E-cigarettes and youth: a major Public Health concern

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Abstract

The use of electronic cigarettes (e-cigarette) and vaping devices started as a potential aid for cessation and reducing the harmful consequences of cigarette smoking, mainly in the adult population. Today e-cigarette use is highly increasing in vulnerable populations, especially young and pregnant women, due to the misconception of its harmless use. Despite the growing acknowledgment in e-cigarette as a potential harmful device, and due to mixed information found concerning its beneficial aid for smokers, along with an insufficient clinical study done in human models, it is important to further evaluate the possible benefits and risks of non-combusting, vaping nicotine or non-nicotine delivery devices. In this review we tried to summarize the latest updated information found in the literature, concentrating mainly in the variety of adverse effects of e-cigarette use and its contribution for recent and future health concerns.

Introduction

Tobacco smoke undoubtedly remains world's leading cause of preventable disease[1]. Over the last decade, reducing cigarette consumption has become a Public Health goal, therefore prevention campaigns intensified and restrictions on their marketing and access escalated[2].

Electronic cigarettes (also known as E-cigs, Electronic Nicotine Delivery Systems-ENDS, vaping device or e-vaporizers) are an electronic device that can vary in size and shape, consisting of a battery, an electrical heater and a liquid, which is aerosolized to be inhaled. Liquid composition can include nicotine, a solvent and an utmost variety of flavorants[3]. Taking shape as a smoking cessation strategy or – in actual fact – as a legal alternative where conventional smoking was prohibited, e-cigarettes, invented by Hon Lik (a Chinese pharmacist), were patented in 2003. However, only in 2007 they became commercially available in USA and Europe[4].

In contrast with a consistent decline in smoking prevalence among youth[5], over the past few years electronic cigarettes have rapidly gained popularity to the point of becoming the most common tobacco product in this age group[6]. Their social acceptance, together with their widespread availability, contributed to drastically increase primary use by adolescents and second-hand exposure in children, outlining the need for an assessment of their health effects in these categories[7].

In 2018, the National Youth Tobacco Survey reported that 20.8% of high school students and 4.9% of middle school students currently used e-cigarettes[8]. Since the introduction of pod-based devices, vaping prevalence has tremendously increased, reaching 28% in 2019[9] and even 40.5% among 12th graders[10]. In Great Britain, during 2020 16.4% of 11–18-year-old students had tried (at least once) e-cigs, compared to 15.4% in 2019 and to 12.7% in 2015. Also current use increased since 2015 from 2.4% to 4.8% [11]. Prevalence of current e-cigarette smokers in Italy doubled from 2014 (8%) to 2018 (18%), whereas the number of ever smokers has

risen by 60% (from 28% to 44%)[12]. According to forecasts, e-cigarettes sales will surpass those of traditional tobacco by 2023[13].

Marketing has certainly played a major role in vaping prevalence inflection among children and adolescents. E-cigarettes can be purchased in vape shops, tobacco vendors, gas stations, groceries, pharmacies and even online[14]. The manufacturing companies, often owned by tobacco firms, address their products to youth by promoting appealing flavours and using multiple communication channels: television advertisings; targeted advertisements at the point of sale; web sites and social media; celebrity partnerships; free samples at youth-oriented events[15–17]. In 2016, 78.2% of middle and high school students have been exposed to e-cigarette advertisements from at least 1 source and increasing exposure seemed associated with higher odds of use[17]. Social media are easily accessible by teenagers and convey the use of e-cigarettes as socially acceptable[18]; despite ENDS being born as a smoking cessation strategy, less than 1% of twitter posts concerning vaping are related to smoke cessation[19]. Apparently, only 8% of adolescents take up e-smoking as a nicotine replacement strategy[20] whereas the most common reasons underlying vaping experimentation in pediatric population are: curiosity, social influence, availability at low cost, enjoyable flavors, ease of concealment[21–23]. Sustained use is then encouraged by misperceptions about safety, nicotine content and social prevalence[21,24–26].

