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EDITOR'S PAGE

Health impact of electronic cigarettes and heated tobacco systems

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Cigarette smoking is the leading cause of preventable disease and premature mortality worldwide [1–3]. The goal of reducing the harm caused by smoking has traditionally been based on preventing smoking initiation and promoting smoking cessation. While these two approaches are, and will continue to be, keystones for reducing the prevalence of smoking, long-term smoking cessation has been proven to be a difficult task for far too many smokers [4, 5].

Compulsion to smoking is very difficult to break with many smokers typically cycling through multiple periods of remission and relapse; this contributes to the slow decline in smoking prevalence [2, 3]. Consequently, there is a pressing need for alternative tactics to reduce or prevent harm for those who continue to smoke. One of these tactics is tobacco harm reduction, a principle acknowledged in the World Health Organization's Framework Convention on Tobacco Control [6]. The goal of tobacco harm reduction is to prevent or reduce the harms to health caused by smoking for people unable or reluctant to stop, as an alternative strategy to the complete abstinence from nicotine use [7]. Tobacco harm reduction is based on the well-established concept that smokers seek to obtain the effects of nicotine, while the real risks are produced by the toxic components in the smoke [8]. In fact, nicotine is unlikely to contribute significantly to the development of smoking-related diseases [1].

Successful integration of harm reduction into existing tobacco control policies requires the endorsement of these significantly reduced risk alternatives. While smoking cessation without the use of alternative nicotine products continues to be the desired and ideal outcome, tobacco harm reduction promotes the substitution of combustion-free forms of nicotine delivery (such as electronic cigarettes or heated tobacco systems) for conventional cigarettes. Thanks to market entrants, substitution is now a realistic alternative that may eliminate or substantially reduce exposure to tobacco smoke toxicants [9].

Electronic cigarettes (ECs) and heated tobacco systems (HTSs) are continuing to gain popularity and acceptance by consumers worldwide. However, too many health professionals are uncertain about the potential benefits or adverse effects of these reduced risk products. Unfortunately, opposing views among experts, often based on limited evidence, are inflaming the scientific debate about the benefits and risks at both the individual and population level.

Research on these emerging products is intense and publications are growing at an exponential rate. Important themes about the products themselves include characterizing aerosol chemistry, quantifying the relative risk of these products compared to smoking, and improving product quality and safety. Issues for public health research include assessing population effects in adults, youth, and special populations (such as in pregnancy) and evaluating the impact on the smoking status of users (smoking history) on tobacco harm reduction interventions. Other research areas include addressing the definitions of regular use, dual use and frequency of use. Additionally, it is critical that research informs the appropriateness of legislation and regulatory policy because they affect access, population perceptions, acceptability and adoption of use.

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In the Topical Collection of *Internal and Emergency Medicine*, titled "Health Impact of Electronic Cigarettes and Tobacco Heating Systems", researchers have expanded the current knowledge base and advanced the scientific debate by investigating phenomena, effects and mechanisms associated with the use of these emerging technologies.

In their study, Diamantopoulou et al. [10] profiled e-cigarette usage in a random population of 309 vape shop customers in Greece and evaluated its impact on their health. Almost without exception, the respondents had smoked cigarettes before initiating e-cigarette use initiation (98%), with a substantial 69.6% reporting that they were no longer smoking at the time of the survey. In the study's logistic regression analysis, the strongest predictor of being a former smoker was daily e-cigarette use. Most participants reported health benefits, mainly improvement in physical status and exercise capacity. In addition, minor adverse reactions of throat irritation and cough were reported.

The same researchers examined the association between e-cigarette use and smoking cessation in a cross-sectional survey of a representative sample of Greek adults [11]. Current e-cigarette use was most prevalent among those who had stopped smoking for three or fewer years, approximately 27%. Current and even more so current daily e-cigarette use were strongly associated with smoking cessation in this group.

Both Greek studies concur with the growing evidence that vaping products may aid cessation or result in an appreciable decrease in the consumption of cigarettes [12, 13]. The main element that explains its success (especially with unsuccessful quitters) is that e-cigarettes are consumer products, not medicines. As a consequence, "quitting smoking" becomes a recreational process that the smoker enjoys while replacing the substantially harmful habit of smoking by substituting for it with e-cigarettes and other reduced risk products that provide the stimulation, sensation and rituals of cigarette smoking. These behavioural and recreational elements are missing from pharmaceutical products such as NRT's and pharmaceuticals (e.g. varenicline or bupropion). The practical limitations of the pharmaceutical approach for smoking cessation have been addressed in a recent editorial [14].

Both papers call attention to the importance of using correctly defined variables (e.g. assessing duration of smoking cessation, frequency of e-cigarette use, etc.) when investigating the impact of e-cigarettes in observational studies and population surveys [15]. Variables that group together regular e-cigarette users with infrequent users (who are predominately experimenters) will result in biased and misleading conclusions.

As much as some might wish, e-cigarettes are not "silver bullets" because many smokers do not find them to be a satisfactory substitute for cigarettes. Greater adoption could be stimulated by more efficient nicotine delivery products, and better nicotine delivery is associated with higher rates of cigarette abstinence [16]. One of these newer products is e-cigarettes that contain nicotine salt (nicotine lactate) formulations. Nicotine salts have improved e-blood nicotine delivery and other sensory properties that appear to increase satisfaction with these products. Little data on e-cigarettes with nicotine salts have been published to date. O'Connell et al. [17] compared nicotine pharmacokinetic (PK) profiles, subjective effects and tolerability between conventional cigarettes and e-cigarettes with varying concentrations of nicotine salt e-liquids. PK data indicate that a nicotine salt formulation is more rapidly absorbed into systemic circulation compared with the free-base formulation used in current products, yet with lower nicotine levels than conventional cigarettes. The rise in blood nicotine levels following use of nicotine salt reduced the desire to smoke, although not as much as a conventional cigarette, and the nicotine salt e-cigarettes were well tolerated. More research is warranted to identify and develop nicotine salt formulations that can improve the appeal of reduced risk products as cigarettes substitutes.

