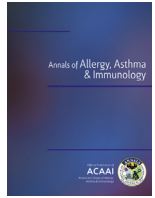




Contents lists available at ScienceDirect



## Review

## Counseling patients with asthma and allergy about electronic cigarettes: an evidence-based approach

Riccardo Polosa, MD, PhD <sup>a,†,‡</sup>, Davide Campagna, MD <sup>a,†,‡</sup>, and Mark Sands, MD <sup>§,||</sup><sup>a</sup> Centro per la Prevenzione e Cura del Tabagismo, Azienda Ospedaliero–Universitaria “Policlinico V. Emanuele”, Catania, Italy<sup>†</sup> Dipartimento di Medicina Clinica e Sperimentale, Università di Catania, Catania, Italy<sup>‡</sup> UOC di Medicina Interna e d'Urgenza, Azienda Ospedaliero–Universitaria “Policlinico V. Emanuele”, Catania, Italy<sup>§</sup> School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, Buffalo, New York<sup>||</sup> The Veterans Administration Healthcare System, Western New York, Buffalo, New York

## ARTICLE INFO

## Article history:

Received for publication July 31, 2015.

Received in revised form September 18, 2015.

Accepted for publication October 8, 2015.

## ABSTRACT

**Objective:** To provide an evidence-based review of common safety concerns and emerging potential benefits deriving from the regular use of electronic cigarettes (ECs) and thus improve counseling between physicians and their patients with asthma and allergy using or intending to use ECs.**Data Sources:** Peer-reviewed articles from the National Center for Biotechnology Information's PubMed about ECs, risk reduction, and harm reversal were appraised.**Study Selection:** Keywords used in the search were *smoking cessation, electronic cigarette, counseling, asthma, allergy, nicotine, tobacco harm reduction, and harm reversal*.**Results:** Vapor toxicology is far less problematic compared with combustible cigarettes, with exclusive EC users having substantial lower risk of exposure to tobacco smoke toxicants and carcinogens compared with cigarette smokers. Moreover, there is emerging evidence that switching to regular EC use could produce significant respiratory health gains.**Conclusion:** Inaccurate and inconsistent information about EC safety and efficacy, tobacco harm reduction, and nicotine toxicity is being offered to smokers and EC users. In particular, most health care professionals cannot communicate a clear and consistent message to their patients with respiratory problems and allergy who use or intend to use ECs. Therefore, it is important for the medical community to take an active role in considering all the pathways available to a smoking patient and recommend those that provide the greatest probability of eliminating exposure to tobacco smoke, including ECs.

© 2015 American College of Allergy, Asthma &amp; Immunology. Published by Elsevier Inc. All rights reserved.

## Introduction

Cigarette smoke contains a mixture of more than 7,000 chemicals, many of which harm the human body, thus causing a broad range of diseases.<sup>1</sup> Smoking is the leading cause of preventable premature mortality in the world; total tobacco-attributable deaths are projected to increase from approximately 5 million per year in 2015 to more than 8 million annually by 2030.<sup>2</sup> Death is caused mainly by ischemic heart disease, stroke, lung cancer, and the catastrophic complications of advanced-stage chronic obstructive pulmonary disease (COPD).<sup>1–3</sup> In addition to

lung cancer and COPD, inhalation of tobacco smoke has been recognized to play a negative role in asthma and allergic diseases.<sup>4–6</sup> Quitting lowers the risk of lung cancer, ischemic heart disease, COPD, stroke, and other cancers.<sup>1–3</sup> Moreover, abstaining from smoking can produce significant health gains in patients who smoke and have COPD<sup>7</sup> and asthma.<sup>8</sup>

Irrespective of their specific respiratory condition, most smokers want to quit and many make attempts to do so, but most of these attempts fail largely because of the powerful addictive qualities of nicotine and non-nicotine sensory and behavioral cues.<sup>9,10</sup> For those willing to quit, a combination of pharmacotherapy and intensive behavioral intervention for smoking cessation can support quit attempts and double or triple quit rates.<sup>11,12</sup> However, outside the context of rigorous randomized controlled trials, efficacy rates are disappointingly low; estimated annual population cessation rates are approximately 4% to 5%.<sup>13–15</sup>

Puffing on an electronic cigarette (EC) activates a battery that heats an element (the coil within the atomizer) that vaporizes a solution (e-liquid) consisting mainly of propylene glycol (PG),

**Reprints:** Riccardo Polosa, MD, PhD, AOU “Policlinico V. Emanuele,” Università di Catania, UOC di Medicina Interna e d'Urgenza, Edificio 4, Piano 3, Via S Sofia 78, 95123 Catania, Italy; E-mail: [danisaitta@unict.it](mailto:danisaitta@unict.it).

