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A debate: Can we recommend electronic cigarettes to our patients? Opinion 2

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Abstract

Electronic cigarettes are more and more frequently used to deliver nicotine. They are used both by the users of regular cigarettes and those who to date have not smoked. The literature about potential impact of electronic nicotine delivery systems on health is constantly growing. Particular concern is expressed about toxicity of chemical compounds and elements delivered with the vapour of electronic cigarettes. It turns out that products that have positive image in media, actually are not so beneficial. Furthermore, they not only may cause damage to health but also death.

Key words: electronic cigarettes, e-cigarettes, electronic nicotine delivery systems

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Introduction

Electronic cigarettes, which belong to electronic nicotine delivery systems (ENDS), are becoming more and more popular, superseding from the market regular nicotine products. Survey research carried out in France in 2014 showed that out of 15365 respondents, as many as 25.7% of subjects aged 15 to 75 years tried smoking electronic cigarettes [1].

In 2010, in Great Britain, 3–4% of smokers or those who quit smoking recently, used electronic cigarettes. In 2014, this percentage increased to 21% [2]. It is observed that children and adolescents also more frequently use ENDS. The studies conducted in the United States of America demonstrated that more young people were using ENDS than traditional tobacco products. It is estimated that even 29% of students of secondary schools smoked electronic cigarettes at least once, and 17–18% of them are current users of ENDS. The same study showed that students using ENDS have less factors of nicotinism risk, compared to people smoking regular cigarettes. The conclusion is that, if e-cigarettes did not exist, these people would not start using nicotine [3].

Therefore, the use of e-cigarettes is of great concern, in particular to health care authorities. The above presented increase in the number of e-cigarettes users poses questions about safety of their use, regarding both long- and short-term evaluation. It has been reflected in the PubMed database, in which after entering "electronic cigarette" on 17 January, 2016, the list of 2505 articles was obtained, of which in 2013, 198 articles were reported; in 2014 — 853, and in 2015 — as many as 1168 articles. It is difficult to select the most important works from such an abundance. The aim of this study is to help to understand the influence of electronic cigarettes on health of people using them in the light of recent literature findings.

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The chemical composition of electronic cigarettes, their toxicity and impact on the respiratory system

The market offers electronic cigarettes produced by various companies. The lack of standardised model of electronic cigarette hinders research. Different products differ in crucial qualities such as electrode temperature and voltage. A wide choice of different flavours of e-liquids does not help to evaluate toxicity of the products. The analysis of particles in e-cigarette vapour showed its similar composition to regular cigarettes and the reference cigarette 1R5F. The chemical compounds include acetaldehyde, acrolein and acetone [4]. It was confirmed by the studies carried out by the team directed by Goniewicz. In addition, they discovered aromatic hydrocarbons, i.e. toluene and p-xylene. The analysis also showed the presence of the following heavy metals: cadmium, nickel, lead, which are also present in the smoke of regular cigarettes [5].

More detailed analysis of the smoke generated by electronic and regular cigarettes adds to the list of typical elements of tobacco smoke the following: sodium, iron, aluminium, potassium, copper, magnesium, zinc, chromium, manganese. The list of elements included in e-cigarette vapour also contains boron, silicon, calcium, sulphur, tin, barium, zirconium, strontium, titanium, lithium. It is of crucial importance as the majority of them have a documented adverse effect on the cells of the respiratory system [6].

In one study, 42 e-liquids manufactured by 14 different producers have been examined. The tests were conducted among others for the presence of chemical compounds including aromatic hydrocarbons. Particularly high concentration of various chemical compounds was found in flavoured e-liquids. It seems distressing that each sample contained formaldehyde whose concentration oscillated between 0.02 and 10.09 mg/L and whose presence in flavoured e-liquids has been confirmed repeatedly. It was also the case with acetaldehyde, whose levels oscillated between 0.10 and 15.63mg/L [7]. Unfortunately, there are no norms or observational studies determining potential adverse effect of these substances on the mucous membrane of the mouth and the epithelium lining the airways.

Diethylene glycol, which is a compound of proven toxic effect on the cells of the respiratory and nervous systems, has also been found in e-liquids [8].