For tobacco harm-reduction strategies, it is mandatory to have a granular delineation of the relative risk of e-cigarette use compared to smoking. This computation calls for more advanced toxicological research methods. Iskandar et al. [18] propose an elegant approach consisting of an in vitro systems toxicology assessment of e-liquids and their aerosols to complement the battery of assays for standard toxicity assessments. The proposed methodology with human organotypic air–liquid interface buccal and small airway cultures compares the biological impact of acute exposure to different e-cigarette aerosols with exposure to cigarette smoke. Cellular responses (multiplex and omics assays to measure secreted inflammatory proteins and whole-genome transcriptomes, respectively) to e-cigarette aerosol exposure were tissue type-specific and were much smaller than those after cigarette smoke exposure. This systems toxicology assessment approach has enabled in-depth analyses of the toxicity-related cellular mechanisms of e-liquids and their aerosols, and these results are in agreement with earlier estimates from Public Health England [19] and the Royal College of Physicians [20]. Iskandar et al. conclude that e-cigarettes pose no more than 5% of the risk of lighting up a conventional cigarette.

Despite these estimates and laboratory findings, the true impact of reduced risk nicotine delivery systems in reducing morbidity and mortality from smoking-related diseases can only be documented after long-term observation because smoking takes decades to inexorably cause severe illness and death. E-cigarettes can contribute to reductions in morbidity and mortality by suppressing tar exposure. Direct evidence for the risk reduction potential of new nicotine delivery technologies—including their potential to reduce the risk

of lung cancer—is not possible due to the latency period for smoking-related diseases. However, using indirect evidence, we can estimate a protective effect on lung cancer risk. For example, several research groups have confirmed lack of mutagenicity and significantly reduced genotoxicity of e-cigarettes aerosols emissions [21–23]. In the Topical Collection of *Internal and Emergency Medicine* "Health Impact of Electronic Cigarettes and Tobacco Heating Systems", Hoeng et al. [24] advance the scientific debate on lung cancer risk reduction potential of using these emerging technologies by proposing a comprehensive mechanism-based approach that utilizes the causal chain of events that leads from smoking to cancer (driven by a combination of genetic damage and inflammation). Their method integrates multiple lines of evidence derived from in vitro, in vivo, as well as clinical studies into the principles of systems toxicology. The authors propose that their approach provides a scientifically sound alternative for the assessment of the risk reduction potential of new nicotine delivery technologies long before epidemiological evidence becomes available.

Studies have shown that reduced risk nicotine products have much reduced biological impact and considerably lower level of combustible toxicants biomarkers compared to cigarettes, but their impact with respect to substantiation of their reduced risk potential or harm reversal in long-term real-life use is virtually unexplored. In trying to address this knowledge gap, Newland et al. [25] have recently designed and launched an ambitious randomized, multi-centre, controlled clinical trial. Their working hypothesis is that following a 1-year switch from cigarettes to a heated tobacco product, participants are expected to experience favorable changes in health effect indicators associated with smoking-related disease development. Data from this study will be a valuable addition to the growing body of evidence on reduced risk nicotine delivery systems in general and heated tobacco products in particular. But we will have to wait until 2020 until the trial is scheduled to be completed.

Given that many smokers continue smoking despite the health risk, combustion-free nicotine delivery technologies should be considered as a valuable and much less harmful asset in the fight against smoking. In the authors' view, the interest among medical community about the potential for risk reduction and harm reversal of these new technologies for smoking substitution will grow exponentially in the next few years. Good quality research will be increasingly important to establish tolerability, safety, effectiveness and harm reduction potential of these new technologies and to add credibility to the tobacco harm reduction paradigm. Technological innovation is already delivering significant improvements not only in their quality, but also in their effectiveness and safety. Given the importance of the topic to the active role that internists and general physicians play in assisting the patient who smoke, *Internal and Emergency Medicine* remains committed to further expanding the current knowledge base and advancing the scientific debate about the impact of electronic cigarettes and tobacco heating systems on human health.

Compliance with ethical standards

Conflict of interest Polosa Riccardo: in relation to his work in the area of tobacco control, RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also received support from The Consumer Advocates for Smoke-free Alternatives (CASAA) for publication and open access costs of one paper. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl. and Health Diplomats (consulting company that delivers solutions to global health problems with special emphasis on harm minimization). Lectures fees from a number of European electronic cigarette industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vapers advocacy no-profit organizations. Publication costs for previous work have been met by independent e-cigarette industry including Happy Liquid, Ritchy Europe, Cuts Ice e-Liquid Laboratories and VDLV e-Liquids. RP is the Director of the Center of Excellence for the acceleration of Harm Reduction at the University of Catania (CoEHAR), which has received a grant from Foundation for a Smoke Free World to develop and carry out 8 research projects. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for tandardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). Konstantinos Farsalinos has no conflict of interest to report for the past 3 years. For the past 5 years, Konstantinos Farsalinos has published 2 studies funded by the non-profit association AEMSA and 1 study funded by the non-profit association Tennessee Smoke-Free Association. Domenico Prisco has no conflict of interest.

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