**Disclosures:** Dr Polosa reports grants from Pfizer and Boehringer-Ingelheim; lecture fees from Novartis and GlaxoSmithKline; and funding from the IMI-JU for European project on severe asthma. Dr Sands receives remuneration as chair of the Asthma Diagnosis and Treatment Interest Section at the American Academy of Allergy, Asthma and Immunology.

<http://dx.doi.org/10.1016/j.anai.2015.10.012>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

vegetable glycerin (VG), distilled water, and flavorings that might or might not contain liquid nicotine. Vaporization produces an aerosol similar in appearance to but substantially different in substance from conventional cigarette smoke and allows for inhalation of vapor (referred to as “vaping”) by the user. ECs do not contain tobacco, do not create smoke, and do not rely on combustion. ECs are an attractive possible long-term alternative nicotine source to conventional cigarettes because of their many similarities to smoking behavior.<sup>16,17</sup> ECs come in a large variety of designs, shapes, and sizes. Some resemble tobacco cigarettes (“ciga-like ECs”) with a mouthpiece resembling a cigarette filter combining the e-liquid-containing tank and the vaporizing system, a low-capacity disposable or rechargeable battery, and a light-emitting diode that glows when the user inhales on the device. Others often ECs that resemble a pen (“pen-like ECs”) that are equipped with high-capacity lithium batteries and a more efficient vaporizing system with a tank that can be refilled with a wide selection of e-liquid flavors and nicotine levels. Most experienced users prefer to customize their own devices (“MODs”) to get the most of the vaping experience by assembling larger-capacity batteries with personalized adjustable and programmable power delivery and customizing specific heating coils and wick configurations in their the vaporizing system. By exploring diversities and similarities in the fast-growing EC portfolio, researchers are beginning to learn that the extent of smoking abstinence is intimately connected with the level of satisfaction in the vaping experience, where smoking cessation might be considered an important “collateral benefit” for many smokers switching to regular EC use.<sup>17</sup> The growing popularity of ECs appears to be driven by different factors: they can be used to decrease cigarette consumption or to quit smoking; they are perceived by users as a much less harmful smoking alternative; their prices are competitive compared with conventional cigarettes; and they mimic the “smoking experience without smoking.”<sup>18–20</sup> Despite their increase in popularity, there is a great degree of public misunderstanding about the relative risk of ECs. Kiviniemi and Kozłowski<sup>21</sup> recently reviewed results from a US survey that showed a significant discrepancy between evidence and public perception of tobacco harm relative to smoking replacement options including ECs. Only 3.5% of those responding to the survey matched perceived risk with scientific evidence.

Miscommunication of scientific findings about EC safety and efficacy is generating confusion and concern,<sup>22</sup> and more and more patients with respiratory problems using or intending to use ECs will be seeking professional medical advice about these products. Because many health care professionals might not be accurately informed about ECs,<sup>23</sup> their personal beliefs could conflict with the evidence base and adversely influence their patients' behavior.<sup>24,25</sup> For example, previous research has shown that health care professionals hold inaccurate views about nicotine and decreasing tobacco harm in general, and that these beliefs are associated with the type of advice offered to smokers.<sup>26,27</sup> Similarly, many scientific societies have adopted statements that seem at odds with the available evidence. For example, the recent position statement of the Forum of International Respiratory Societies recommends that EC use should be restricted or banned based on the precautionary principle (not scientific evidence).<sup>28</sup>

In agreement with recent commentaries,<sup>29,30</sup> it is important for the medical community to take an active role in learning about ECs to inform their patients correctly. The authors of the present review intend to provide health care professionals with an evidence-based interpretation of common safety concerns and with the emerging findings about potential benefits deriving from the regular use of ECs. The literature search included peer-reviewed literature from the National Center for Biotechnology Information's PubMed Web site and official reports and/or monographs from reputable governmental organizations that the authors have recently appraised

because of major ongoing interest in ECs, risk reduction, and harm reversal. Keywords used in the search were *smoking cessation, electronic cigarette, counseling, asthma, allergy, nicotine, tobacco harm reduction, and harm reversal*.

The reviewers hope this evidence-based guide will improve counseling between physicians and their patients with asthma and allergy using or intending to use ECs.

