REVIEW ARTICLE

E-cigarettes and their impact on health: from pharmacology to clinical implications

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ABSTRACT

Worldwide, cigarette smoking is the major cause of premature mortality and diseases that can be prevented. Given that people continue smoking despite associated health risks, delivering nicotine without combustion should be considered a valuable and much less harmful way to reduce the public health burden caused by smoking. E-cigarettes could play such a role if they were proven to be less harmful than combustible cigarettes. Although the number of clinical trials and human studies assessing the safety of e-cigarettes is limited, numerous in vitro and in vivo studies reported on the potential harmful effects of the aerosol generated from e-cigarettes. This article reviews the results of major clinical trials and laboratory studies with regard to cancer as well as cardiovascular and respiratory risk associated with the use of e-cigarettes. Additionally, it also discusses the potential application of e-cigarettes as smoking cessation tools. Most studies have indicated so far that e-cigarettes are less harmful, but this applies only to smokers who completely switched to e-cigarettes. In the opinion of the authors, good-quality research is crucial to establish the tolerance, safety, efficacy, and harm reduction potential of new technologies. Considering a significant role that physicians and other health providers play in helping smokers, there is an urgent need for evidence-based guidelines and recommendations for clinical practitioners on potential benefits and risks of e-cigarette use.

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Recent outbreak of acute lung injuries related to vaping The year 2019 brought news about many tragic deaths linked to electronic cigarette (e-cigarette) use (vaping). By February 2020, the Centers for Disease Control and Prevention reported 2758 hospitalizations for acute lung failure (e-cigarette, or vaping, product use–associated lung injury [EVALI]), 64 of which ended in death.[1,2] The patients were mostly young people at a median age of 24 years who regularly used e-cigarettes. The first case was recorded in March 2019, and the peak number of hospital admissions was observed in September 2019. After January 2020, the outbreak of the disease appeared to diminish and only a few cases have been reported recently.

In view of these tragic events, the question of why this condition was not previously reported among regular e-cigarette users (commonly called "vapers") has become relevant, despite the fact that vaping products have been available on the United States market since 2007. The answer appeared quite quickly. The problem occurred mainly among e-cigarette users who primarily vaped tetrahydrocannabinol (THC)-containing products. Research showed that e-cigarette refill fluids (e-liquids) used by hospitalized patients contained THC, a psychoactive substance derived from cannabis or cannabidiol, and were largely purchased on the black market.

Chest imaging of hospitalized patients with EVALI showed, among others, acute eosinophilic pneumonia, diffuse alveolar damage, and lipid pneumonia.[3] Lipid pneumonia is an inflammatory response to the presence of lipids in the alveolar space, which usually results from inhalation of oily substances. Preliminary findings indicated that this oily substance was tocopherol acetate (vitamin E acetate), a lipophilic diluent used in some THC-containing e-liquids.[4-6]

The evidence on causes of EVALI has become so prominent that, on October 4, 2019, the United States Food and Drug Administration (FDA)

issued a statement that unambiguously encouraged the public to discontinue using vaping products containing THC and avoid purchasing e-cigarettes from unknown sources.[7] In addition, in December 2019, the United States Centers for Disease Control and Prevention recommended people to refrain from adding any other substances (not intended by a manufacturer) to e-cigarette products, including those purchased through retail outlets.[2]

What are e-cigarettes? Developed in 2003 by the Chinese pharmacist Hon Lik (Han Li), electronic devices introducing nicotine to the user's body were, according to the inventor, meant to help quit smoking.[8] Although there is no combustion process involved, these new devices were named as electronic cigarettes, or e-cigarettes, mainly due to the first-generation products resembling a cigarette and the similar way of use. Despite some scientific community members suggested using the name Electronic Nicotine Delivery System (ENDS), the name e-cigarette has become widely accepted, which stigmatizes the device as another tobacco product. Since smokers are generally aware of the extreme harmfulness of tobacco products, e-cigarettes were also perceived as another potentially dangerous tobacco product. In addition, the limited availability of scientific publications after introduction of these products did not help potential users and health professionals to differentiate potential health risks of vaping compared with smoking.