A cross-sectional analysis pointed out that positive expectancies regarding e-cigarette use (e.g. gaining respect of peers and chances of being liked by partners, reducing stress, enjoying throat sensation) are related with a greater prevalence of current use[27]. Users exhibit the lowest perceptions of harm and more positive attitudes towards e-cigarettes when compared with non-users[28]. Adolescents perceptions – which affect their decision-making process – are generally biased in the direction of their own experience, a phenomenon referred to as "false consensus effect"[29]: for instance, teens tend to overestimate actual smoking rate among peers[30], therefore they may be more prone to develop such addiction. In this regard, Gorukanti et al.[28] administered 9th and 12th graders from California an online survey to investigate their attitudes towards e-cigarettes and whether they differ by past use. Findings showed that prevalence of both e-cigarette and cigarette use among parents, siblings, and close friends was higher in adolescents who have ever used an e-cigarette. At the same time, vapers believed more peers and relatives smoke e-cigarettes than do non-users. A variable – but worrying – percentage of participants agreed that smoke from e-cigs was water, that they do not contain tobacco or tar and that vaping felt cleaner and safer than smoking. Ever cigs or e-cigs users were more likely to agree about. Nonusers, instead, were more prone to consider e-cigarette vapor harmful to children. Participants were more open to e-cigs use both indoor and outdoor, compared to traditional cigarettes.

Technical specifications and device evolvement

E-cigarettes different models share a basic operating mode. The mouthpiece allows the vaper to draw air, whose flow activates a sensor, causing the heating of a filament inside the atomizer. A capillary action brings the liquid to the filament. The warmed filament vaporizes the fluid; then, the condensation of the produced gas with atmospheric water generates an inhalable aerosol. Products lacking the air-flow sensor are provided with a button whose pressure closes a circuit that activates the battery[31].

Throughout the years, e-cigarettes design and technical features evolved, providing the market with updated products meeting consumers' different demands. First generation ECs, usually referred to as cig-a-likes, have been conceived to resemble the design and feeling of traditional cigarettes. They are equipped with low voltage batteries, available in different versions: the 3-piece style, composed of independent atomizing unit, battery, and fluid reservoir; the 2-piece style, with the battery being the only separable element; the 1-piece disposable, to be discarded after one use. Since the fragile atomizers can be easily damaged, variations in performance aren't unlikely[32,33]. In second generation ECs, known as "clearomizers", larger batteries of variable voltage are provided with a removable atomizing unit enclosed in a shell which is screwed into the fluid reservoir and the battery. Their larger fluid reservoirs are fillable[34–36]. Using a third generation EC ("mods"), in which the reservoirs disassemble, the consumer can regulate battery voltage and power. The atomizing units exists in three versions (various styled, replaceable dripping, sub-ohm). Despite some metal components being absent, the overall amount of metal is greater. The concurrent increase in battery

power makes third generation products able to release higher concentrations of metals into the aerosol. Furthermore, the presence of two filaments in some atomizers enhances heat distribution, resulting in a more abundant production of aerosol[37]. For the replaceable dripping atomizers, vapers build their own coils and drip the fluid directly onto them; otherwise a fluid thank encases the atomizer[37,38].

E-cigarettes modernisation process helped contain health implications. In early models, tin solder joints tied the filament to a thicker wire. These joints could be friable, eventually releasing tin in aerosols, a flaw remedied by coating the thick wire with silver, using stable tin solder joints outside of the atomizer, or joining wires by clamping or brazing rather than soldering. The thick wire, made of nickel or copper coated with either tin (associated with stannosis and pneumoconiosis[39]) or silver, was not included in second generation products and later[40]. By removing the silicon sheath from second and third generation products, its presence in aerosols drastically decreased[41]. Nonetheless, the empowerment in 2nd and 3rd generation batteries, accompanied by the increase in atomizer size and mass of metal, allowed to generate larger amounts of aerosol[37], resulting at the same time in a greater transfer of particles, metals, toxicants[35,36]. Furthermore, as voltage/power ratio increased, new potentially toxic by-products could emerge from the liquid[41]. Likewise, in larger reservoirs such as those of second and third generation ECs, fluid stagnation could enrich aerosols with additional toxicants through repeated use[36].

Fourth generation ECs, referred to as pod mod devices and equipped with fix voltage batteries, have become popular among teenagers as a socially acceptable alternative to conventional cigarettes due to their stylish design (e.g. USB or teardrop shape), wide selection of flavours and user-friendly functions[42,43]. Their likeness to an USB memory stick allows them to be discretely used in no smoking areas and easily concealed from parents, contributing to a new widespread phenomenon, known as "stealth vaping"[19,44,45]. A distinctive feature of fourth generations devices is the use of nicotine in its protonated form, which reduces the irritating effect on throat mucosa while increasing the amount of nicotine delivered in aerosols[46].

