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Review Article

Risks and Benefits of e-Cigarette Usage Relative to Conventional Cigarettes

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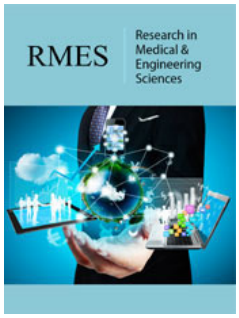

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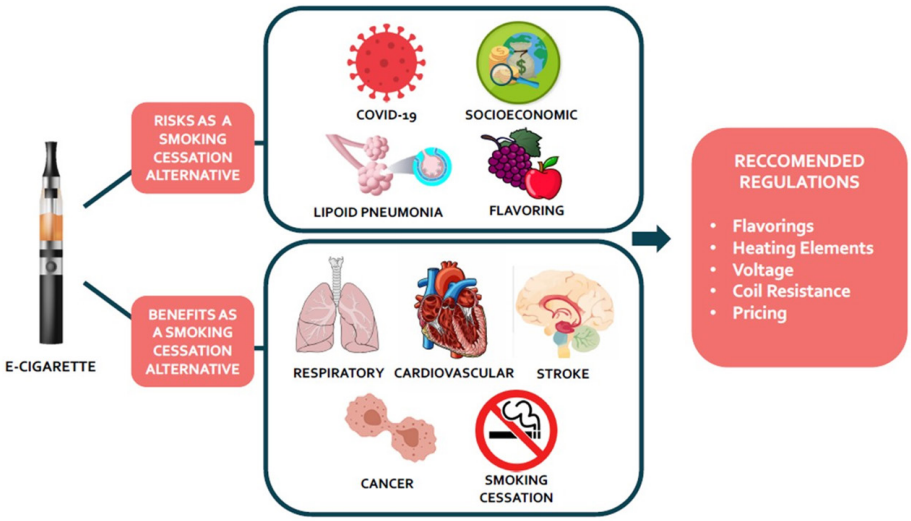
Abstract

E-cigarettes have grown in popularity since their inception in 2004. Although initially introduced for smoking cessation, with its enticing flavors, designs, and marketing as a healthier alternative to conventional cigarettes, there are growing concerns regarding its true efficacy for its designed purpose, in addition to its overall safety. In this review, current data on the effect on health system's (i.e. cardiovascular, respiratory, stroke, cancer), as well as how flavorings and socioeconomics impact the risks and/or benefits of e-cigarette usage. Generally, studies have demonstrated that there is a relatively reduction in harm of e-cigarettes when compared to conventional cigarettes; however, more longitudinal studies are needed given reported increases in inflammatory markers, oxidative stress, and DNA damage. In addition to concerns over potential harm to users, regulating flavorings, heating elements, voltage, coil resistance, and pricing may improve user safety. Regardless, more studies are needed to truly access the safety of e-cigarettes for use as an effective smoking cessation approach.

Keywords: E-cigarette; Risks; Benefits; Vaping

Graphical Abstract



Introduction

Electronic cigarettes (e-cigarettes) were first introduced in 2004 in China, then brought over to the United States in 2007 [1]. They were initially developed to function as a smoking cessation device and have demonstrated to be effective in this regard and in serving as a substitute to traditional combustible cigarettes [2]. However, despite containing fewer harmful chemicals than traditional combustible tobacco cigarettes, e-cigarettes have raised

concern over health consequences [3], safety of device usage [4], and true efficacy in smoking cessation [5]. This call to action has in part been due to an increase in non-smokers using e-cigarettes [6]. Individual's impression that they are a healthier alternative to conventional cigarettes has significantly boosted their popularity among both non-smokers and young adults [6], and with more than 7,000 different e-liquid flavorings [7], adolescent populations have also become drawn into using the devices [7]. In 2013, there were ~263,000 youth reportedly using e-cigarettes in the US and by 2021, this number rose to 2 million (2021 National Youth Tobacco Survey).