Since the introduction of e-cigarettes to the global market, a significant number of studies on potential health risks of vaping have been conducted and published. Currently, over 5300 records appear after typing the phrase "electronic cigarette" in the PubMed database. Many of those studies have looked at the relative risk of vaping compared with smoking. In general, studies have suggested that the use of e-cigarettes is associated with a lower health risk compared with smoking tobacco cigarettes. Although this conclusion appears to be consistent across most of the studies, there are some limitations that need to be considered and are discussed below.

Limitations in the evaluation of e-cigarette safety

One of the challenges in assessing the harmfulness of e-cigarettes are their rapidly changing design and product characteristics. For example, newer generations of e-cigarettes are significantly more effective in delivering nicotine to users than the previous generations of these products. Farsalinos et al[9] demonstrated that the plasma nicotine concentration measured after 5 minutes of smoking a conventional cigarette was 286% and 185% higher compared with the use of the first- and second-generation e-cigarettes, respectively. Currently, the fourth generation e-cigarettes (Pod systems) may deliver nicotine to the same or even greater extent as conventional cigarettes, thus increasing the likelihood of addiction.[10,11]

For some types of e-cigarettes, the battery voltage can be adjusted—the higher the voltage, the higher the temperature of e-liquid. A substantial increase in vaporization temperature inside an e-cigarette device may lead to thermal decomposition of 2 commonly used e-liquid solvents (glycerin and propylene glycol). Both solvents break down to formaldehyde, a toxic chemical with a proven carcinogenic potency. Kośmider et al[12] demonstrated that an increase in the battery voltage from 3 V to 4.8 V causes a higher than 10-fold increase in the amount of formaldehyde in the aerosol to a level similar to that present in tobacco smoke. Another study showed that very small amounts of e-liquid on e-cigarette coil may result in overheating the device and lead to a 15-fold higher emission of formaldehyde compared with that of a traditional cigarette.[13] However, this work elicited a lot of controversy in the scientific community, as the presented results were obtained for an unrealistic pattern of e-cigarette use.[14-17]

Another difficulty in assessing the potential risk associated with e-cigarette use is the variety of flavoring substances present in e-liquids. In 2014, it was estimated that over 460 brands and over 7700 unique flavors of e-cigarettes were available on the consumer market.[18] The authors of the discussed study also demonstrated that, unlike older brands emphasizing lesser harm compared with that caused by conventional cigarettes, manufacturers of newer e-cigarette brands focused more on various models and flavor options to choose from to increase their products' appeal especially among young people. Such a great variety of product options results in safety concerns. For example, aerosol generated from cherry-flavored liquids was found to contain more benzaldehyde than tobacco smoke. Benzaldehyde is a potential respiratory irritant that causes burning sensation in the nose and throat, cough, and feeling of breathlessness.[19]

E-liquids of sweet taste (eg, toffee, milk, and chocolate) may also contain prominent respiratory toxicants: diacetyl and 2,3-pentanedione.[20] Although these compounds are relatively safe when ingested, they have been shown to cause significant lung damage when inhaled. Inhalation of these compounds have been linked to reduced first-second intensive expiratory volume resulting in the development of bronchitis.[21] A condition called popcorn lung was reported among the employees of popcorn plants who were exposed to a high concentration of diacetyl. Since some e-liquids contain the same toxicant, some authors suggested that the use of e-cigarettes may also lead to the same disease.[22] However, the concentration of diacetyl in the traditional cigarette smoke is several hundred times higher and the popcorn lung disease has not been reported among regular smokers.[23]

