corticosteroids in Asthmatic Patients Who Smoke

A 1996 study by Pedersen et al⁸⁰ examined the impact of low- and high-dose inhaled budesonide or oral theophylline treatment on lung function, bronchial hyper-reactivity, and blood inflammatory markers in 85 asthmatic patients. A post hoc subgroup analysis of asthmatic smokers versus nonsmokers in the study showed that the smokers had no improvement in FEV₁, histamine PC₂₀, blood eosinophil counts, eosinophil cationic protein, or eosinophil protein x after 9 months of treatment with either dose of inhaled budesonide. This was the first study to report corticosteroid resistance in asthmatic smokers.⁸⁰ Subsequently, Chalmers et al⁸¹ performed a prospective, randomized, double-blind, crossover, placebo-controlled study examining the effects of either inhaled fluticasone propionate (500 µg twice daily) or placebo for 10 weeks in patients with mild asthma. The nonsmoking patients in the study experienced a significantly greater improvement in morning peak expiratory flow (PEF) than those who smoked ($P = .0006$). No significant changes in PEF, FEV₁, geometric mean methacholine PC₂₀, or sputum eosinophil counts were found among the patients that smoked.⁸¹

Resistance to short-term, high-dose oral corticosteroids in asthmatic smokers also has been reported.⁸² Fifty patients with chronic stable asthma were randomized to receive either oral prednisolone 40 mg or placebo tablets for 14 days each, followed by a 2-week washout phase. There was no improvement in prealbuterol FEV₁, morning PEF, nighttime PEF, daytime symptoms, nighttime symptoms, use of rescue medication, or asthma control score among the asthmatic smokers versus the nonsmokers.⁸² In contrast, 19 smokers with moderate to severe asthma responded as well as nonsmokers to 4 weeks of treatment with high-dose inhaled fluticasone, suggesting that some asthmatic smokers may respond to high-dose inhaled corticosteroid (ICS) therapy.⁸³

In 2005, Tomlinson et al⁸⁴ compared the effect of either 400 µg or 2000 µg daily inhaled beclomethasone among asthmatic smokers and nonsmokers. After 12 weeks, nonsmokers had significantly higher mean morning PEF measurements than the smokers (adjusted difference, -18 ; 95% CI, -35 to -1). Among patients who received low-dose beclomethasone, the smokers had no improvement in mean morning PEF measurements compared with non-

smokers (-6 vs 19 ; adjusted difference, -25 ; 95% CI, -45 to -4). In contrast, there was no significant difference in the change in mean morning PEF measurements between the smokers and nonsmokers who received high-dose beclomethasone (11 vs 18; adjusted difference, -15 ; 95% CI, -50 to 21). Smokers also had significantly more asthma exacerbations than the nonsmokers (6 vs 1, respectively; $P = .007$). Corticosteroid resistance in asthmatic smokers might be overcome through the use of higher corticosteroid doses, though larger trials are needed to confirm these results.⁸⁴

Lazarus et al⁸⁵ also reported corticosteroid resistance in 39 asthmatic smokers who received 8 weeks of therapy with inhaled hydrofluoroalkane beclomethasone (160 µg twice daily) compared with 44 nonsmokers. Compared with the nonsmokers, the smokers only experienced significant improvements in daily morning PEF (mean difference 8.30; 95% CI, 0.80–15.81) and sputum eosinophil counts (mean difference -3.44 ; 95% CI, -6.56 to -0.32). Though the overall differences between the smokers and nonsmokers were not statistically significant, this could be because the small sample size.⁸⁵

A post hoc analysis of the Gaining Optimal Control in Asthma trial showed that asthmatic smokers who received fluticasone for 1 year experienced increased rates of asthma exacerbations compared with people who had never smoked (0.35 vs 0.17 per patient per year, respectively). Asthmatic smokers in the study also had a higher probability of having poorly controlled asthma versus nonsmokers (OR, 2.757; 95% CI, 2.061–3.689).⁸⁶ In addition to having poorer disease control, asthmatic smokers may not derive benefit from corticosteroids in terms of preserving lung function. A 23-year observational study of 122 asthmatic patients in The Netherlands revealed that men with >5 pack years of smoking failed to show improvement in the yearly decline of FEV₁ after therapy with ICS was initiated (27.8 mL/year before treatment [range, 14.3–41.3 mL/year]; 16.1 mL/year after treatment [range, 3.3–28.9 mL/year]).⁸⁷ In contrast, a 10-year observational study of 234 asthmatic patients reported that smokers experienced significant improvement in FEV₁ after treatment with ICS (57.9 mL/year vs 30.8 mL/year; $P = .035$).⁸⁸ In addition, a post hoc analysis of the Inhaled Steroid Treatment as Regular Therapy Trial by O'Byrne and colleagues⁸⁹ reported that patients with newly diagnosed mild asthma who smoked did show significant improvements in post bronchodilator FEV₁ measurements

after 3 years of treatment with inhaled budesonide 400 µg daily (71.5 mL in smokers [$P = .011$] vs 46.5 mL in nonsmokers [$P = .001$]). More studies are needed to fully elucidate the effects of smoking on lung function decline among asthmatic smokers.