The heterogeneity outlined above complicates research on potential health effects, since the variability in design and technical features prevents us from discussing e-cigarettes as a single device. For instance, power output affects yield and aerosols content: in order to resemble cigarettes, closed systems are provided with lower-voltage batteries and/or higher resistance heating elements[47], whose thermal breakdown can produce toxicants normally absent in traditional cigarettes[48]. Devices allowing the user to drip liquid onto the heating element can generate an amount of aldehyde equal or higher than tobacco cigarettes, due to the high temperatures reached[49]. Furthermore, besides type and age of the device, e-cigarette health impact depends on multiple variables including ambient factors (e.g. climate conditions, room size and density of people) and user's habits (puff length and frequency)[50].

Content

Aerosol composition is affected even by the solvent employed, being vegetable glycerin (VG), propylene glycol (PG) and their mixture the most widely used. They can also influence particle-size distribution, therefore the region of deposition in the respiratory system[51]. A higher percentage of propylene glycol seems enhancing flavour and strengthening the so-called "throat hit", whereas a higher percentage of vegetable glycerine may increase vapor production[52]. Vegetable glycerine exposure has been associated with irritation of eyes, lungs, and oesophagus mucosa[53]. Likewise, its higher boiling point requires the heating element to reach higher temperatures, resulting in a greater risk of toxicants emission[49]. The highest yield of aldehydes occurs in devices containing propylene glycol[54], also related to upper respiratory infection-like symptoms[55]. It has been documented that a PG/VG mixture produces more ROS than each component alone[56] .

A vast amount of studies aimed at characterizing e-cigarettes emissions and variously reported measurable amounts of ethanol, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), silicon, lead, nickel, air pollutant, formaldehyde, acetaldehyde, isoprene, acetic acid, 2-butanodione, acetone, and propanol[56–58]. Volatile organic compounds can provoke eye and respiratory tract irritation, neurological impairment and liver damage[59]. Polycyclic aromatic hydrocarbons demonstrated carcinogenic, respiratory, immunological, neurological and reproductive effects[60]. Reactive carbonyls such as aldehydes and acrolein

(product of glycerol constituents vaporization[61]) elicit airway constriction, direct damage to airway epithelium and alterations in gene expression, in addition to neutrophils activation, degranulation and apoptosis[62].

The extraordinarily wide variety of flavorants available amplifies the heterogeneity in E-cigs aerosol composition. These chemical components are generally employed in food industry and recognized as safe additives but this does not imply their harmlessness when inhaled[63]. Some are known allergens (e.g. cinnamaldehyde for cinnamon aroma)[64], others may provoke ocular and airway irritation (e.g. benzaldehyde for fruity aromas)[65]. Pre-clinical studies demonstrated that flavoring chemicals elicit pro-inflammatory responses in lung epithelial cells and fibroblasts and decrease transepithelial resistance in bronchial epithelial cells[66]. Likewise, diacetyl and acetyl propionyl (butter flavoring volatiles) seem to underlie bronchiolitis obliterans, as seen in microwave pop-corn producing factory workers [67,68]. Besides, flavored e-cigarettes are misleadingly considered less harmful than those with tobacco flavor, therefore used carelessly by youth[69].

An additional concern is represented by the inconsistencies between declared nicotine levels and actual nicotine content, which have been detected even in liquids supplied from the same company[70].

Moreover, e-cigs nicotine derives from tobacco plant, thus e-liquid can include other tobacco-related toxicants, such as tobacco-specific nitrosamines (TSNAs)[71].

Vaping health implications

An uncountable amount of studies aimed at evaluating e-cigarette potential consequences on human health and the most updated panorama of scientific literature provides increasing evidence of vaping harmfulness. According to the centre for disease control and prevention (CDC)[72], although e-cigarettes harmful effects are fewer in comparison to burned cigarettes, they are considered unsafe, harmful for brain development and increase the risk to future addictions especially in kids, adolescence and young adults.

Respiratory effects

Among e-cigarettes adverse health effects, respiratory impact is by far the most extensively studied. In the same way as conventional cigarettes smokers, vapers' pulmonary epithelium is typically damaged[73] and bronchial mucosa chronically inflamed[74]. Proteomics of e-cigarette users' sputum document higher levels of myeloperoxidase, neutrophil elastase and proteinase-3, indicative of neutrophil activation. Furthermore, chronic vapers' neutrophils display a greater propensity for NET formation when compared to cigarette smokers or non-smokers[62]. Bronchial inflammation result in a higher respiratory impedance and flow resistance[75] (evidenced by a lower FEV_1 and FEV_1/FVC [76]) as well as a significant decrease in fractional exhaled Nitrogen Oxide[77], both observed in e-cig users.