Toxic compound emissions from e-cigarettes and conventional cigarettes Tobacco smoke contains several thousand compounds, many of which have been shown to be toxic. On the other hand,

aerosol generated from e-cigarettes contains a dozen to several dozen compounds. In 2012, the FDA published a list of 93 harmful and potentially harmful compounds found in tobacco and tobacco smoke.[24] Out of these, only 5 compounds are present in the aerosol generated from the majority of commercially available e-liquids in quantities that may pose a potential health hazard to the user. These include acetaldehyde, acetone, acrolein, formaldehyde, and nicotine.[25] Lower yields of toxic compounds in the e-cigarette aerosol compared with tobacco smoke were also confirmed by a multicenter study, in which authors found out that the amount of toxic compounds present in the aerosol is 9- to 450-fold lower than in the tobacco smoke.[26]

Margham et al[27] compared the exposure to toxic compounds present in the aerosol generated by an e-cigarette and the standard 3R4F cigarette. This included the toxic compounds listed by the World Health Organization, FDA, and Health Canada. The reduction in the number and yields of toxic chemicals in aerosol compared with tobacco smoke ranged between 92% and 99%. Also the United States Surgeon General report, entirely devoted to e-cigarettes, states that "e-cigarette aerosol is not harmless 'water vapor,' although it generally contains fewer toxicants than combustible tobacco products." At the same time, it adds that "the health effects and potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavoring agents, and toxicants, are not completely understood."[28]

A significant reduction in toxic compound yields in e-cigarette aerosols compared with tobacco smoke, as shown in the laboratory product testing, was confirmed in a population study of 5105 participants including regular e-cigarette vapers and tobacco cigarette smokers. The urinary concentrations of biomarkers of exposure to toxic components of tobacco smoke, ie, nicotine, tobacco-specific nitrosamines (nicotine-derived nitrosamine ketones [NNKs]), metals, volatile organic compounds, and polycyclic aromatic hydrocarbons, were shown to be lower than those observed in current exclusive smokers and dual users of both products.[29]

The lower exposure to toxic substances from e-cigarette aerosols compared with tobacco smoke suggest that e-cigarettes are potentially less harmful products compared with combustible cigarettes, smoking of which is the primary cause of premature mortality in developed countries mainly due to cancer as well as cardiovascular and respiratory diseases.[30] Replacing combustible tobacco products with e-cigarettes will undoubtedly bring significant public health benefits if the reduction in toxicant exposure is proven to be associated with a lower health risk.

E-cigarettes and cancer risk Smoking is the main cause of initiation of the cancer process in the body resulting from several dozen carcinogenic compounds present in tobacco smoke, especially including 9 compounds classified by the International Agency of Research on Cancer as group 1 carcinogens with proven carcinogenic effects on humans. Apart from traces of NNKs found in e-cigarette liquids, there is a single compound from this group, ie, formaldehyde, that has been reported in e-cigarette aerosols.

The carcinogenicity of various complex mixtures, including tobacco smoke and aerosol emitted from e-cigarettes, can only be established on the basis of a documented relationship between the exposure to the factor and increase in the incidence of cancer in exposed humans or animals (epidemiological studies). Such a relationship was documented for smokers but not for e-cigarette users, as these products have been recently introduced on the consumer market. The reason behind this are the long cancer latency periods ranging from several to several dozen years. Although no epidemiological studies are available at the moment, we can roughly assess the relative cancer risk of e-cigarette use by measuring biomarkers of exposure to carcinogens and compare the measured values to exposure levels observed in smokers and nonsmokers.

In one of the first exposure assessment studies, traditional smokers completely substituted their tobacco cigarettes with e-cigarettes for 2 weeks. That study showed a drastic reduction in exposure to carcinogens, including 1,3-butadiene, benzene, acrylonitrile, and NNKs. Concentrations of the corresponding biomarkers decreased by 57% on average after the first week and by 67% after the second week.[31]

A cross-sectional study of 181 volunteers showed that former cigarette smokers who gave up smoking in favor of e-cigarettes for at least 6 months had significantly reduced exposure to carcinogenic and toxic compounds compared with those who continued smoking. Levels of biomarkers of exposure measured in e-cigarette users were similar to those observed in subjects who used nicotine replacement therapy (NRT).[32] Importantly, no reduction in exposure was observed in individuals who concurrently smoked cigarettes and vaped e-cigarettes.

