

Electronic cigarette: a threat or an opportunity for public health? State of the art and future perspectives

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Abstract

The e-cigarette, also known as e-cig, represents an emerging issue of great concern for public health. The aim of the present report was to explore the scientific literature about the use of electronic cigarette (e-cig), with a particular reference to the features of "toxicological safety", "effectiveness in overcoming the addiction to smoking the traditional cigarette" and "necessary research agenda". The efficacy of e-cig for smoking cessation is uncertain: some authors found that it can be a valid support, but long-term cessation rate has not been assessed. Other studies evidenced that e-cig is often used not for quitting smoking but to avoid smoking ban for traditional cigarettes and, even, some researches evidenced that it appears to contribute to nicotine addiction. E-cig smoking seems to be less dangerous of conventional cigarettes, but its use is not risk-free. Besides, cases of accidental or intentional poisoning with liquid solutions of e-cig have been reported. Also, the smoke of e-cig decreases indoor air quality, releasing particulate matter and other toxics that can persist on surfaces for days and generating passive exposure. These phenomena are similar to environmental tobacco smoke produced by conventional smoking, that is the sum of second- and third-hand smoke. We propose to call them "environmental electronic smoke", "electronic-second-hand smoke" and "electronic-third-hand smoke", respectively. Uncertainties relating to e-cig features determined the sequence, in the short term, of warnings and regulations approved and then replaced. In conclusion, although in recent years many researches were performed, evidences is limited and there is a need to study in deep all these issues. *Clin Ter* 2015; 166(1):32-37. doi: 10.7417/CT.2015.1799

Key words: e-cig, electronic cigarette, regulation, smoking cessation, toxicological safety

Introduction

In recent years, a new phenomenon has emerged in the context of the field "tobacco smoking": the electronic cigarette, a device very similar to the traditional cigarette but without the burning of tobacco.

The e-cigarette, also known as e-cigarette or e-cig, is an integrated electric device, including a wide range of

products defined as personal vaporizers, advanced personal vaporizers or electronic nicotine delivery systems. These devices have different designs even if, usually, they are made with very similar appearance to traditional cigarette. E-cig are generally constituted by a stainless steel shell, a lithium ion battery assembly, a smart chip with program controlled circuits, and an atomization chamber. Besides e-cig presents a removable cartridge containing flavouring, a mixture of propylene glycol and other products obtained from an extraction of tobacco flavours and, in some cases, other aromas to the mixture such as: mint, strawberry, orange etc. Also, some removable cartridges contain nicotine at different concentrations together with flavor (1, 2).

The possibility to inhale nicotine as an alternative to tobacco smoke is one of the most important reasons of the popularity of e-cig: smokers may continue to "smoke" and inhale nicotine (the most responsible of tobacco dependence) avoiding to inhale the other toxic compounds of traditional smoke (3). Besides, e-cig has been also considered as a possible method for smoking cessation (4, 5).

But what is the scientific evidence about the e-cig? Despite the great number of scientific articles published in recent years (from 2009 to 2014), it is still not possible to define an "evidence-based risk profile" for the use of e-cig. Indeed, all the systematic reviews and meta-analyses published to date on this issue did not define practical conclusions, but they only suggested recommendations and the necessity to study in deep this problem. For these reasons, we considered proper to draw up a "state of the art" about all the emerged critical points on this topic. Thus, the aim of the present review report was to investigate literature data about the e-cig, with particular reference to the features "toxicological safety", "effectiveness in overcoming the addiction to smoking the traditional cigarette", "regulatory issues" and "necessary research agenda".

Interventions for tobacco smoking cessation: why?

Scientific evidences on adverse effects associated to smoking versus the high number of smokers

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Tobacco smoking is a well-known risk factor for human health, and it is associated with a great and increasing number of carcinogenic and non-carcinogenic effects (6). Indeed, the carcinogenicity of tobacco smoking was already evidenced many years ago, with the first scientific evidence of the association between cigarette smoking and lung cancer published in 1950 (7). These results represented the rationale of one of the most important research on the adverse effects determined from cigarette smoking: the British Doctors' Study, an epidemiological study designed by Richard Doll and Austin Bradford Hill, conducted from 1951 to 2001 on a very large cohort of British doctors (more than forty thousand subjects) that produced many of the current knowledge about the risks posed by smoking (8). A great number of studies have been performed on adverse effects derived from tobacco smoking, both for active and passive smokers and, over time, an increasing number of adverse effects and diseases have been linked to tobacco smoke (6).