### What about Potential Harm?

The World Health Organization has labeled the EC a threat to public health and urged policy makers to limit their use by prohibition or strict regulation.<sup>31</sup> This and other negative campaigns are starting to have an alarming effect of persuading smokers that ECs are as harmful as cigarettes<sup>32</sup> and discouraging them from making the switch.<sup>20</sup> This approach does not weigh the potential benefit of ECs against their potential harm. There is a sufficient body of evidence to conclude that health care professionals and public health authorities should encourage smokers who cannot stop smoking or do not want to do so to switch to ECs.<sup>33,34</sup> Nonetheless, the controversy is spreading fear and confusion in the public by adversely changing the relative risk perception of smoking and vaping, possibly deterring smokers from making a switch that could save their lives.<sup>20,34</sup> British and American surveys have indicated that misperceptions have increased in recent years. A large survey of adults sponsored by the British group Action on Smoking and Health found that the share of respondents who incorrectly described ECs as “more harmful” than tobacco cigarettes increased from 1.4% in 2013 to 2.3% in 2015, and those describing them as “equally harmful” increased from approximately 6% in 2013 to 19.8% in 2014.<sup>35</sup> According to a Reuters poll completed on June 2015,<sup>36</sup> only 35% of 5,679 Americans understood that “e-smoking is healthier than traditional cigarettes.” The remaining respondents, nearly two thirds, disagreed with that statement or did not know. These large and swift changes confirm that the public is confused about the relative risk perception of ECs.<sup>21</sup>

Therefore, it is likely that more and more patients with asthma and allergy using or intending to use ECs will be seeking professional medical advice for reassurance.

Nicotine is perceived as a primary source of concern by many users. Health professionals should explain that the damage done by conventional cigarettes comes not from the nicotine, but from the process of burning tobacco and inhaling thousands of toxic chemicals in the smoke. As Michael Russel, the father of tobacco harm reduction and the developer of nicotine gum, put it in 1976: “People smoke for nicotine but they die from the tar.”<sup>37</sup> Because the delivery of nicotine without combustion is anticipated to substantially lower the harm associated with tobacco smoking (ie, tar), the ECs have a theoretical advantage in decreasing health risks compared with conventional cigarettes.<sup>38</sup>

Smoking-related diseases are pathophysiologically attributed to oxidative stress, activation of inflammatory pathways, and direct toxic effect of thousands of chemicals and carcinogens present in tobacco smoke.<sup>39</sup> These chemicals are emitted mostly during the combustion process, which is absent in ECs. Nicotine does not contribute to smoking-related diseases and is not classified as a carcinogen by the International Agency for Research on Cancer.<sup>40</sup> Up to 5 years of nicotine gum use in the Lung Health Study was unrelated to cardiovascular diseases or other serious side effects.<sup>41</sup> A meta-analysis of 35 clinical trials found no evidence of cardiovascular or other life-threatening adverse effects caused by nicotine intake.<sup>42</sup> Even in patients with established cardiovascular disease, nicotine use in the form of nicotine replacement therapies did not increase cardiovascular risk.<sup>43,44</sup> The latest US Surgeon General's report examined the harm caused by nicotine and concluded that although it can adversely affect fetal and adolescent brain

development, it does not contribute to smoking-related diseases.<sup>1</sup> In theory, EC use might promote people to introduce higher nicotine doses than available in tobacco (ie, nicotine overdosing), thus becoming a potential source of harm to the cardiovascular system. However, there is no evidence to suggest that ECs promote higher nicotine consumption and no adverse cardiovascular events have been reported with their use. In fact, the opposite is true because ECs are generally much less efficient than conventional cigarettes at delivering nicotine to the body.<sup>45–47</sup> Although compensatory puffing behaviors can contribute to higher nicotine intake in exclusive EC users and those who engage in smoking and vaping, the overall level of plasma nicotine and cotinine (a stable metabolite of nicotine) is comparable (not higher) to that of smoking cigarettes.<sup>48,49</sup>

Nonetheless, nicotine is a powerful psychoactive substance and there is concern that EC use can perpetuate or promote an addictive behavior. However, there is increasing evidence that ECs might decrease measures of nicotine dependence.<sup>50,51</sup> Moreover, it is a common trend in EC users to decrease the nicotine strength of e-liquid over time,<sup>52–54</sup> suggesting that regular EC use might decrease nicotine dependence in the long term. A possible explanation for the lower addictive potential of ECs is that these products are much less efficient than conventional cigarettes at delivering nicotine to the body.<sup>45–47</sup>