Cadmium is one of the International Agency of Research on Cancer group 1 carcinogens present in the tobacco smoke. A cross-sectional study of 156 volunteers showed that, after switching from cigarettes to e-cigarettes, a 69% decrease was observed in the concentration of cadmium in blood after 6 months.[33]

The most comprehensive, and probably the most representative and up-to-date, report of the United States National Academies of Sciences, Engineering, and Medicine (NASEM) states that the current evidence related to the potential link between e-cigarette use and cancer is too scarce to draw meaningful conclusions about the cancer process or intermediate clinical endpoints.[34]

E-cigarettes and the risk of cardiovascular diseases

According to the United States Surgeon General report, the mechanism through which smoking affects the cardiovascular system is complex yet well documented.[35] It was proven that nicotine, carbon monoxide, and tobacco combustion products are primarily responsible for cardiovascular dysfunction in smokers.

Nicotine activates the sympathetic system and releases catecholamines, adrenaline, and noradrenaline, which enhance the myocardial function and oxygen demand by rapidly increasing blood pressure, accelerating heart rate, and vasospasm. There is no reason to believe that nicotine in the e-cigarette aerosol affects the cardiovascular system differently than nicotine in tobacco smoke.

Carbon monoxide reacts with hemoglobin to form carboxyhemoglobin, which is not capable of carrying oxygen, resulting in a reduction in oxygen availability. However, this does not happen with e-cigarettes owing to the absence of combustion.

Combustion products of tobacco, such as polycyclic aromatic hydrocarbons, oxidizing compounds, free radicals, and respirable particles, play a significant role in this process. According to the harmful and potentially harmful constituent list, toxic effects on the cardiovascular system can be attributed to at least 12 compounds present in tobacco smoke. Only 2 of these, acrolein and propionic aldehyde, are present in e-cigarette aerosol due to thermal decomposition of the solvents. However, some cardiovascular toxicants that are absent in e-liquids could be generated from flavoring agents and additives during vaporization. For example, benzene has been shown to be generated from certain flavorings used in e-liquids when e-cigarette users take puffs on the device.[36]

To date, the comparison of solid particles in tobacco smoke and aerosol remains controversial. Their composition and characteristics in aerosol differ significantly from those in tobacco smoke. At the same time, the data to determine their cardiovascular toxicity is insufficient.[37]

Combustion products induce inflammation, which activates platelets and leads to vascular endothelial dysfunction. Many researchers believe that endothelial dysfunction is an essential element of the future development of atherosclerotic damage. Hence, it is designated as "the risk of the risk factors."[38] By quitting tobacco products and switching to e-cigarettes, the smoker greatly reduces the inhalation of compounds resulting from tobacco combustion. Consequently, the negative effect of the aerosol on vascular endothelial dysfunction is expected to be reduced. This has been confirmed by an extensive review by Knura et al.[39] Based on the available data, the authors concluded that e-cigarette aerosol damages the vascular endothelium, yet to a lesser extent than tobacco smoke.

Using an e-cigarette also causes oxidative stress induced by oxidative compounds, which is, however, comparatively lesser than that exerted by a conventional cigarette.[40]

A randomized clinical study, perceived as the "gold standard" for the analysis of treatment results by many, showed that flow-induced vasodilatation in the brachial artery significantly increases 1 month after switching to e-cigarettes.[41]

Based on the previous clinical studies, Benowitz et al[42,43] concluded that the overall acute circulatory failure associated with e-cigarettes is consistent with the nicotine effect. Additionally, the authors believe that the cardiovascular risk caused by nicotine inhaled from e-cigarettes is quite low in people without preexisting cardiovascular disease. However, people with diagnosed cardiovascular disease are still prone to the risk, but it is comparatively lower than that noted in the traditional smokers. If conventional cigarettes are completely replaced by e-cigarettes, the harmfulness of smoking can be significantly reduced and smokers who completely switch to e-cigarettes would mitigate the cardiovascular risk.