From a clinical perspective, these pathophysiological alterations could underlie the considerable increase in asthma and bronchitic symptoms reported by e-cigarettes users, especially adolescents. According to various studies involving high school students, vapers have a twofold higher risk of chronic cough, phlegm or dyspnea, together with a greater incidence of asthma[78,79]. A higher prevalence of e-cigarette use is reported among adults living with a child affected by asthma[80], whose risk of acute exacerbation can increase by 30%[81]. Schoolwork is indirectly affected too, as a result of absenteeism secondary to the aforementioned symptoms[82]. Preclinical studies[83]suggest also a detrimental effect on mucociliary clearance which, coupled with a decreased cough sensitivity[84] and the overexpression of PAF-R (pneumococci's receptor [85]), predispose vapers to increased rates of pneumonia[86].

In parallel to the increasingly wide distribution of e-cigarette, a growing number of cases helped characterize a new nosological entity, which is now referred to as E-cigarette or Vaping Associated Lung Injury (EVALI). It is a diagnosis of exclusion that requires use of e-cigarettes and related products 90 days prior to symptom onset in addition to pulmonary infiltrates on imaging[87]. The prevalence seems higher in youth: indeed, the median age of the initially reported cases was 19[88]. The hypothesized causative agent of lung injury is vitamin E acetate, which may be found in cartridges of THC flavored e-cigarettes, widespread among high school students[89]. Its aerosolization generates ketene, that is irritant to airways and disrupts phospholipid bilayer decreasing surfactant effectiveness[90]. EVALI can occur with shortness of breath, cough, tachycardia,

tachypnea, pleuritic pain and rarely hemoptysis. Nausea and abdominal pain, as well as fevers and chills are not infrequent. Up to 30% of the affected require mechanical ventilation and up to 70% the admission to intensive care units[90–92]. Bilateral lower-lobe predominant ground glass and consolidative opacities with subpleural sparing are the most typical findings at chest imaging. Other possible radiographic patterns include dense consolidative opacities (as in Acute Respiratory Distress Syndrome), diffuse patchy and confluent consolidative opacities (as in Cryptogenic Organizing Pneumonia) or upperlobe ground glass opacities with air trapping (as in hypersensitivity pneumonitis)[92,93]. After ruling out other respiratory infections (viral panel, urine antigen testing, sputum and blood cultures), a bronchoscopy with Bronchoalveolar Lavage and, if possible, transbronchial biopsies, should be performed unless clinical severity precludes it[90,94]. Steroids should be started concomitantly with antibiotics, especially in patients with respiratory failure; in less severe presentations they can be delayed after infectious causes are ruled out. Response to methylprednisolone is generally excellent[91]. Based on the severity of the clinical picture, patients can benefit from high-flow oxygen therapy, noninvasive ventilation or require mechanical ventilation[88,91,95].

Case reports point out an association between e-cigarette smoking and lipoid pneumonia, acute eosinophilic pneumonia, subacute bronchial toxicity and even reversible cerebral vasoconstriction syndrome[96–99].

Second- and thirdhand exposure

Concerning e-cigarettes impact on pediatric population, an often-underestimated aspect is second- and thirdhand smoke. Approximately 20% of parents using e-cigarettes follow strictly enforced vape-free home and car policies; among dual users, 64% has a smoke-free and only 26% a vape-free home policy, which implies a general misperception about e-cigarettes safety. Furthermore, younger parents are more likely to lack a home and car policy[100]. There is evidence that nicotine metabolites in serum, as well as saliva and urine cotinine levels, are superimposable among non-using adults secondhandedly exposed to e-cigarettes and conventional cigarettes[101]. Even secondhand particular matter exposure levels can equal that of traditional smoking[102] and appear to be greater in nicotine-free devices[103].

Vaping during pregnancy (fetal developmental effects)

Of no less importance is fetal exposure to nicotine during pregnancy. Vaping prevalence in pregnant women has been estimated to stand between 0.6% and 15%[104]. Nicotine can cross the placenta and measurable nicotine levels can been detected in offspring of mothers smoking during pregnancy[105]. In uterus nicotine exposure increases the risk for eclampsia, premature birth, cleft lip and palate, reduced birth weight[106–108], sudden infant death syndrome, altered corpus callosum, auditory defects, besides being related to future compromised fertility, type 2 diabetes, obesity, hypertension and respiratory dysfunction[109,110]. Nicotinic acetylcholine receptors regulate critical stages of brain development and nicotine neurotoxic effects on the developing brain have been widely demonstrated, including future hyperactivity, cognitive impairment, anxiety, mood and attention symptoms, sensitivity to stimulant drugs[109,111–115]. To date, e-cigarette impact on pregnant women and fetuses remains uncertain and further research should be established. A vast amount of studies carried out on animal models suggest pre- and postnatal alterations related with the exposure to both, nicotine and nicotine-free aerosols, including the down-regulation of genes implied in lung development[116], an inverse relationship between plasma and urine cotinine level and body weight[117], in addition to neurobehavioural and developmental disorders similar to those resulting from conventional cigarette exposure[118].