Another area of concern is heavy metals being released in the EC aerosols. It is not unusual to detect some contamination with metals because these products have several metal parts in direct contact with the e-liquid. Goniewicz et al<sup>55</sup> examined 12 samples for the presence of metals and found only trace levels of nickel, cadmium, and lead in the vapor (a few nanograms per 150 puffs). In another study of an early first-generation EC, several metals were detected in the aerosol, which in some cases were similar or slightly higher compared with conventional cigarettes.<sup>56</sup> However, these levels were generated under extreme experimental conditions that bear little relevance to routine use. Moreover, it is unlikely that these levels pose a serious threat to users' health. Even if all the aerosol were absorbed by the consumer, the average user would be exposed to 4 to 40 times lower amounts for most metals than the maximum daily dose allowance from impurities in medicinal products.<sup>57</sup>

Propylene glycol and VG are considered GRAS (Generally Recognized As Safe) by the US Food and Drug Administration (FDA) and the US Environmental Protection Agency. Despite the good safety profile of PG and VG,<sup>30</sup> a hypersensitivity response to components in the vapor can occur in predisposed individuals. PG is a common but often unrecognized cause of allergic contact dermatitis<sup>58</sup> and direct exposure to PG has been reported to cause signs and symptoms compatible with contact dermatitis around the mouth or in the oral mucosa of EC users.<sup>59</sup> In this regard, it is noteworthy that a hypersensitivity response to VG has never been reported, and for a hypersensitivity response to PG, it is advised to switch to PG-free e-liquids. However, it is reasonable to suspect that the presence of unknown, potentially irritating or allergy-producing contaminants or by-products in the EC vapor should be suspected in hypersensitivity responses developing during or immediately after EC use.

More recently, thermal degradation of the PG and VG in the course of vaporization has been raising concern in consumers. There are limited data on long-term exposure of these chemicals to humans by inhalation, although the emerging evidence from cytotoxicity and toxicologic animal studies is reassuring (reviewed by Farsalinos and Polosa<sup>33</sup>). Nonetheless, concern about thermal degradation of PG and VG is legitimate, because toxic aldehydes (including formaldehyde, acetaldehyde, and acrolein) can be generated when vaping. Studies evaluating ciga-like ECs found that formaldehyde, acetaldehyde, and acrolein are found at much lower

levels compared with cigarette smoke.<sup>55,60</sup> Nevertheless, a recent study examining aerosol generated from more advanced products at high power levels reported that levels of aldehydes could approach or even exceed levels found in cigarette smoke.<sup>61</sup> This report has generated concerns that EC use at high power levels is associated with significant exposure to harmful toxic chemicals. However, high aldehyde levels are generated during overheating of these devices in the course of certain standardized experimental protocols that bear little relevance to normal use.<sup>62</sup> Moreover, under these extreme conditions, the excess in aldehyde release is associated with the perception of a strong unpleasant taste by the user ("dry puff phenomenon").<sup>63</sup> At dry puff conditions, EC users are not expected to be exposed to such high levels of aldehydes, because in practice it is impossible to tolerate the taste of such unpleasant aerosol. In any case, at normal vaping conditions, the aldehyde emission levels are far lower than in cigarette smoke. Moreover, newer models being introduced to the market have been fitted with an automatic temperature control feature. For the US population, anticipated FDA regulation of devices would advance safety and potentially allay concerns in this area.

### Informing about Potential Benefits

Although the FDA's Center for Tobacco Product has repeatedly claimed that it is intending to regulate ECs based on results of scientific research, a close examination of the Center for Tobacco Product's research portfolio shows that the agency is heavily funding research on the potential risks of ECs, but does not have a single long-term clinical trial to evaluate their potential benefits.<sup>64</sup> There is emerging evidence that abstaining from smoking can produce significant respiratory health gains in "healthy" smokers and smokers with asthma who switch to regular EC use.<sup>65</sup> ECs are becoming increasingly popular in smokers and ex-smokers with asthma; in a recent international survey of approximately 19,000 regular EC users, 6.1% reported physician-diagnosed asthma.<sup>19</sup> Although these products have been shown to be effective conventional cigarette substitutes in clinical trials of healthy smokers,<sup>66–68</sup> only limited data are available regarding the health effects of EC use in patients with pre-existing asthma. In particular, it is unknown whether regular EC use could result in improved or worsened respiratory-related outcomes or in hypersensitivity. The very few studies on respiratory health outcomes in EC users have shown minor acute effects on lung function.<sup>69,70</sup> The results of these small studies are consistent with the notion that a prompt defensive response against irritants from e-vapor inhalation can cause immediate physiologic changes detected with highly sensitive respiratory functional tests. The question of whether such an irritation could translate into a clinically meaningful problem for the "twitchy" airways of patients with asthma remains unanswered. To date there is no evidence to suggest that there are any clinically significant adverse lung effects, at least acutely. Long-term improvement has been described in a large group of "healthy" smokers who were invited to quit or decrease their tobacco consumption by switching to a first-generation EC. Significant early positive changes from baseline of a sensitive measurement of obstruction in more peripheral airways (ie, forced expiratory flow measured between 25% and 75% of forced vital capacity) were detected at 3 months after switching in those who completely gave up tobacco smoking, with steady progressive improvements being observed at 6 and 12 months (R. Polosa, unpublished observation). Moreover, self-reported high prevalence of cough or phlegm (43.1%) and shortness of breath (34.8%) at baseline virtually disappeared when study participants were invited to quit or decrease their cigarette consumption by switching to ECs. Longer (multiyear) safety studies are still needed to fully address these important issues.