Resistance to Inhaled Corticosteroids in Asthmatics Exposed to SHS

A 2004 study by Halterman et al⁹⁰ comparing school-based supervised ICS treatment versus usual care of asthma among 180 children between the ages of 3 and 7 showed that quality of life, absence rates, and number of symptom free days improved in the school-based group compared with usual care; however, significant improvements were only seen in children who were not exposed to SHS. Children who were not exposed to SHS also had fewer days requiring quick relievers ($P = .03$) and were less likely to have 3 or more acute care visits for asthma ($P = .03$).⁹⁰

Mechanisms of Corticosteroid Resistance

There are several proposed mechanisms of corticosteroid resistance in asthmatic smokers. Table 4 summarizes the effects of smoking and SHS on the response to oral corticosteroids and ICS. Airway mucosal permeability is increased in smokers with normal lung function and in asthmatic patients who do not smoke.^{99,100} Another proposed mechanism of corticosteroid resistance is the down-regulation of β_2 -adrenergic receptors in lymphocytes that is caused by cigarette smoking.¹⁰¹ Changes in levels of cytokines and inflammatory mediators may also play a role. Cigarette smoke has been shown to increase the production of interleukin 4, interleukin 8, and tumor necrosis factor- α and decrease the production of interleukin 10.^{102–105} Another potential mechanism for corticosteroid resistance is the overexpression of GR- β receptors and underexpression of GR- α receptors. GR- α receptors are functional, whereas GR- β receptors are not; therefore, an increase in the number of GR- β receptors could lead to decreased binding and activity of glucocorticoids in vivo.^{106,107} Altered corticosteroid cell-signaling systems may also play a role.

Conclusion

The evidence reviewed in this article regarding the multiple negative effects of smoking and SHS on patients with asthma should underscore the obliga-

Table 4. Effects of Smoking and Secondhand Smoke (SHS) on Response to Corticosteroids

Effects	References
It is unknown if there is a synergistic effect of smoking and asthma on airway mucosal permeability; however, this could contribute to increased clearance of inhaled corticosteroids from the airways of asthmatic smokers	91
Chronic hypersecretion of mucus is caused by cigarette smoking in patients with asthma, and this could impede the ability of inhaled corticosteroids to bind to GRs in the airways	92
β_2 -agonists increase the nuclear localization of GRs, which may potentiate the effects of corticosteroids	93
Cigarette smoke leads to increased numbers of neutrophils and CD8+ lymphocytes and decreased numbers of eosinophils in the airways, which may contribute to corticosteroid resistance	91
Nitric oxide in cigarette smoke has been shown to decrease the binding affinity of glucocorticoid receptors (GR) in vitro; it remains to be seen whether or not nitric oxide shows the same effect in vivo ⁹⁴	94
Other proposed mechanisms include overexpression of proinflammatory transcription factors such as NF- $\kappa\beta$, activator protein-1, and signal transduction-activated factor	95, 96
HDAC activity is necessary for corticosteroids to fully suppress cytokine production, and smokers have decreased HDAC activity in alveolar macrophages, which could lead to corticosteroid resistance	97
The p38 mitogen-activated protein kinase signaling pathway may be activated in asthmatic smokers which phosphorylates GRs and decreases corticosteroid affinity	98

GR, glucocorticoid receptor; HDAC, histone deacetylase.

tion of primary care physicians and other health care professionals to assist patients and those they live with to quit smoking. Specific instructions for family members, caregivers, and friends of patients with asthma should include never smoking in the home, car, or workplace. Simply smoking in another room of the house is not sufficient, nor are any forms of air cleaners effective in reducing SHS exposure.¹⁰⁸

The specific methods of tobacco abuse counseling and treatment are beyond the scope of this review, but recent studies shed some light on the effectiveness of interventions. Parental perceptions about the harmful effects of SHS exposure on their asthmatic child are often underestimated, as is the degree of SHS expo-

sure.¹⁰⁹ With successful smoking cessation, a parent can add an average of 7 years to his or her life, eliminate SHS exposure to other family members, and reduce tobacco-related pregnancy outcomes.¹¹⁰

In a survey of parental smokers, 80% self-reported making attempts to quit in the past, with an average of 3 attempts each. Only 4.4% of those surveyed received assistance from a health care provider.¹¹¹ A study of pediatric resident training on tobacco cessation found that, although 70% of the parents reported that residents asked about cigarette smoking and half of these patients indicated the resident talked with them about SHS, only 10% of smokers stated their physician offered to help them stop smoking, and 25% of all parental/guardians indicated that their physician offered to help them stop exposing their child to SHS in the home or elsewhere.¹¹¹

Given the significance of the effects of SHS and primary smoking on asthma control and treatment, as health care professionals there is ample room for improvement in our interventions to reduce exposure to cigarette smoke. We urge family medicine physicians to discuss primary smoking in addition to SHS exposure with *all* of their patients because this could potentially change a patient's and/or their loved ones' quality of life.

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