Cardiovascular effects

Laboratory studies have pointed out that exposure to e-cigarette can induce platelet aggregation by upregulating expression of CD41 (GPIIb), CD42b, and CD62p (P-selectin)[119]. It also underlies oxidative stress elevation, impairment of antioxidant defenses (vitamin E reduction) and endothelium dysfunction/damage, evidenced by the detection of endothelial progenitor cells and microvescicles into the bloodstream[120–122]. All these alterations could play a role in cardiovascular risk increasement. It has been proven, indeed, that daily vaping represents an independent risk factor for myocardial infarction[123], synergically amplified by exposure to nicotine, a parasympathomimetic alkaloid increasing heart rate and blood pressure[124]. Additionally, a 30 minutes vaping session seems inducing an unfavorable effect on aortic stiffness similar to traditional

smoking[125].

Neurological effects

Nicotine is widely recognized as a psychoactive substance[126]. Vapers experience craving, impaired capacity to stop and withdrawal symptoms during abstinence (e.g. irritability), which all suggest e-cigs potential of inducing nicotine dependence[127,128]. Similarly to other substance use disorders, adolescents are characteristically more vulnerable to addiction[129].

Despite ENDS representing a tobacco cessation strategy, the risk of transition to conventional cigarettes in previously never smokers represents an emerging issue of critical relevance, especially in young people[130–133]. A recent meta-analysis showed that in a population of teens and young adults who have never smoked, odds of smoking initiation were 3 to 6 times higher in those who have ever used e-cigarettes[134]. Evidence suggest also that higher nicotine concentrations may heighten the likelihood of progression[135]. In this perspective, the renormalization of a smoking culture among teenagers threatens to subvert decades of anti-smoking efforts.

Structural and neurochemical changes in the central nervous system lie beneath the behavioral evolution that characterizes adolescence. Against this background, nicotine can affect its regular course, contributing to attention and cognitive deficits and exacerbating mood disorders[136].

Furthermore, in such a critical phase of human development, nicotine exposure may prime the brain's reward system increasing pleasing effects of other substances of abuse[137,138]. As evidence of this, youngsters smoking e-cigarettes display a greater risk of co-occurring alcohol and/or marijuana use[139].

Acute adverse effects

As regards e-cigarettes potential harmful effects, consideration should be given to acute injuries. A fair amount of reports to poison centers concern children incidentally exposed to e-cig liquids through ingestion (70%), inhalation (15%), ocular (8.5%) and dermal contact (6%)[140]. Nicotine poisoning can result in tachycardia, dizziness and even seizures[141]. Ingestion of 0,1 mg/kg of nicotine-containing fluid can be fatal to a child[7]. Acute exposure to e-cigarettes seems associated with a worse prognosis compared with that of conventional tobacco[142]. As electronic devices, batteries could also explode provoking severe burns[143].

COVID-19 and future perspectives

It has been recently demonstrated that a nicotine-related overexpression of ACE-2 in bronchial epithelial cells is mediated by α7-subtype nicotinic receptors[144]. Within the framework of the ongoing COVID-19 pandemic, such a finding orients scientific interest towards the relationship between SARS-CoV2 and smoking or, more specifically, inhalation exposure to nicotine.

Conclusions

While traditional tobacco impairing effects have been widely demonstrated, vaping mid- and long-term complications remain unclear. Nonetheless, there is increasing evidence that e-cigarettes can no longer be considered as harmless devices. As a result of its cross-generational diffusion, vaping health implications have become an issue of pediatric interest, being children at greater risk of the still unknown chronic effects. According to a precautionary principle, e-cigarettes should be in any event considered unhealthy and consequently banned in this age group. In this perspective, governments should strengthen prevention strategies as well as restrictions and regulations on e-cigarettes marketing and advertisings. At the same time, teachers and pediatricians must play a crucial role in children and parents' education by raising their awareness about vaping harmful effects and dispelling widespread misperceptions. Given its ever-growing relevance as a worldwide health concern, further investigation is in our main interest.

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