As mentioned earlier, only limited data are available regarding the health effects of EC use in users with pre-existing pulmonary diseases. A recent retrospective clinical survey conducted to ascertain the efficacy and safety of regular EC use in mild to moderate asthma failed to detect deterioration in respiratory physiology and subjective asthma outcomes.<sup>71</sup> Smokers with asthma who quit or substantially decreased tobacco consumption by switching to regular ECs showed progressive significant improvement in the Juniper's Asthma Control Questionnaire (ACQ), forced expiratory flow in 1 second, forced vital capacity, forced expiratory flow measured between 25% and 75% of forced vital capacity, and airway hyperresponsiveness (AHR) to inhaled methacholine throughout the 1-year reporting period. EC use was very well tolerated and exposure to e-vapor in this vulnerable population did not trigger any asthma attacks. However, standard issues associated with retrospective studies do not allow establishing a causal relation. Subsequently, this group of EC users with asthma was followed prospectively for an additional year at the authors' outpatient clinic to document longitudinal changes in asthma outcomes; it was confirmed that regular EC use ameliorated lung dysfunction, AHR, and ACQ, with beneficial effects persisting in the long term.<sup>72</sup> Moreover, consistent improvements in subjective and objective asthma outcomes were observed in dual users (ie, users of ECs and conventional cigarettes), with no real difference in dual compared with single users by the end of the follow-up. This could be due to the fact that dual users in this study substantially decreased their daily tobacco consumption by at least 70% to 80% (ie, "heavy reducers"). These confirmatory findings are in agreement with the positive results of prospective studies examining the effect of stopping smoking on lung function in asthma.<sup>73,74</sup> Taken together, the evidence suggests that the harmful effects of smoking on asthmatic airways can be reversed with abstinence. The attenuation in the proinflammatory effects of cigarette smoke on the airways after decreasing smoking consumption by switching to ECs might have caused overall improvement in lung function.<sup>4</sup>

Given the close relation between airway inflammation and AHR in asthma,<sup>75</sup> it is not surprising to observe significant and persistent improvements to the provocative concentration of inhaled methacholine causing a decrease in forced expiratory volume in 1 second of 20% in smokers with asthma who had been abstinent or decreased their tobacco consumption. This also is consistent with the results of prospective studies in smokers with allergy for whom an objective proof of cessation was documented.<sup>76</sup> The observed improvement in AHR could have important clinical implications because it is a risk factor for asthma symptoms and attenuated pulmonary function levels.<sup>77,78</sup> Thus, improvement in AHR is likely to confer some clinical benefit as documented by the early and stable decrease in asthma symptoms (ie, ACQ scores). In support of this view, deterioration in the provocation concentration of methacholine causing a decrease in forced expiratory volume in 1 second of 20%, lung function, and ACQ scores was noted in the 2 patients who relapsed to exclusive tobacco smoking.

The observed positive findings in patients with asthma who have become regular EC users are consistent with the results from an Internet survey of approximately 2,500 regular EC users with asthma and COPD.<sup>19</sup> An improvement in symptoms of asthma after switching to ECs was reported in 65.4% of respondents. Although alleviated asthma symptoms were noted more often in exclusive EC users, improvement was reported in dual users. Worsening after switching was reported in only 1.1% of respondents with asthma. Taken together, these findings provide emerging evidence that harm reversal from tobacco smoking can be achieved in patients with asthma who switch to exclusive EC use and in those who substantially decrease their level of cigarette consumption by vaping (ie, heavy reducers). Although only large prospective studies will provide a definite answer regarding the long-term impact on

lung health, the current evidence is generally supportive of a beneficial effect of EC use in patients with asthma.

