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ORIGINAL ARTICLE

E-cigarettes and Associated Medical Burden: For Better and For Worse

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Abstract: *The harmful effects of smoking cigarettes on human health are well documented; thus various smoking cessation methods have been assessed and new options are currently under development to provide a "better' alternative to the "worse" one, namely smoking. However, no ideal method of ending or replacing conventional smoking has been developed so far, and actually, none of them has been proven entirely effective or safe. The laxity, or rather the absence of regulations in the first decade of existence of electronic nicotine delivery systems (ENDS) allowed their use with prohibited substances instead of nicotine or other substances with detrimental effect, with the emergence of a severe syndrome - e-cigarette and vaping-associated lung injury (EVALI), whose treatment required even lung transplantation in young people without any prior underlying lung disease. This narrative review aims to provide a brief overview of concerns about medical issues associated with e-cigarette use, particularly cardiovascular and respiratory panels. We organized the data in several micro-sections varying from practical aspects of understanding ENDS to clinical issues. To combat tobacco addiction, electronic cigarettes are increasingly widely accepted. A global regulatory framework is required to prevent the emergence of an illicit e-cigarette business with detrimental impacts on health.*

Keywords: *e-cigarettes, EVALI, smoking, lung, respiratory, cardiovascular, pulmonary, electronic cigarette, ENDS*

INTRODUCTION

The harmful effects of smoking cigarettes on human health are well documented – from a simple addiction to a significant risk factor for lung cancer. Recent data places smoking as the leading risk factor for lung cancer, the most common type of cancer in the world, which is responsible for more deaths annually. The detrimental effects on cardiovascular, pulmonary, and reproductive systems are also considerable. Therefore, various smoking cessation methods have been assessed – behavioral, pharmacological, and combined methods and new options are currently under development to provide a "better' alternative to the "worse" one, namely smoking. However, no ideal method of ending or replacing conventional smoking has been developed so far, and actually, none of them has been proven entirely effective or safe [1-4].

Therefore, that's why there has been a continuous struggle to find smoking methods that do not involve burning nicotine, with heat-not-burn devices being the best, safest alternative, and an efficient smoking cessation tool. However, in the last decade, considerable evidence has been presented showing an induction of addiction in adolescents and smoking initiation in those who have never smoked both adolescents and adults. On the other hand, the laxity, or rather the absence of regulations in the first decade of existence of electronic nicotine delivery systems (ENDS) allowed their use with prohibited substances instead of nicotine or other substances with detrimental effects, with the emergence of a severe syndrome – e-cigarette and vaping-associated lung injury (EVALI), whose treatment required even lung transplantation in young people without any underlying lung disease. After the emergence of EVALI, which unfortunately has been overshadowed by the coronavirus disease-19 (COVID-19)

pandemic, an increasing number of countries around the world have imposed regulations on the use of ENDS, which are now considered medical devices in some countries and are banned in others. Since it has been determined that the numerous flavors available to users have led to an increase in their use by adolescents, current legislation in most countries that have regulations limits the number and type of flavors available [5-8].

Aim

We aim to provide a brief overview of concern for medical issues associated with e-cigarette use.

METHODS

This is a narrative review of literature with no timeline restriction of research. We organized the data in several micro-sections varying from practical aspects of understanding ENDS to clinical issues.

ENDS – electronic nicotine delivery systems

ENDS include various devices, such as electronic cigarettes, e-hookahs, advanced personal vaporizers, and cig-a-likes. Currently, there are two main types of heat-not-burn products – tobacco heating devices and electronic cigarettes (four generations). From its first release in China in 2003 until today, the e-cigarette has undergone numerous improvements, with the current generation allowing a complex control of the device with significantly improved user safety. Electronic cigarettes are composed of an energy source (a rechargeable battery available from the second generation), a heating device - an atomizer, responsible for the generation of aerosols, a flow generator, a refillable (available from second generation) cartridge for e-liquid (water, propylene glycol, nicotine, flavors, and glycerol) and a mouthpiece. The third generation of e-cigarettes allows resistance and power adjustment while the fourth generation offers the possibility of temperature control (generally temperatures range from 40-65 Celsius), allowing for the modulation of the oropharyngeal experience [9-13].

It has been observed that by increasing the heating temperature, the aerosol generation rate also increases, and the aerosol particle size is modified as well (staying in the 100-600 nm range), with a potential impact on aerosol toxicity. Tobacco heating devices consist of a holder, an accumulator, and a nicotine heating unit (blade or induction heat technology) with aerosol generation. The differences between tobacco heat devices and e-cigarettes consist of user experience, the first one having a different operating time (6 minutes and a maximum of 14 puffs) and the temperature at which it operates (conventional smoking requires 200-600 Celsius). Nicotine is present in the tobacco that is used in the device. Also, not all e-cigarette devices use e-liquid with nicotine [14-19].