The research in toxicity of electronic cigarettes reached the point where in aerosols generated by electronic cigarettes, the concentration of benzaldehyde was measured. Automatic smoking simulator was used as a generator. The study included 145 available on the market e-liquids, and benzaldehyde was found in 108 samples. The highest concentration of benzaldehyde was detected in e-liquids with cherry flavour (5.129–141.2 μg/30 puffs) and they were significantly higher compared to other flavours ($p < 0.0001$) [9]. The presence of benzaldehyde, which absorbs well while inspiring its vapour, may lead to such suffering as sore throat and cough. Negative effect of acrolein on epithelial cells of the respiratory system was proved by Sun and his team. Its toxicity appears through the activation of macrophages to the production of reactive forms of oxygen and proinflammatory cytokines (TNF-α, IL-6, IL-12, IRF5) [10].

Using nematodes as an approved animal model, it was shown that e-liquids and vapour extracts increase oxidative stress leading to weaker growth of particular nematodes. Their reproductive capacity and vitality have been weakened too. It is believed that it was caused by propylene glycol, which is the most powerful inducer of the mentioned changes [11].

Other researchers confirm that consumption of e-cigarettes results in increased oxidative stress and resistance in the airways [12]. The use of e-cigarettes also leads to higher level of nitrogen oxide in exhaled air. However, there are no data comparing the concentration of nitrogen oxide in e-cigarette consumers and those smoking conventional cigarettes [13].

The tests conducted on mice showed that exposure to e-cigarette vapour results in increased level of IL-6 in bronchoalveolar lavage fluid, which is proinflammatory cytokine. This has not been observed in the mice from the control group. Human airway epithelial cell line H292 behaves similarly. The levels of IL-6 and IL-8 determined after 16 hours from exposure to e-cigarette aerosol were significantly higher, compared to the control group. Contrary to IL-6, in the case of IL-8, dose-depending effect was not observed. It seems crucial that concentration of IL-8 was higher in the group of flavoured e-liquids [14]. Controversy surrounding flavoured e-cigarette solutions is evidenced by other researches assessing cytotoxicity of e-liquids. The researchers discovered relation between observed cytotoxicity and the level of chemical substances used as flavourings [15]. Flavourless e-liquids, to date considered safe, were examined for release of various cytokines and chemokines. The conducted tests proved that it is not the case. For the first time it has been shown that exposure to e-cigarette vapour free of flavour results in the release of the following cytokines and chemokines: PDGF-BB, FGF, IL-8, IL-12, IL-17, GM-CSF, IP-10, MCP-1 and MIP-1β [16]. It has not been observed that short-term use of e-cigarettes leads to increased concentration of IL-2, TNF-α, EGF, whose growth was noticed directly after consumption of a regular cigarette [17]. The effect of long-term exposure to e-cigarette vapour is unknown. Direct comparison of cytotoxicity of smoke from regular cigarettes with e-cigarette vapour showed smaller cytotoxicity of the latter. But again, flavoured e-liquid was the most cytotoxic in the group. It was coffee flavoured solution [18]. In another study, which also evaluated cytotoxicity of various e-liquids, the most distinctive was that of cinnamon and cookies flavour [19]. Bipolarity of e-cigarettes was shown by Yan and D'Ruiz who examined the level of nicotine in serum, the contents of carbon monoxide in exhaled air and cardiovascular effects in 23 subjects, who were randomly assigned to the group consuming electronic cigarettes (5 different products) and to the group using classic Marlboro cigarettes. The obtained data revealed that carbon monoxide concentration in exhaled air is significantly lower in the group of people using e-cigarettes. Other data, such as level of nicotine in serum are not so convincing. It is worth mentioning that in different periods of time, nicotine level frequently exceeded the level noted in people smoking regular cigarettes [20]. It was also observed that during one-hour e-cigarette smoking session, when the subjects made on average 46 puffs, the concentration of nicotine measured in blood of the subjects increased since 5th minute of smoking and was the biggest when measured at the end of *ad libitium* session. Heart rate also increased in the 5th minute of observation and, similarly to nicotine, it persisted until the end of *ad libitium* session [21]. While comparing the level of cotinine (metabolite of nicotine) in serum of active users of e-cigarettes with the consumers of regular cigarettes, it was found to be similar in both groups (mean concentration of cotinine 60.6 vs 61.3 ng/mL). The cotinine level in passive smokers was comparable (2.4 vs 2.6 ng/mL). Yet these results are contradictory with those obtained by Van Staden. In the same study lung function was assessed and it was observed that active smoking of traditional cigarettes significantly reduced ($p < 0.001$) the value of FEV_1/ /FVC — by 7.2% on average. This fact has not been observed among passive smokers and e-cigarettes smokers [22]. Cotinine concentration in saliva of people using electronic nicotine delivery systems was similar to that found in individuals smoking regular cigarettes. Lower cotinine levels were discovered in subjects using nicotine replacement therapy (NRT) [23]. The important component of e-cigarettes is an electrode which heats up e-liquid. Vapour appears when voltage exceeds 3 V and it is enough to produce formaldehyde, glyoxal, acetaldehyde and acrolein. The relation between the composition of vapour and ingredients used to produce e-liquid was discovered [24]. The quantity of nicotine generated by e-cigarettes of various brands is not constant. During the analysis of 20 series at 15 puffs (it is considered that one series is equal to one cigarette), it was calculated that delivered dose of nicotine depending on the producer amounts from 0.5 to 15.4 mg (from 0.025 to 0.77 mg of nicotine per series). These values are lower than those observed during traditional cigarettes smoking, when it is considered that one cigarette delivers between 1.54 to 2.60 mg of nicotine [25]. However, it is worth mentioning that freedom to choose the place and time of consumption of e-cigarettes may impact the way and frequency of using thereof. Therefore, we believe that comparisons assuming the same model of both regular and e-cigarettes smoking should be treated carefully. It is possible that further research should go into finding the most frequent pattern of e-cigarettes smoking.