## Conclusion

Smoking cessation should be strongly encouraged in patients with asthma who smoke, and they should be offered effective personalized strategies.<sup>8</sup> In addition to pharmacotherapy and behavioral support, other options should be made available to manage smokers who frequently relapse and for those who are unable or unwilling to quit. A realistic alternative is to encourage these smokers to switch to ECs, a much less harmful source of nicotine.<sup>33,38</sup> The growing popularity of ECs proves that many adult smokers are ready for new alternative technologic forms of smoking. ECs and vaping are used in contexts of cigarette substitution or as an activity independent of combustible tobacco use. The argument for ECs must be framed within the correct context. ECs represent an option for harm reduction in existing smokers. With any emerging behavior associated with exposure to inhalational agents, there is legitimate cause for concern and a need for study of potential harm. However, this potential risk must be taken in the context of the known harm of cigarette smoking in populations with and without asthma. Indeed, under normal conditions of use, vapor toxicology is far less problematic than that of conventional cigarettes,<sup>33</sup> e-vapor products are at least 96% less harmful compared with combustible cigarettes,<sup>79</sup> and exclusive ECs users have significantly lower urine levels of tobacco smoke toxicants and carcinogens compared with cigarette smokers.<sup>80</sup> In future, larger and longer-term studies will better define any residual risks from EC use; this knowledge will guide the establishment of appropriate quality control and safety standards and decrease any residual risks to as low as possible. In the meantime, expected regulatory measures should primarily address manufacturing quality standards, child-proof caps on liquid containers, verification of accurate nicotine levels and product ingredients, complete and accurate package labeling, safety warnings, and postmarketing surveillance addressing any potential unintended consequences of any proposed actions that policy makers might overlook.<sup>81</sup> With this in mind, clinicians can more objectively and responsibly respond to inquiries from their patients with allergy about use of ECs and related products.

## References

- [1] US Department of Health and Human Services. *The Health Consequences of Smoking: 50 Years of Progress: A Report of the Surgeon General*. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
- [2] World Health Organization. *WHO Report on the Global Tobacco Epidemic, 2008—The MPOWER Package*. Geneva: World Health Organization; 2008.
- [3] Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 year observations on male British doctors. *BMJ*. 2004;328:1519–1528.
- [4] Polosa R, Thomson NC. Smoking and asthma: dangerous liaisons. *Eur Respir J*. 2013;41:716–726.
- [5] Polosa R, Russo C, Caponnetto P, et al. Greater severity of new onset asthma in allergic subjects who smoke: a 10-year longitudinal study. *Respir Res*. 2011;12:16.
- [6] Polosa R, Knote JD, Russo C, et al. Cigarette smoking is associated with a greater risk of incident asthma in allergic rhinitis. *J Allergy Clin Immunol*. 2008;121:1428–1434.
- [7] Tønnesen P. Smoking cessation and COPD. *Eur Respir Rev*. 2013;22:37–43.
- [8] Polosa R, Caponnetto P, Sands MF. Caring for the smoking asthmatic patient. *J Allergy Clin Immunol*. 2012;130:1221–1224.
- [9] Buchhalter AR, Acosta MC, Evans SE, Breland AB, Eissenberg T. Tobacco abstinence symptom suppression: the role played by the smoking-related stimuli that are delivered by denicotinized cigarettes. *Addiction*. 2005;100:550–559.
- [10] Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*. 2004;99:29–38.
- [11] Polosa R, Benowitz NL. Treatment of nicotine addiction: present therapeutic options and pipeline developments. *Trends Pharmacol Sci*. 2011;32:281–289.