Despite these strong scientific evidences, data relating to the adverse effects caused by smoking showed that this habit is still one of the most significant problems for public health worldwide. The World Health Organization (WHO) estimates that tobacco smoke is currently responsible for the death of approximately five million people globally each year, and many of these deaths occur prematurely. Moreover, future predictions are not encouraging: in the next two decades it is expected that the number of deaths caused by smoking will be greater than eight million (9). These figures do not surprise, considering that there are more than one billion smokers worldwide, and that about 10 million cigarettes are purchased every minute, with an equivalent of 15 billion cigarettes sold every day (10).

As regard to Italian smokers, data show that even in our country the smoking habit results in a significant problem: the National Institute of Health estimated that, in 2013, the prevalence of smoking in the Italian population was equal to 20.6%, with a percentage of males and females equal to 26.2 and 15.3%, respectively (11).

Given the adverse effects on human health caused by smoking and the high number of smokers, smoking cessation represents a global priority action for public health.

Smoking cessation: smoking habits versus nicotine addiction

"Giving up smoking is the easiest thing in the world. I know because I've done it thousands of times". The aphorism of Mark Twain can make you smile, but it represents a sad reality for smokers. Certainly smoking cessation is very difficult for smokers, especially due to physical and psychological addiction determined by tobacco products.

The current use of the term "smoking habits" should be recognized as improper in light of the fact that cigarette smoking and other forms of tobacco use are actually recognized as a behavior determined by nicotine addiction. Tobacco smoking, indeed, is a real illness, included in the list of mental and behavioural disorders due to psychoactive substance use in the 10th revision of the International Classification of Diseases ICD-X (12). Nicotine is a component of the tobacco products, it is vaporized together with the burning of tobacco, and it reaches the lungs through the aspiration of the smoke. After about 10-15 seconds from the aspiration

of smoke, nicotine enters the bloodstream and reaches the central nervous system, where it can interact with nicotinic cholinergic receptors. This interaction results in the release of several neurotransmitters, which produce the typical "rewarding" effects such as pleasure, excitement, relaxation, reduction of anxiety, etc. Thus, prolonged abstinence from nicotine and from all the effects of its intake is a major cause of failure of the attempt to quit smoking (3). In addition, together with physical abstinence from nicotine, smoking cessation involves the loss of the daily gesture of a smoker, which is also what justifies the definition of "smoking habits". This loss results in an additional factor for the failure of smoking cessation. For these reasons, drug therapies or nicotine replacement therapy associated with psychological support resulted the best interventions to help smokers who want to quit smoking (13-16).

Electronic cigarettes: history and epidemiological profile

Electronic cigarette was ideated by the Chinese pharmacist Hon Lik in 2000, with the intention of making the first cigarette containing nicotine but no tar. Later, in 2003, an ultrasound device that nebulized nicotine dissolved in a solution of propylene glycol was produced in China and, in 2006, this product was exported all over the world with a very remarkable success (17). The popularity of the e-cig in the smokers community has grown exponentially worldwide, becoming the leader product between the various alternatives to cigarette smoking (nicotine replacement therapy, other therapeutic approaches, etc). Even, in the Korean market, e-cig was introduced as a "healthy" alternative to cigarettes, and it was publicized as an effective device for smoking cessation (18). The success of this device is also highlighted by the great number of new commercial points that were opened worldwide with the unique purpose of selling e-cig.

A systematic review on awareness, use, reactions and beliefs about e-cig evidenced that the awareness and the use e-cig increased, respectively, from 16% to 58% and from 1% to 6% in very few years (2009-2011), with some differences according to studied countries (19).

In the United States, for example, the prevalence of adult vapers (user of e-cig) has doubled from 2010 to 2011 (2.1 - 3.3 and 6.2%, respectively) (20-23).

Likewise, the number of vapers has been gradually increased in Europe: a recent Eurobarometer survey indicates that 7% of Europeans tried e-cig (almost 30 million people) (24).