The impact of electronic cigarettes on the cardiovascular system

The authors of this paper encountered contradictory studies about the influence on the cardiovascular system. Some researches do not show any influence, others list effects that may be hazardous to health. In 2012 Czogala *et al.* [26] did not note that e-cigarette consumption significantly influenced blood pressure or heart rate.

Opposite conclusions were reached by Lippi *et al.* [27]. Their research has shown that using e-cigarettes on a regular basis results in increased blood pressure — in particular the diastolic one, tachycardia and chest pain.

More worrying are conclusions arrived at by Middlekauf *et al.* [28] who observed adverse effect of e-cigarettes on the autonomic nervous system. These results are different from those described above and include hypotonia, bradycardia and attacks of atrial fibrillation.

Interestingly, it has been shown that exposure to tobacco smoke in passive smokers in childhood and fetal development results in more frequent atrial fibrillation in adulthood [29]. Similar observations will be possibly made in the future, but for the time being, we have to bear in mind relatively short period of examination of e-cigarette consumers.

Another problem is the impact on diastolic function of the heart. Farsalinos *et al.* [30] did not observe the influence on diastolic function of the left ventricle, simultaneously showing that smoking one regular cigarette significantly hinders this function. However, the question could be explored whether the lack of immediate effect after the vaping session equals a complete lack of influence on diastolic function of the heart. It is possible that longer exposure would lead to similar conclusions.

Impact on smoking cessation

During 6 month-long observation, it has been shown that bigger proportion of e-cigarette consumers (7.3%) will not smoke traditional cigarettes, compared to the proportion of people using plasters containing nicotine (5.8%) or e-cigarettes with placebo (4.1%) [31]. However, smoking cessation through replacement of regular cigarettes for electronic cigarettes does not seem to be a real success. Particularly, given that there is no reliable data indicating advantages of such behaviour. Whereas negative effects of ENDS on health has been confirmed. Available literature reports more cases of replacement of regular cigarettes for the electronic ones, which, according to the authors of these studies, should be perceived as success - Caponetto *et al*. described among others the cases of smoking cessation consisting in the above mentioned substitution by individuals who repeatedly tried to stop smoking using other available methods and who succeeded only when they started to use e-cigarette [32]. Some people claim that e-cigarettes may be more attractive as far as smoking cessation is concerned as they may have less noticeable adverse effects, compared to nicotine replacement therapy, and they may become a kind of hobby [33].