- [12] Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2012;10: CD008286.
- [13] Alpert HR, Connolly GN, Biener L. A prospective cohort study challenging the effectiveness of population-based medical intervention for smoking cessation. *Tob Control*. 2013;22:32–37.
- [14] Pierce JP, Cummins SE, White MM, Humphrey A, Messer K. Quitlines and nicotine replacement for smoking cessation: do we need to change policy? *Annu Rev Public Health*. 2012;33:341–356.
- [15] Zhu SH, Lee M, Zhuang YL, Gamst A, Wolfson T. Interventions to increase smoking cessation at the population level: how much progress has been made in the last two decades? *Tob Control*. 2012;21:110–118.
- [16] Caponnetto P, Russo C, Bruno CM, Alamo A, Amaradio MD, Polosa R. Electronic cigarette: a possible substitute for cigarette dependence. *Monaldi Arch Chest Dis*. 2013;79:12–19.
- [17] Caponnetto P, Maglia M, Polosa R. Electronic cigarettes—from smoking cessation to smoking sensation and back. *Addiction*. 2015;110:678–679.
- [18] Siegel MB, Tanwar KL, Wood KS. Electronic cigarettes as a smoking-cessation tool: results from an online survey. *Am J Prev Med*. 2011;40:472–475.
- [19] Farsalinos KE, Romagna G, Tsiapras D, Kyzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11:4356–4373.
- [20] Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res*. 2015;17:127–133.
- [21] Kiviniemi MT, Kozłowski LT. Deficiencies in public understanding about tobacco harm reduction: results from a United States national survey. *Harm Reduct J*. 2015;12:21.
- [22] McNeill A, Etter JF, Farsalinos K, Hajek P, le Houezec J, McRobbie H. A critique of a World Health Organization-commissioned report and associated paper on electronic cigarettes. *Addiction*. 2014;109:2128–2134.
- [23] Hiscock R, Goniewicz ML, McEwen A, et al. E-cigarettes: online survey of UK smoking cessation practitioners. *Tob Induc Dis*. 2014;12:13.
- [24] Michie S, Johnston M, Abraham C, Lawton R, Parker D, Walker A. Making psychological theory useful for implementing evidence based practice: a consensus approach. *Qual Saf Health Care*. 2005;14:26–33.
- [25] Graham I. I believe therefore I practise. *Lancet*. 1996;347:4–5.
- [26] Borrelli B, Novak SP. Nurses' knowledge about the risk of light cigarettes and other tobacco 'harm reduction' strategies. *Nicotine Tob Res*. 2007;9: 653–661.
- [27] Patwardhan SR, Murphy MA. Survey of GPs' understanding of tobacco and nicotine products. *Drugs Alcohol Today*. 2013;13:119–150.
- [28] Schraufnagel DE, Blasi F, Drummond MB, et al; Forum of International Respiratory Societies. Electronic cigarettes. A position statement of the Forum of International Respiratory Societies. *Am J Respir Crit Care Med*. 2014;190: 611–618.
- [29] Nickels AS, Joshi AY, Dinakar C. Electronic cigarettes: navigating the vapor. *Ann Allergy Asthma Immunol*. 2014;112:481–483.
- [30] Ebbert JO, Agunwamba AA, Rutten LJ. Counseling patients on the use of electronic cigarettes. *Mayo Clin Proc*. 2015;90:128–134.
- [31] Conference of the parties to the WHO Framework Convention on Tobacco Control, second report. [http://apps.who.int/gb/fctc/PDF/cop6/FCTC\\_COP6\\_10-en.pdf](http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10-en.pdf). Published 2014.
- [32] Tan AS, Bigman CA. E-cigarette awareness and perceived harmfulness: prevalence and associations with smoking-cessation outcomes. *Am J Prev Med*. 2014;47:141–149.
- [33] Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf*. 2014;5:67–86.
- [34] Hajek P, Etter JF, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit. *Addiction*. 2014;109:1801–1810.
- [35] Action on Smoking and Health. Use of electronic cigarettes (vapourisers) among adults in Great Britain. [http://www.ash.org.uk/files/documents/ASH\\_891.pdf](http://www.ash.org.uk/files/documents/ASH_891.pdf). Published May 2015.
- [36] Ipsos. Ipsos Poll Conducted for Reuters E-smoking 06.04.2015. <https://www.ipsos-na.com/download/pr.aspx?id=14594>. Published June 2015.
- [37] Russell M. Low-tar medium-nicotine cigarettes: a new approach to safer smoking. *Br Med J*. 1976;1:1430–1433.
- [38] Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. *Harm Reduct J*. 2013; 10:19.
- [39] Environmental Protection Agency. EPA Report/600/6-90/006F. *Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders* 1992. Washington, DC: Author. [http://oaspub.epa.gov/eims/eimscmm.getfile?p\\_download\\_id=36793](http://oaspub.epa.gov/eims/eimscmm.getfile?p_download_id=36793).
- [40] WHO-IARC. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Volume 83, Tobacco Smoke and Involuntary Smoking* 2004. Geneva: Author. <http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf>.
- [41] Murray R, Bailey W, Daniels K, et al. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. *Chest*. 1996;109:438–445.
- [42] Greenland S, Satterfield M, Lanes S. A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Saf*. 1998;18:297–308.
- [43] Benowitz N, Gourlay S. Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol*. 1997;29:1422–1431.