E-cigarettes are constantly being modified, with companies putting out variations of the device and different constituents in the e-liquids. Unfortunately, there is very little data regarding these alterations. The hardware typically consists of four main components: the power source, the reservoir to hold the e-liquid, a heating element for vaporization, and the mouthpiece to inhale the aerosol [8]. To date, there are more than 460 marketed e-cigarette brands. The constituents in the e-liquid typically contain nicotine, propylene glycol, vegetable glycerin, flavorings, and a multitude of additives [9]. Certain chemicals used in flavorings have been associated with health-related issues, however a lack of research regarding their level of harm complicates the situation. There is insufficient data on the impact of the e-liquid vapor on various organs, including, but not limited to, cardiovascular and pulmonary systems. Some studies have reported cases of lipoid pneumonia and diffuse alveolar hemorrhage, in addition to acute respiratory distress [10]. Additionally, studies have also seen an association between adolescents who use e-cigarettes and SARS-Cov2 (COVID-19) symptomatic outcomes [11]. However, reports are often with preliminary data and without an in-depth analysis on the long-term adverse health effects.

Due to e-cigarettes being in the US market for only 16 years, there is a limited amount of data related to its long-term use. With the marketing of e-cigarettes as the "healthier alternative," there is a need for more education on their true health effects. Herein, is a consolidation of current research related to health risks/benefits of e-cigarette usage.

Benefits as a Smoking Cessation Alternative

Cancer

One of the most widely reported benefits of e-cigarettes is the lowered amount of toxins in the vapor produced, relative to conventional combustible cigarettes [12]. Currently, combustible cigarettes are attributed to at least 12 types of cancers [12]. Stephens conducted a study focused on carcinogenic risk of e-cigarette and tobacco smoke. The research focused on known carcinogenic compounds, specifically 1,3-butadiene, acrylonitrile, and acetaldehyde. The variability in the cancer potency ratio estimate was used to determine e-cigarette vapor danger relative to tobacco smoke [13]. For traditional tobacco smoke, the cancer potency was obtained by weighing the unit risk values by its concentration in undiluted smoke [13]. Findings from the study demonstrated that the carcinogenic potency of e-cigarettes was approximately 1,000 times less than tobacco smoke. As a comparator, the carcinogenic potency of ambient air is 10,000 times less than tobacco smoke. Stephens also made an estimation of the lifetime cancer risk of e-cigarettes based on daily smoke exposure, mean daily cigarette usage, and breathing rate. The excess cancer risk for a lifetime of smoking, when inhaling 30L vapor/day from e-cigarettes at normal power, was found to be lower, compared to smoking 15 conventional cigarettes daily [13].

Additionally, studies have demonstrated that the voltage power used with e-cigarettes has an influence on cancer potency [13]. A prior study indicated that as the e-cigarette atomizer power increased, there was more than a two order of magnitude increase in formaldehyde and acetaldehyde generated [13]. Thus, with carcinogenic potency being dependent on factors such as device settings, liquid formulation, and vaping behavior, Stephen [13] concluded that when studied in optimal settings, e-cigarettes are much less harmful than conventional cigarettes [13].

Goniewicz [14] and colleagues studied 12 different brands of e-cigarettes and analyzed them for toxic volatile organic compounds (VOCs) and heavy metals generation. They identified three toxic carbonyls: specifically, formaldehyde, acetaldehyde, and acrolein [14]. Additionally, three other VOCs; benzene, toluene, and aniline were detected in the vapor. Some toxic heavy metals in e-cigarettes vapors include cadmium, lead, and mercury [14]. Despite these various toxic compounds found within the e-cigarette vapor, they were still 9-450 times lower in concentration compared to conventional combustible cigarettes [14]. Mravec et al. [12] drew a similar connection between e-cigarette use and cancer risk. They agreed that e-cigarettes are a less hazardous option than tobacco-based cigarettes and should be recommended by clinicians to patients who are not able to quit smoking [12]. However, they emphasized that they should be indicated as harmful for cancer progression.

Other studies have reported that e-cigarette vapor has a comparable carcinogenic effect as conventional cigarettes, due to triggering similar gene expression in human bronchial epithelial cells [12]. Additionally, cells in the epithelial airway are known to secrete inflammatory cytokines, IL-6 and IL-8 when exposed to e-cigarette vapor [15]. An increase in IL-6 can lead to lung cancer through the STAT3 signaling cascade [16]. Mravec [12] suggested that despite the data regarding its carcinogenesis, e-cigarettes have not been on the market long enough to determine the indirect effect of their long-term use [12].