The phenomenon shows a similar trend in Italy: more than 45 million Italians know e-cig, 3.5 million tried it, and more than 600,000 subjects regularly used it in 2013 (25). However, after about six months (from the end of 2013 to the half of 2014), Italian situation about e-cig and vapers was reversed. A survey conducted by the National Institute of Health evidenced a decrease of the e-cig users from 4.2% to 1.6% adults (26), and most of the commercial points were closed. This phenomenon is very recent and, consequently, its explanation is not certain. The decrease in the use of e-cig is probably related to different factors, such as the uncertainty about its efficacy and safety, the new regulation

on e-cig, and the recommendations of caution in their use expressed by leading public health agencies (National Institute of Health, WHO, etc.). These topics will be discussed individually in the following paragraphs.

Electronic cigarettes: evidences on its effectiveness for smoking cessation

A very recent review on the effectiveness of e-cig as a method for smoking cessation can help to understand the actual scientific evidence about this issue. The review evaluated 6 clinical studies and the most significant results were that e-cigarettes significantly reduced the need of smoking, the number of cigarettes smoked every day, and the concentrations of exhaled carbon monoxide levels. Nevertheless, long-term cessation was not sustained at 6 months (27). Another recent systematic review on the same issue reported very similar results, highlighting that e-cig can help to decrease the number of cigarettes smoked and to reduce the withdrawal symptoms (28).

On the other hand, the results of further studies evidenced that:

- e-cig is not discouraging the use of conventional cigarettes among youths, but it seems to contribute to nicotine addiction (29-31);
- about 10% of e-cig vapers are also stable smokers of traditional cigarettes and present difficulty in achieving smoking cessation (32);
- e-cig is used by smokers not only as a method to reduce or quit smoking, but also to smoke in an indoor environment avoiding the smoking bans for enclosed environment, such as cinemas, restaurants, public transports, etc. (4, 5);
- smokers, especially young, do not seem motivated to quit smoking conventional cigarettes, but rather they are attracted by the novelty (33). It is well-known that young people has always been a segment of the population most involved in the use of new products and abuse of drug substances (34);
- even if e-cig is more commonly used by smokers, it is not limited to them; several researches estimated that the prevalence of experimentation of e-cig in never-smokers population ranged from 0.1 to 3.8% (35);
- e-cig is often perceived as a safer smoking alternative by smokers, including pregnant women; thus, since nicotine can determine fetal adverse effects, pregnant mothers that smoke e-cig could cause even greater fetal damage because women can use these devices more freely respect to traditional cigarettes during pregnancy (36, 37).

The efficacy of e-cig was compared to other nicotine replacement therapy; in particular, e-cig contains 16 mg of nicotine, used ad libitum, was compared with the patch containing 21 mg of nicotine, (one day) in a large sample of smokers. The results evidenced that, after six months, 7.3% of the subjects who used the e-cig and 5.8% of the individuals treated with the patch were completely abstinent. In addition, 57% of e-cig group and 41% of the patch group reduced by at least half the consumption of tobacco cigarettes. Consequently, according to this study, e-cig may be considered slightly more effective than patch in smoking cessation (38).

Another recent study investigated the reasons associated with the use of e-cig for cessation help versus the use of other proven cessation aids. E-cig resulted a valid alternative “smoking” experience for smokers that wish to quit smoking not because of concerns about health, but for the immediate and undesirable consequences of tobacco smoking (smell, ash, litter, etc). Consequently, e-cig may be efficacy to reduce tobacco exposure among smokers who do not want to quit smoking for intrinsic motivation (39).

Several limitations emerged from these studies: small or unrepresentative population samples, a high number of losses during follow-up, the short duration of the follow-up. Researchers should make efforts to overcome these limitations, in order to obtain more robust scientific evidences on effectiveness of e-cig to quit smoking.

Electronic cigarettes: evidences on toxicological safety

In the last years studies on the toxicological safety of e-cig are increased, as demonstrated by the growing number of scientific papers published on this issue. A simple literature search on PubMed using the key words “e-cigarette” and “safety” involves the finding of 88 scientific articles, the first published in 2009 and more than half published in 2014.