- [44] Woolf K, Zabad M, Post J, McNitt S, Williams G, Bisognano J. Effect of nicotine replacement therapy on cardiovascular outcomes after acute coronary syndromes. *Am J Cardiol*. 2012;110:968–970.
- [45] Nides MA, Leischow SJ, Bhattar M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav*. 2014;38:265–274.
- [46] Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)*. 2014;231: 401–407.
- [47] Farsalinos KE, Spyrou A, Tsimopoulou K, Stefanopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep*. 2014;4:4133.
- [48] Behar RZ, Hua M, Talbot P. Puffing topography and nicotine intake of electronic cigarette users. *PLoS One*. 2015;10:e0117222.
- [49] Pacifici R, Pichini S, Graziano S, Pellegrini M, Massaro G, Beatrice F. Successful nicotine intake in medical assisted use of e-cigarettes: a pilot study. *Int J Environ Res Public Health*. 2015;12:7638–7646.
- [50] Etter JF, Eissenberg T. Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. *Drug Alcohol Depend*. 2015;147:68–75.
- [51] Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res*. 2015;17:186–192.
- [52] Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction*. 2013;108:1115–1125.
- [53] Farsalinos KE, Romagna G, Tsiapras D, Kyzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst Abuse*. 2013;7:139–146.
- [54] Polosa R, Caponnetto P, Cibella F, Le-Houezec J. Quit and smoking reduction rates in vape shop consumers: a prospective 12-month survey. *Int J Environ Res Public Health*. 2015;12:3428–3438.
- [55] Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*. 2014;23: 133–139.
- [56] Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One*. 2013;8:e57987.
- [57] US Pharmacopeia. Elemental impurities limits. [http://www.usp.org/sites/default/files/usp\\_pdf/EN/USPNF/key-issues/e232-final.pdf](http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/e232-final.pdf). Published 2013.
- [58] Hannuksela M, Forstrom L. Reactions to peroral propylene glycol. *Contact Dermatitis*. 1978;4:41–45.
- [59] Hua M, Alfi M, Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J Med Internet Res*. 2013;15:e59.
- [60] Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl compounds generated from electronic cigarettes. *Int J Environ Res Public Health*. 2014;11:11192–11200.
- [61] Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med*. 2015;372:392–394.
- [62] Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*. 2014;16:1319–1326.
- [63] Farsalinos KE, Voudris V, Poulas K. E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. *Addiction*. 2015;110:1352–1356.
- [64] National Institutes of Health Office of Disease Prevention. Research portfolio. <https://prevention.nih.gov/tobacco-regulatory-science-program/research-portfolio>. Updated April 28, 2015.
- [65] Polosa R. Electronic cigarette use and harm reversal: emerging evidence in the lung. *BMC Med*. 2015;13:54.
- [66] Caponnetto P, Campagna D, Cibella F, et al. Efficiency and Safety of an Electronic cigarette (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2013;8:e66317.
- [67] Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382:1629–1637.
- [68] Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health*. 2014;14:1159.
- [69] Vardavas C, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly G, Behrakis P. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest*. 2012;141:1400–1406.
- [70] Flouris A, Chorti M, Pouliantiti K, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol*. 2013;25:91–101.
- [71] Polosa R, Morjaria JB, Caponnetto P, et al. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int J Environ Res Public Health*. 2014;11:4965–4977.
- [72] Polosa R, Morjaria JB, Caponnetto P, et al. Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov Med*. 2015 (in press).
- [73] Tonnesen P, Pisinger C, Hvidberg S, et al. Effects of smoking cessation and reduction in asthmatics. *Nicotine Tob Res*. 2005;7:139–148.
- [74] Chaudhuri R, Livingston E, McMahon AD, et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med*. 2006;174:127–133.

- [75] Joos GF, O'Connor B, Anderson SD, et al; ERS Task Force. Indirect airway challenges. *Eur Respir J*. 2003;21:1050–1068.
- [76] Piccillo G, Caponnetto P, Barton S, et al. Changes in airway hyper-responsiveness following smoking cessation: comparisons between Mch and AMP. *Respir Med*. 2008;102:256–265.
- [77] Sparrow D, O'Connor G, Colton T, Barry CL, Weiss ST. The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The Normative Aging Study. *Am Rev Respir Dis*. 1987;135:1255–1260.
- [78] Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. *Am J Respir Crit Care Med*. 1996;153:1802–1811.
- [79] Nutt DJ, Phillips LD, Balfour D, et al. Estimating the harms of nicotine-containing products using the MCDA approach. *Eur Addict Res*. 2014;20:218–225.
- [80] Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and carcinogen metabolites in the urine of e-Cigarette users versus cigarette smokers. *Nicotine Tob Res*. 2015;17:704–709.
- [81] Caponnetto P, Saitta D, Sweanor D, Polosa R. What to consider when regulating electronic cigarettes: pros, cons and unintended consequences. *Int J Drug Policy*. 2015;26:554–559.