According to the NASEM report, there is no evidence available to confirm whether the use of e-cigarettes is associated with ischemic heart disease, stroke and peripheral artery disease, and subclinical arteriosclerosis. There is also insufficient evidence that the use of e-cigarettes is related to long-term changes in heart rate, blood pressure, and heart geometry and function. However, there is convincing evidence that heart rate increases shortly after nicotine inhalation from e-cigarettes. There is also moderate evidence that diastolic blood pressure increases shortly after inhaling nicotine from e-cigarettes.[34]

Although the current, but still limited, literature suggests that the use of e-cigarettes may lead to less negative cardiovascular effects than traditional cigarettes, some researchers see a need for additional, high-quality randomized controlled trials to clearly establish the cardiovascular safety of e-cigarettes. Future studies should continue to focus on the study of both long- and short-term effects of exposure to e-cigarettes and their potential role in the development of cardiovascular disease.[44]

E-cigarettes and the risk of respiratory diseases

As e-cigarettes are products purported for inhalation use, one may expect that any potential risk of these products would be reflected particularly in respiratory dysfunction. The e-cigarette users inhale relatively large amounts of 2 substances that are only present in small quantities in tobacco smoke. These substances are glycerin and propylene glycol that served as nicotine solvents and carriers in e-cigarettes and as humectants in tobacco cigarettes. In e-liquids, they constitute about 80% of their overall content. Although these compounds are commonly used in cosmetics, pharmaceuticals, and food industries, the long-term inhalation risk has not been well studied previously.

The longest study (3.5 years) looked at changes in respiratory symptoms in e-cigarettes users and nonusers. Changes in hemodynamic parameters, respiratory function, and high-resolution chest computed tomography were evaluated in 31 volunteers who never smoked cigarettes, but started and continued to use e-cigarettes. No significant changes were observed compared with the control group of persons who had never smoked.[45]

A 2-year study of 209 e-cigarette users included examination of vital parameters, electrocardiography, lung function testing, exposure to nicotine and selected compounds, urges to smoke a cigarette, and withdrawal effects. No serious health events were observed. The most common negative health symptoms reported by the volunteers included headache (28.7%), nasopharyngeal inflammation (19.6%), sore throat, and cough (16.9%).[46]

A systematic review of clinical data related to the effects of e-cigarette use on the respiratory system showed that replacing combustible tobacco cigarettes with e-cigarettes significantly improved health outcomes in patients with chronic obstructive pulmonary disease and chronic asthma.[47]

In contrast, a representative, national (United States), longitudinal study from the years 2013 to 2016 demonstrated that e-cigarettes appeared to be an independent risk factor for respiratory diseases. Among those who did not report respiratory diseases (chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma), a longitudinal analysis revealed significant relationships between previous (adjusted odds ratio [AOR], 1.31) and current use of e-cigarettes (AOR, 1.29) and lung diseases. Smoking was also significantly associated with some respiratory disease, but the odds ratio was twice as high as for vaping (AOR, 2.56). An even higher value was recorded for dual users (AOR, 3.3). The authors concluded that switching from combustible tobacco products, including cigarettes, to e-cigarettes may reduce the risk of developing respiratory diseases. At the same time, the authors pointed to a high incidence among smokers using both products, which is associated with an increased risk beyond the use of combustible tobacco products. This is a prevailing argument that dual use of e-cigarettes and tobacco cigarettes does not reduce the respiratory risk from smoking, but may actually increase such risk.[48]

Similar conclusions were presented in the NASEM report, particularly with regard to dual users. Although the report concluded that there is no evidence available that e-cigarettes cause respiratory diseases in humans, it also states that there is limited evidence of improved lung function and respiratory symptoms in adult asthma smokers who switch to e-cigarettes in full or in part (dual use). This also applies to adult smokers with obstructive lung disease.[34]