The majority of these papers are critical or systematic reviews regarding toxicological data presented in specific technical reports produced for single e-cigs (40-44). However, given the wide range of devices, cartridges and flavoring, it is difficult to draw general conclusions applicable to the entire range of products. Besides, the production and the import/export of the products are not well controlled and, consequently, it is difficult to regulate these products. In addition, at today there are no standardized methodologies for generating and testing the aerosol generated by e-cig as those used for traditional cigarettes. Moreover, even in the case of a toxicological evaluation of the compounds content in e-cig, it is difficult to provide a valid human exposure assessment and a human risk evaluation because the mode of use of e-cig is very individual. Also, considering the recent introduction of e-cig, long-term studies to evaluate the effects of e-cig after chronic exposure are not still performed. Finally, notice that many studies are financed by e-cig producers and, thus, possible conflict of interest should be considered.

Traditionally, the attention of the researches evaluating the safety of e-cigs has been focused on the possible risks on human health derived from nicotine, flavours and propylene glycol (the major ingredient of e-cig). However, very recently some authors demonstrated possible additional risks related to the release of a not negligible amount of some heavy metals from the devices itself (45), and the presence of diacetyl and acetyl propionyl in the sweet-flavoured e-cigs liquids. These compounds are approved for food use but, at the same time, are associated with respiratory diseases when inhaled (46).

Some answers about the safety of e-cigs were given by experts in the field (40-44): they confirmed the lower toxicity of e-cigs when compared to the conventional tobacco products. However, all authors agree that available data are too limited to draw strong conclusions.

Electronic cigarettes: evidences on other possible harms

In addition to the toxicological harms linked to the smoking of e-cig, other additional risks for human health were recently highlighted.

The liquid mixture used for refilling the cartridge may pose several risks of exposure. The National Poison Control Centre in Milan (Italy), for example, handled 172 cases of exposures to liquid derived from different exposure scenarios. Some cases occurred in children < 5 years old, due to unintentional ingestion or dermal/mucosal contact as a result of uncontrolled access to mixtures. Other cases were related to the exposure (by ingestion, inhalation, or dermal/mucosal contact) to liquid accidentally leaked during the use of e-cig. Further accidental exposures derived from the misapplication of the liquid solution for e-cig instead of drugs to be administered in drops. Few cases, finally, were related to intentional exposures for suicidal purpose or to the abuse of e-cig (47).

Another relevant issue related to e-cig is represented by its use in indoor environments, that determines a decrease of air quality due to the emission of particulate matter (PM) and other pollutants and passive smoking via inhalation of non-vapers (48). Pellegrino et al. (49) found that the smoke of e-cig increases ultrafine PM of the indoor environments, slightly exceeding WHO air quality guidelines (50), even if these levels resulted 15 times lower than emissions of traditional cigarettes (51). Besides, e-cig smoking releases several toxicants such as nicotine and, in some cases, tobacco-specific nitrosamines and other compounds that may persist for many days on surfaces (52-54).

Thus, passive smoking of e-cig emissions consists both of an exposure concurrent with e-cig use and an exposure that occurs after e-cig use. This phenomenon is well known for conventional cigarettes, and is called Environmental Tobacco Smoke (ETS). ETS is a mixture of chemical compounds released from the smouldering of tobacco products. Notice that ETS is an important threat for the health of the non-smokers (6, 55), especially for children. In particular, early exposure to ETS (first years of life) may determine the development of diseases in adult age, such as leukaemia, other cancers, chronic respiratory and cardiovascular diseases etc. (56-58). ETS is a combination of second- and third-hand smoke. Secondhand smoke (SHS) is the inhalation of chemicals due to the smoke exhaled by a smoker together with the smoke from a burning cigarette, while third-hand smoke (THS) is the combination of tobacco smoke pollutants that persist, long after the extinguish of the cigarette, on clothing and hair of smokers and on surfaces, furnishings, and dust of indoor environments. Thus, SHS exposure is the unintentional inhalation of smoke that occurs close to people smoking, while THS exposure consists of unintentional intake of smoke that occurs in indoor environments in the absence of concurrent smoking (59, 60).

In the same way, the use of e-cig in indoor environments determines a type of passive smoking that we propose to call Environmental Electronic Smoke (EES). EES is the sum of electronic SHS (e-SHS) and electronic THS (e-THS). This issue represents a critical research agenda and should be studied in deep.