ENDS chemical compounds

E-liquid compounds include solvents (humectants or stabilizing agents), nicotine, cannabinoids, metals (in both the nicotine extract and the device constituents – nickel, manganese, copper, iron, arsenic, and lead), and flavors. The harmful effects of smoking are due to the inhalation of toxic products in cigarette smoke, generated by the combustion and pyrolysis of nicotine. Smoke from regular cigarettes contains more than 7000 different substances, including at least 70 carcinogens [20-24].

Unfiltered cigarette smoke is an aerosol with more than 400-500 gaseous components (nitrogen, oxygen, carbon monoxide and carbon dioxide, water, hydrogen, ammonia, argon, nitric oxide, hydrogen cyanide, hydrogen sulfide, methane, volatile alkenes, volatile alkenes, aromatic hydrocarbons - benzene, toluene, styrene, acids - formic acid, acetic acid, propionic acid, aldehyde - formaldehyde, acetaldehyde, acrolein, acetone, methanol, furan, pyridine, methylamine, etc.) as well as over 3500 other particulate constituents (nicotine, nornicotine, anatabine, anabazine, non-volatile hydrocarbons, carcinogenic polynuclear aromatic hydrocarbons, phenols, phthalates, polyphenols, acids – palmitic, stearic, oleic, linoleic, linolenic, lactic, indoles, quinolones, aromatic amines, nitrosamines and glycerol). In addition to these, various flavorings, pesticides, and metals are also present. Cigarette smoke contains 72 carcinogens and at least six compounds that harm reproduction [25-29].

Because they inhale both mainstream and sidestream smoke, passive smokers are more exposed to these dangerous substances than regular smokers. The amount of nicotine delivered by the e-cig is the result of several factors – smoking pattern (experienced versus inexperienced), aerosol characteristics (pH, particle size), pharmacokinetic and pharmacodynamics features, the site of absorption (oral or pulmonary), and of course the nicotine level in the e-liquid. The new generations of e-cigarettes deliver more aerosols and consequently higher amounts of nicotine, as demonstrated by their serum levels. The amount of nicotine in traditional cigarettes ranges between 10-15 mg nicotine/cigarette, of which 1-2 mg nicotine/cigarette is systemically absorbed, compared to 0-36 mg/mL liquid in electronic cigarettes [30-35].

E-liquid includes propylene glycol, vegetable glycerine, nicotine, and flavors. The e-cig structure includes absorbent materials in the atomizer (silicon, organic cotton, rayon fibers, stainless steel mesh, bamboo yar), as well as heating coils

manufactured from different iron, chrome, aluminum, or nickel alloys. The usual heating temperature in early generation ENDS ranged from 45 to 60 degrees, but in new generations that allow the user to adjust the temperature, it can reach over 200 Celsius, resulting in the release of potentially harmful carbonyl products, such as acrolein in increased quantities at voltages above 3.3 V [36-39].

The most commonly encountered flavorings in e-cigarettes are diacetyl, acetoin (buttery flavor), benzaldehyde (almond/ cherry aroma), cinnamaldehyde (cinnamon aroma), cresol (leather aroma), eugenol (clove aroma) or isoamyl acetate (banana flavor). The products resulting from the conversion of liquid into aerosol can vary, the temperature obtained by heating in e-cigs not being uniform and depending on several factors – the volatilization rate, the effectiveness of aerosol absorption, product design, and battery voltage. Thus, by converting solvents, formaldehyde, acetaldehyde, acrolein, methyl glyoxal, and glyoxal are obtained, and from vitamin E, ketene, benzene, and alkene are generated [33-39].

Cardiovascular effects

As a result of nicotine absorption, there is a release of catecholamines with a secondary increase in heart rate, blood pressure, and heart contractility, concomitant with reduced coronary vascular flow and increased musculoskeletal flow. The decreased risk of cardiovascular disease has been demonstrated in both in vitro and in vivo studies. It has been shown a reduction in monocyte cell adhesion to endothelial cells, a reduction in platelet activation markers (thromboxane B2), oxidative stress markers (prostaglandin F2 alpha), and C-reactive protein and cholesterol [37-40].

The currently available studies have assessed both short-term and medium to long-term effects (years). Heart rate and blood pressure abnormalities have been shown to vary according to the smoking status of e-cigarette or former conventional tobacco smokers. Thus, in short-term use of e-cigarettes with or without nicotine, an increase in heart rate and blood pressure was observed, whereas in chronic smokers the data are not conclusive. In e-cig smokers, an increase in arterial pressure was found only for short-term users. In contrast to conventional cigarette smokers converted to e-cigarettes, the switch to ENDS reportedly promotes a reduction in cardiovascular risk and BP [41-45].

Respiratory system effects

Studies have consistently identified a significant association between using electronic cigarettes and respiratory disorders. At the pulmonary level nicotine acts by activating nicotinic receptors for acetylcholine resulting in bronchoconstriction by action on bronchial smooth muscle. Epigenetic changes resulting in reduced PPAR-gamma (mesenchymal peroxisome proliferator-activated receptor gamma) receptor expression results in an asthmatic phenotype. Lung nicotine levels are more than 200 times the systemic peak in both conventional smokers and vapers [46-48].