E-cigarettes as a cigarette smoking cessation tool

Although the intent of the e-cigarette inventor, the Chinese pharmacist Hon Lik, was to develop a device for smokers that would help them quit smoking, only a few clinical trials and population-based studies evaluated the efficacy of e-cigarettes in smoking cessation. The potential effectiveness of e-cigarettes in helping smokers to quit smoking is an area of much controversy. This is perfectly illustrated by 2 meta-analyses published by Kalkhoran and Glantz[49] and Malas et al.[50]

The first team analyzed 30 studies and the second one—38 studies, 25 of which were analyzed by both research teams. From these 25 studies, the first team excluded 10 works due to lack of a control group of people who did not use e-cigarettes. The results obtained were diametrically different. In the first study, the odds ratio (OR) was 0.72 (95% CI, 0.57–0.91), leading authors to the conclusion that the use of e-cigarettes among smokers reduces their chances of quitting. In the second meta-analysis, the OR of quitting was higher (OR, 1.63; 95% CI, 1.17–2.27) suggesting that e-cigarette users are more likely to quit smoking than smokers who do not use these products. This is an example of how different methodological approaches can lead to contradicting conclusions.

The NASEM report included an analysis of studies and clinical trials published until the beginning of 2018.[34] The authors concluded that there is limited evidence that e-cigarettes can be effective in promoting and supporting smoking cessation and moderate evidence from randomized clinical trials that e-cigarettes with nicotine are more effective than nicotine-free e-cigarettes. Observational studies showed that more frequent use of e-cigarettes is associated with an increased likelihood of quitting smoking. However, there is insufficient evidence from randomized studies on the efficacy of e-cigarettes as quit-smoking aids compared with the absence of antinicotine therapies or FDA-approved treatments.

These conclusions about the limited efficacy of e-cigarettes as a tool to help smokers quit cigarette use need to be updated, since 2 comprehensive and large randomized clinical trials have been published recently.[51,52] In the first trial, 886 participants were randomized to e-cigarette use or NRTs. Both groups were provided with a supportive behavioral therapy. The 1-year abstinence rate was 18% in the e-cigarette group compared with 9.9% in the NRT group. The second trial involved 1124 volunteers and compared the efficacy of e-cigarettes combined with nicotine patches versus nicotine patches alone. A 6-month abstinence rate was 7% and 2%, respectively. Given that the pharmacokinetic profiles of nicotine from smoking and vaping are similar, it could be assumed that combination therapy (e-cigarette plus NRT) can become an important strategy to improve smoking cessation rates.

A recently released report by the United States Surgeon General[53] on smoking cessation also evaluated the potential application of e-cigarettes as smoking-cessation tools. The conclusions were consistent with those of the NASEM report cited

above. The authors of the report pointed out that e-cigarettes can be attractive to traditional cigarette smokers, because their use reflects some of the sensorimotor characteristics of traditional cigarette smoking, including stimulation of the upper respiratory tract, sensations, and taste of the e-cigarette aerosol in the mouth, hand movements, inhalation and exhalation of the aerosol that visually often resembles cigarette smoke. Given the potentially important role of such factors in the abuse liability of tobacco cigarettes, their presence in the process of vaping may actually make e-cigarettes more attractive to smokers, who may see those products as better substitutes for cigarettes than NRT.

It becomes particularly relevant to assess the scientific evidence on the impact of e-cigarettes on smoking cessation among adult smokers in the context of the significant uptake of e-cigarettes by youths. The popularity of e-cigarettes among adolescents and young adults has drastically increased in recent years, particularly after the introduction of the fourth generation of e-cigarettes in the shape of USB flash drives.[54]

Summary The skyrocketing use of e-cigarettes among the youth and the recent EVALI epidemic observed in 2019 have intensified the controversy around e-cigarettes and questioned their potential for public health benefits as a substitute for traditional cigarettes. Numerous opinions and editorial pieces, as it relates to public health consequences of e-cigarette use, have been published by many prestigious and influential medical journals.