Electronic cigarettes: recommendations and regulations

When e-cig was introduced in trade, it was not regulated. Then, the exponential increase in their use asked for an official opinion of public health experts about its efficacy for smoking cessation and its safety. For this reason, in September 2008, WHO declared that e-cig can not be considered as a method to quit smoking, due to inadequate researches demonstrating its effectiveness. Besides, WHO suggested caution in its use, until the possible risks related to some of its ingredients and constituents is better evaluated (61, 62). Successively, in 2014, WHO expressed a new opinion on e-cig, calling for local regulations that inhibit the promotion of e-cigs and the use of unproved health claims, and ban their use indoors (63, 64).

The recommendations of WHO on e-cig came under pressure from both pro-e-cig and contra-e-cig supporters. In contrast to the conventional tobacco debate with the agreement of the entire scientific community, the actual debate on e-cig finds public health scientists on both sides, and both expressed their opinion to WHO: On 29 May 2014, 53 scientists signed a "pro" letter sent to WHO, three weeks later, 129 researchers signed a "contra" letter sent in reaction to the first one (65).

The "pro" letter referred to e-cig as "an innovation with potential to save many millions of lives". The signatories of this letter highlighted that after one decade of rapid raise of e-cig and an increasing number of researches, there is still a lack of evidence of any harms associated with their use; consequently, if any risk related to the use of e-cig is ever found, it should not be as common as lung cancer related to tobacco smoking. Besides, even the strongest antagonists to e-cig do not predict that the risk in the use of smokeless tobacco or e-cig by smokers may be comparable to the hazards related to traditional cigarettes. In addition the "pro" e-cig scientists considered the risk of the use of e-cig by young non-smokers as a theoretically possible threat, but not yet been supported by any study (66). The reply "contra" letter highlights the scientific evidences emerged on the health risks related to the nicotine, the vapour and some heavy metals contained in e-cig, and the lack of evidence about the effectiveness of e-cig as a method for smoking cessation; thus, the use of e-cigs must be considered with the proper caution and it must be subject to appropriate regulation (67).

At today, regulation about e-cig is still not harmonized. The European Commission in 2012, for example, included e-cigs in the proposal for a novel Tobacco Product Directive, but considering only the products containing more than 2 mg nicotine per unit or 4 mg nicotine/ml liquid. Then, at the end of 2013, the European Parliament amended a proposal that dismissed any upper limit with regard to the nicotine contents in these products, with the exception of products containing more than 30 mg nicotine/ml liquid. Afterward, on February 2014, the negotiations between European Council, Commission, and Parliament, led to the approval of a proposal that set at 20 mg/ml, or 200 mg per 10 ml refill bottle the upper limit for nicotine content (68).

As regard to the Italian legislation on e-cig, regulations are changed widely in few months. In June 2013, a specific law banned the use of e-cig from public places, but in Sep-

tember 2013 a new decree permitted the use of e-cig both indoors and outdoors, excluding schools. After 3 months, an additional act introduced the ban for e-cig in the indoor environments together with a maxi-taxation for e-cig sale (an increase of 200%), that was withdrawn very soon after its approval (69).

Conclusions

Considering all the arguments discussed in the present report, we can highlight some bullet points:

1. there is a strong need for harmonizing the methods for assessing the risks related to the use of e-cig, both for smokers and those exposed to EES;
2. the human health risk assessment process and the evaluation of the safety both of e-cig device and liquid solutions must be performed before the introduction in trade of these products;
3. there is a need for the evaluation of the effectiveness of these devices as methods for smoking cessation;
4. the sale of e-cigs, especially those containing nicotine, must be treated as the other devices containing potential toxic compounds or nicotine replacement therapies; a valid possibility is the pharmacy. In fact pharmacists have the right competence and contact with patients/customers for guide their choices on e-cigs, and follow them over time;
5. there is a need for clear and harmonized regulations on e-cigs both for protecting vapers and people exposed to EES;
6. advertising and information on e-cig, sometimes positive and sometimes negative, has created much confusion in general population; there is a need for an appropriate risk communication process, managed by official public health operators, to avoid misunderstandings on this new health issue.

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