Propylene glycol and vegetable glycerine are used as humectants, but repeated inhalation is not associated with significant changes in lung function if the exposure is limited. On the other hand, the new generations of devices, which can reach temperatures above 300 Celsius, can generate toxic carbonyl volatile compounds – formaldehyde and acetaldehyde (at temperatures above 215 Celsius) and acrolein at temperatures above 270 Celsius, two compounds that are associated with exacerbation of bronchial asthma. Diacetyl (2,3 butanedione) a butter flavoring is known to induce irreversible acute bronchiolitis obliterans (long popcorn). Other flavorings such as cinnamaldehyde are known irritants for asthma and benzaldehyde is an irritant for the mucous membranes of the respiratory tract. Yet, benzaldehyde higher levels provided by newer generation ENDS were proven to suppress allergic inflammation in a murine model by decreasing the number of inflammatory cells in lung and nasal tissues [49-53].

Destructive effects on respiratory epithelial cells have been demonstrated in several in vitro studies, as well as on nasal epithelial cells [49-53]. In vivo research has shown reduced lung cancer risk in ENDS users [54-56]. Increased oxidative stress and mitochondrial dysfunction have also been demonstrated in in vivo studies [57-60].

Shortly before the COVID-19 pandemic, a new outbreak occurred in ENDS users- EVALI, with more than 2500 cases reported in the US over 5 months [61-72]. The predominant symptomatology was respiratory – dyspnea, cough, and chest pain, associated also digestive symptoms and fever. Most cases were caused by exposure to tetrahydrocannabinol while the remainder by exposure to vitamin E acetate which was used as a thickening agent. The latter is thought to alter the structure of the surfactant and by heating may generate keten, a toxic compound [73-77]. The introduction of regulations on ENDS status has led to a dramatic decrease in EVALI cases.

DISCUSSION

Apart from the mentioned inflammatory issues and the cardiovascular/respiratory associated entities related to the use of e-cigarettes, other medical consequences have been identified, yet, with various levels of statistical significance and some require further exploration to adequately assess their clinical impact.

For instance, while most studies have focused on pulmonary

and cardiovascular effects, smoking is a well-known risk factor for oral cancer.

Current data shows a similar effect of e-cigarettes when compared to traditional tobacco smoking in terms of oxidative stress, wound healing arrest, promotion of a pro-inflammatory environment by increased pro-inflammatory cytokines, and incidence of periodontal disease, caries, and edentations.

However, the few available data on the carcinogenic effect of e-cigarette use have not led to any relevant practical conclusions, as they did not have a well-defined duration of exposure that enabled an objective risk assessment [78-84]. In addition to the direct effects on the user's health, environmental effects are described, which are attributed to the combination of compounds in mainstream and sidestream smoke.

Finally, as mentioned the most dramatic consequence in relationship with e-cigarette use is EVALI which particularly affects young individuals. While severe COVID-19 forms of infection might mimic an episode of EVALI, during pandemic years a growing number of hospitalizations for this syndrome had been registered.

The medical community increased the level of awareness concerning EVALI and recently various public health resources and scientific papers have been released to address this particular aspect [85-88].

CONCLUSIONS

Although ENDS are promoted as a safe alternative to smoking tobacco, it has been shown that adolescents who use them are more likely to start smoking tobacco again or start smoking it for the first time. Smoking is a significant global public health issue. The methods for quitting smoking have changed over time, but none have achieved perfect success. To combat tobacco addiction, electronic cigarettes are increasingly widely accepted. A global regulatory framework is required to prevent the emergence of an illicit e-cigarette business with detrimental impacts on health.

Conflicts of interest and sources of funding

The authors declare no conflict of interest.

Authors' contribution

Conceptualization, C.N., A.-P.C., O.-C.S., A.C., A.-I.T, A.-M.G., and M.C.; methodology, C.N., A.-P.C., A.C., A.-I.T, A.-M.G., and M.C.; software, C.N., A.-P.C., O.-C.S., A.-M.G., and M.C.; validation, C.N., A.-P.C., O.-C.S., A.C., A.-M.G., and M.C.; formal analysis, C.N., A.-P.C., O.-C.S., A.C., A.-I.T, A.-M.G., and M.C.; investigation, C.N., A.-P.C., A.-M.G., and M.C.; resources, C.N., A.-P.C., O.-C.S., A.C., and M.C.; data curation, C.N., A.-P.C., and M.C.; writing—original draft preparation, C.N., and A.-P.C.; writing—review and editing, C.N., A.-P.C., and M.C.; visualization, C.N., A.-P.C., O.-C.S., A.C., A.-I.T, A.-M.G., and M.C.; supervision, C.N., A.-P.C., and M.C.; project administration, C.N., A.-P.C., O.-C.S., A.C., A.-I.T, A.-M.G., and M.C.; funding acquisition, C.N, and M.C.. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

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