However, there is no reliable data supporting the theory that alternative tobacco products (including e-cigarettes) are a useful tool to cease smoking [34]. It has been confirmed by the results of metaanalysis conducted by Kalkhoran and Glantz who have found that the use of e-cigarettes is related to reduced chance of smoking cessation. They have proved that among e-cigarette consumers who used e-cigarettes as the way to quit smoking, the proportion of those who succeeded was smaller by 28%, compared to the group not using e-cigarettes [35].

Thus, the question arises whether the change from addiction to cigarette smoking to dependence on other sources of nicotine, may be treated as form of addiction treatment. From the point of view of psychiatrics, systematic regular consumption of nicotine activates the mesolimbic dopaminergic pathway, giving a sense of pleasure. A sudden discontinuation of nicotine consumption, either in the form of a cigarette or another one, results in abstinence symptoms. The use of e-cigarette in this context has to be treated as a form of nicotine dependence that is listed in the classification of psychiatric diagnoses number ICD-10 F17.2. A real nicotine dependence consists of making the independent human reward effect of any form of nicotine.

It seems that irrefutable evidence of doubtful effectiveness of e-cigarettes as a useful tool of smoking cessation is the WHO report of 2014 showing insufficient evidence to consider electronic cigarettes a therapeutic option [36].

Infrequent adverse effects and legal situation

In 2013, FDA issued statement on adverse effects associated with the use of e-cigarettes. It was assumed that conventional cigarettes are responsible for 36 types of adverse effects, whereas the electronic ones for 47. The effects included among others: exacerbation of chronic heart failure, aspiration pneumonia, second-degree burns on the face (due to e-cigarette explosion), chest pain, tachycardia, choking of e-cigarette cartridge by infants, migraine headaches [37]. It is particularly dangerous when e-liquids are administered orally. For example a 5 ml cartridge of e-liquid with 20 mg/ml nicotine concentration contains 100 mg of nicotine. It is estimated that a lethal dose in adults is 30-60 mg, and in children 10 mg [38]. The possibility of deliberate use of e-liquids in order to achieve a specific result or even death causes grave concern. In 2013, in Great Britain, three cases of intentional use of liquid nicotine in order to commit suicide were reported [39]. In the Internet there are even instructions on how to commit suicide with the help of liquid nicotine [40]. The case of intravenous administration of e-liquid in order to commit suicide has been also reported [41].

Concerns about the use of e-cigarettes have been also voiced by the European Commission. Since May 2016, the market of e-liquids and cartridges for e-cigarettes is governed by the European Union directives (2001/83/EC; 93/42/EEC; 2014/40/EU). Taking into account many doubts associated with the use and wide availability of these products, it seems to be a crucial forward step in normalising the market of electronic cigarettes. There were attempts to assess the following aspects: information content on the label, the compliance of nicotine quantity with its declared contents, the presence of other components, the possibility of unintentional use by children. It has been shown that 40% of the examined popular e-liquids and e-cigarettes had not at all or out-of-date contact data of the supplier. 76.5% of the analysed products have not provided information about nicotine as an addictive substance. 53% of products have not informed about possible harmful effects on pregnant women and breastfeeding mothers. 33% of the analysed brands have not put on the packet information about toxicity of the contents. It is required in the case when the contents of nicotine exceeds 1% of the solution volume. A notice concerning the applied flavourings and colour additives has been generally limited to information that they are approved. There was no information on chemical substances used in the production process. Next to many discovered shortcomings, a good news is that only one tested product has not offered child-resistant fastening [42].

Conclusions

Electronic cigarettes are becoming more and more popular, among both the users of conventional tobacco products and those who to date has not used any nicotine delivery systems. It seems that literature concerning electronic cigarettes is extensive but it is not the case. There are no studies treating in an overall manner the problem of harmful influence of electronic cigarettes on health. There are single papers that gather many reports and which frequently are case reports. But even these works raise serious doubts as to safe use of e-cigarettes. It seems of vital importance that patients should be made aware that each method of nicotine delivery is harmful. Following the example of western European countries, nicotine dependent people should be referred to specialistic anti-smoking centres in order to face the problem with the help of an expert and not to the tobacco companies generating large profits from e-cigarettes market.

The authors do hope that the readers of this paper will join people combatting nicotinism, both its traditional and most modern variations.

Conflict of interest

The authors declare no conflict of interest.

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