



Guest Editorials

Evidence vs advocacy in the e-cigarette debate: to vape or not to vape, that is the question



In the current issue of the *Annals*, Polosa et al¹ advance the argument that the electronic cigarette (e-cigarette) may have a role in reducing the incontrovertible adverse health risks of the traditional cigarette in an active smoker and thus may be a potentially safer alternative in the tobacco-smoking patient with asthma. This review complements the authors' own notable pilot study in 18 smoking patients with asthma, which suggested an improvement in airway hyperresponsiveness, pulmonary function, and asthma control in asthmatic smokers who were able to reduce their cigarette smoking with e-cigarettes or switch completely to e-cigarettes.² The premise is that the e-cigarette may address the issue of tobacco harm reduction in an established smoker by reducing the user's exposure to the thousands of toxic chemicals and carcinogens derived from burning tobacco; the nicotine in the cigarette, although stimulating the brain and nervous system, may not directly contribute to smoking-related illness, although it likely contributes enormously to the addiction. The article carefully references the current state of knowledge regarding the health effects of e-cigarettes to argue that the e-cigarette is a realistic option for harm reduction in asthmatic patients who are existing smokers and cannot otherwise quit.

It must be recognized that although e-cigarettes could be safer than conventional cigarettes, they may not be altogether safe. Leaving aside the physiologic effects of nicotine and any concern about addiction, there remain reasonable questions about the short- and long-term health effects of inhaling a vaporized aerosol that consists of propylene glycol, vegetable glycerin, and flavorings and other unregulated additives, in addition to the nicotine. The potential for health effects from e-cigarettes involve not only the individual user but also second- or third-hand exposure through contact with the e-cigarette liquid or from the vapor and aerosol. Reported adverse effects of e-cigarettes include nausea, vomiting, dizziness, and even burn injuries.³ Inhaled propylene glycol is an airway irritant, and long-term exposure can be associated with decreased lung function.⁴ The e-cigarette aerosol contains a large variety of volatile organic compounds, including formaldehyde, that are potentially carcinogenic in humans.⁵ The risks of these compounds may increase with long-term exposure. E-cigarettes also account for a significant increase in toxic effect-related calls to poison control centers, with more than 50% of the calls involving children.⁶ Murine asthma model studies with e-cigarette liquid have found increased infiltration of airway eosinophils, increased airway hyperresponsiveness, and increased serum TH₂ cytokines

and IgE after allergen challenge.⁷ Thus, the potential for both predictable and unforeseen health consequences due to e-cigarettes still remains.

To address the utility of e-cigarettes in smoking cessation specifically, randomized clinical trials of smoking cessation involving e-cigarettes vs nicotine patches did not suggest an advantage of the e-cigarette over the nicotine patch.⁸ A recent Cochrane review identified 2 trials suggesting that e-cigarettes helped cigarette smokers stop smoking compared with placebo e-cigarettes but that the small number of quality trials, low event rates, and wide CIs limited confidence in these conclusions.⁹ Given that the e-cigarette was introduced into the US market in 2007 or so, there certainly are no significant durable long-term efficacy data in this regard.

What also cannot be ignored is that the e-cigarette is popular among young people, with the highest prevalence of e-cigarette use in young adults aged 18 to 24 years compared with the general smoking population. The e-cigarette is also increasingly popular among children. According to the Centers for Disease Control and Prevention, from 2011 to 2014, in middle and high school students in grades 6 through 12, e-cigarette use increased from 1.5% to 13.4%, with an estimated 2.4 million minors using e-cigarettes.¹⁰ It may be fair to say that the increasing popularity and sales of e-cigarettes are due to the advertising and marketing efforts of large, established tobacco companies who consider the e-cigarette a growth product and whose advertising often portrays the e-cigarette as a safer and cleaner alternative to a traditional cigarette. The e-cigarette is also not currently federally regulated, and thus nicotine content, flavorings, chemical additives, and delivery systems escape safety oversight and standardization and quality controls. As such, safety data generated using one particular e-cigarette liquid formulation and delivery system may not be broadly applicable to other formulations, and user-dependent customizations and modifications to the vaporizing delivery systems may alter the user's exposure to chemicals or other potential carcinogens in unpredictable and potentially significant ways.

Thus, physicians, public health specialists, and the general public continue to harbor reasonable concerns about the risks of e-cigarettes and their potential gateway effect to conventional smoking or other addictive behaviors in young people. To be fair, Polosa et al¹ are advancing the argument that in tobacco-addicted individuals with asthma the e-cigarette may be an option for reducing the harm of cigarettes in active smokers; the authors are not advocating e-cigarette use by children. Polosa et al¹ recommend smoking cessation in tobacco-smoking individuals with

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asthma, additional studies focusing on long-term health effects of e-cigarettes, and improved regulation and safety standards. Nevertheless, the gradual accrual of e-cigarette safety data does not match the rapid growth in e-cigarette use worldwide, and the jury may still be out with regard to the safety and long-term health consequences of the e-cigarette.