The Lancet's editorial stated that there is no firm evidence to claim that e-cigarettes are healthier than cigarettes or can support quitting smoking. In addition, the renormalization of smoking in the form of e-cigarettes, not only among smokers but also among young people and nonsmokers, poses a risk of nicotine use to the entire population and may lead to large-scale addiction.[55] This article was criticized by Professor John N. Newton, director of Health Improvement at Public Health England, who stated that there is an international consensus that the use of e-cigarettes is likely to be much less harmful than smoking and that e-cigarettes have an important role to play in tobacco control.[56]

Beaglehole et al,[57] in their commentary published also by *The Lancet*, considered e-cigarettes as a strategy to minimize harm caused by smoking. E-cigarettes have a potential to be used as a complementary harm reduction strategy, but currently this strategy is underestimated, because achieving total nicotine abstinence is the overriding goal for many regulators and public health advocates. In the United States, the effectiveness to achieve total nicotine abstinence in the years 2014 to 2015 was significantly higher than that for 2010 to 2011 (5.6 vs 4.5). Considering that e-cigarettes started to gain popularity about 2010, an increase in total nicotine abstinence might be explained by increasing their use in the population. This is supported by the fact that 38.2% of current smokers and 49.3% of recent quitters had tried e-cigarettes, and 11.5% and 19% used them currently (every day or some days).[58] Those data suggest that e-cigarettes have a potential as a harm reduction product, which should be considered, especially because current methods for nicotine addiction treatment used by providers have limited effectiveness and result in low quit rates.

The authors of the article in *Science* expressed opinions that regulatory approaches to e-cigarettes in the absence of scientific evidence certainty must include many compromises. Finding the optimal balance between providing smokers with fully regulated nicotine vaping products, while significantly reducing the risk of using e-cigarettes in young people at the same time, appears to be a proper compromise. In this context, the authors cite the example of the United Kingdom, which adopted nicotine vaping harm reduction as a safer alternative to combustible products, and was able to make appropriate regulations that led to a consensus between the risks to young people and the benefits to smokers.[59]

The authors of the article in *JAMA* emphasized that healthcare providers should remember that smoking remains a major public health threat. They point out the significant reduction in the prevalence of smoking after introduction of e-cigarettes. Indeed, the smoking prevalence has reached its lowest level in many countries despite a sharp increase in the use of e-cigarettes, and perhaps partially because of this. It is important that former cigarette smokers who use e-cigarettes do not return to traditional cigarettes, which are likely to pose a much higher risk than e-cigarettes.[60]

There are a number of questions about e-cigarettes that lack answers: whether the use of e-cigarettes among the youth will lead to smoking (the so-called gateway effect), whether banning flavored e-cigarettes will discourage young people from using them, whether reducing nicotine levels in e-cigarettes will encourage smokers who have completely switched to e-cigarettes to return to combustible tobacco products, or to what extent long-term vaping affects the health of the user.

In our view, high-quality clinical trials will be increasingly important to establish safety, efficacy, and harm reduction potential for new technologies. Despite many areas of ambiguity, current evidence suggests that e-cigarettes are less harmful than combustible products, but this only applies to smokers who completely switched to e-cigarettes. Thus, e-cigarettes still hold a great potential to reduce the incidence of tobacco-related diseases and could be part of the strategy to reduce the damage caused by smoking. Therefore, mechanisms should be developed to protect young people from using e-cigarettes, but support smokers in their decisions to quit smoking with e-cigarettes. Considering the importance of this issue

for public health, we encourage internists and general practitioners to expand their knowledge on e-cigarettes, as new evidence on the impact of e-cigarettes on users' health will emerge in the future.

ARTICLE INFORMATION

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CONFLICT OF INTEREST In 2015, AS accepted personal honoraria from the eSmoking Institute in Poznań, Poland, and nonfinancial support from Chic Group, Ltd., a manufacturer of electronic cigarettes in Poland. LK worked as an expert for the Polish National Committee for Standardization and for the European Committee for standardization of requirements and test methods for e-liquids and emissions. MŁG receives honoraria for serving in an advisory board from Johnson & Johnson and grant support from Pfizer. BK declared no conflict of interest.

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