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Blood eosinophils: the Holy Grail for asthma phenotyping?



Asthma has been generally defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness and reversible variable airflow obstruction, affecting 6% to 8% of the US population.¹ For many years, the mainstay of therapy has been inhaled corticosteroids (ICSs) and systemic corticosteroids. However, not all individuals with asthma respond to these standard treatments. Approximately 5% to 10% of individuals with asthma can be classified as having severe asthma based on the international European Respiratory Society/American Thoracic Society guidelines definition that requires treatment with a high-dose ICS plus a second controller and/or systemic corticosteroids to prevent asthma from becoming uncontrolled or asthma that remains uncontrolled despite this therapy.² Given this unmet clinical need and heterogeneous response to standard treatments, new biologic approaches are being pursued that target specific molecular pathways believed to be important in asthma pathogenesis. By incorporating the interaction of environmental and genetic factors with observable characteristics, numerous asthma phenotypes have emerged. Biomarkers for these phenotypes are needed to help clarify the heterogeneity in asthma.

Although the importance of eosinophils in determining treatment response in asthma was reported as early as 1958, when an asthmatic cohort with elevated sputum eosinophils responded better to systemic corticosteroids than those without eosinophils,³ the concept of phenotyping asthma to determine responder groups has only more recently become central to asthma research and management. A PubMed literature search for articles published in the past 10 years using the keywords *asthma* and *phenotypes* generated 3,458 articles, whereas an identical search from the 10 years prior to this generated 1,294 articles, revealing an increase of more than 267%. An important study identified a type 2 inflammatory gene signature in human airway epithelial cells (periostin, *CLCA1*, and *serpin B2*) in 50% of a mild asthma population. This type 2 phenotype was associated with more airway hyperreactivity and atopy, higher tissue and blood eosinophil counts, and greater improvement with ICSs than those without this signature.⁴ Successful trials of molecularly targeted therapies in specifically defined asthma phenotypes (by eosinophils or other surrogates for

type 2 inflammation) have underscored the importance of identifying and understanding these phenotypes.

In their study published in the *Annals*, Tran et al⁵ retrospectively evaluated the distribution and overlap of atopic, eosinophilic, and T_H2 -high inflammatory phenotypes in a self-reported general asthma population of 269 children and 310 adults in the United States who completed the National Health and Nutrition Examination Survey in 2005–2006 using readily available biomarkers, such as blood eosinophils and specific and total serum IgE obtained during that year. The frequency of participants classified as having any or all of these 3 phenotypes was determined by the following definitions: allergic (≥ 1 allergen specific IgE level ≥ 0.35 IU/mL), eosinophilic (blood eosinophil count ≥ 150 , 300, or 400/ μ L), and T_H2 -high asthma (total serum IgE level ≥ 100 IU/mL and blood eosinophil count ≥ 140 / μ L). They hypothesized that there would be significant overlap of these phenotypes among patients with asthma.

Despite failing to define responders to the interleukin (IL) 13 monoclonal antibody lebrikizumab in adults with inadequately controlled asthma taking a moderate-dose ICS and a LABA, Tran et al used the same definition for T_H2 -high asthma.⁶ Using that threshold of a total serum IgE level of 100 IU/mL or higher and a blood eosinophil count of 140/ μ L or higher, Tran et al⁵ report that T_H2 -high asthma was numerically higher in the pediatric vs adult population (48% vs 37%).

In the benchmark study that linked T_H2 inflammation and blood eosinophils, mild corticosteroid-naïve adults with asthma in the T_H2 -high subgroup had a median serum IgE level of 244 IU/mL and a mean blood eosinophil count of 370/ μ L,⁴ which are much higher than the thresholds used in this study. Their choice to apply this definition for T_H2 -high asthma in the current mixed population of adult and pediatric patients with asthma, in whom level of severity, control, and the concurrent use of ICSs and LABAs is unknown, makes these results difficult to interpret.

When phenotyping eosinophilic asthma, the exact cut point for blood eosinophils remains uncertain because several studies have used different values. In the Dose Ranging Efficacy And Safety With Mepolizumab (DREAM) study, patients with asthma were defined as having T_H2 /eosinophilic inflammation on the basis of sputum eosinophil counts of 3% or greater, blood eosinophil counts of 300/ μ L