A study by Lee et al. [17] looked at exposing mice to e-cigarette vapor and conventional cigarette smoke through nose inhalation over a 3-week period [17]. The conventional cigarette group displayed significantly higher lung weight, coupled with significantly lower liver weight, relative to the e-cigarette group [17]. Furthermore, mice exposed to conventional cigarette smoke had significant changes in the respiratory tract, such as nasal epithelial erosion, metaplasia, and inflammation. Conversely, the e-cigarette vapor exposed mice had only minor amounts of squamous metaplasia in the larynx and respiratory epithelium. Changes in exposure to propylene glycol (a carrier for e-liquid), resulted in hyperplasia in the e-cigarette exposed mice. Overall, significantly less biologic changes in the mice exposed to e-cigarette vapor was reported [17].

Tang et al. [18] also conducted research to understand the carcinogenic properties of e-cigarette vapor, focusing on the impact on lung, as well as bladder cancer [18]. The study was conducted over a 54-week period, comparing mice exposed to e-cigarette vapor with those exposed to ambient air. There were 17% greater incidences of lung adenocarcinoma and 58% greater incidences of bladder urothelial hyperplasia with e-cigarette vapor exposure. The findings also revealed a significant amount of nicotine mediated, nitrosamine ketone derivative 4-(methylnitrosoamino-4-(3-pyidul)-1-butanol). However, this derivative was reported to be only 5% of the levels found in the urine and saliva of conventional tobacco smoker users. E-cigarette vapor can also localize concentrations in the distal bronchioles and alveoli, causing DNA damage and inhibit repair of lung tissues [18]. Although the findings point towards e-cigarette vapor being a carcinogen for both the lung and bladder, the study sample size was small and focused on mice.

Molony et al. [16] conducted studies to further understand the effect of e-cigarettes on bladder cancer, which the prior study [18] and others [5,16,19] have suggested as a possible association. They specifically focused on the potential carcinogenic risk that e-cigarette vapor poses towards bladder cancer derived extracellular vesicles (BCEVs) [16]. Conventional cigarette smoke and e-cigarette vapor can trigger BCEVs inflammatory responses, oxidative stress, and DNA damage to urothelial cells [16]. The group exposed a grade IV human TCCSUP bladder cancer cell line to cigarette smoke extracts, as well as unflavored or menthol flavored e-liquid vapor. They found that menthol flavored e-liquid vapor was attributed to a greater clinical risk of bladder cancer [16]. However, this risk may not be a direct result of the e-liquids, but due to menthol toxicity. Previous studies have shown that e-liquids with menthol have a lower pH and contain both formaldehyde and acrolein [20]. The authors concluded that e-cigarettes potentially increase the risk of bladder cancer, however, unflavored e-liquids do not significantly enhance the urothelial cell transformation, relative to the menthol e-liquids. Additionally, no acute toxicity with cigarette smoke extract treatment was observed, which was surprising to the authors due to previous studies reporting it as a risk factor for bladder cancer [16,19].

Cardiovascular

Although e-cigarette vapor does not have as many chemicals as found in conventional cigarette smoke, it does contain nicotine, which has prompted further research into its potential cardiovascular risk [21]. Many of the current studies, in regard to cardiovascular impact of e-cigarettes, are related to additive chemicals [21,22]. Konishi et al. [23] reported that short-term exposure of nicotine leads to increased angiogenesis, while chronic exposure causes a suppressed response of the vascular neuronal nicotinic acetylcholine receptors (nAChR), resulting in impaired angiogenesis [23]. For e-cigarette users, peak nicotine levels tend to be lower, relative to conventional cigarette smokers [22]. E-cigarette users often take more time between inhalations, resulting in a slower absorption of the nicotine [22]. However, the amount of nicotine delivered varies depending on the specific generation of the device. First generation devices were more "cigarette-like" and tended to deliver greater amounts of nicotine. Newer, third generation devices typically deliver a greater amount of aerosol with less nicotine [24].

Benowitz and Fraiman [22] attributed any findings that strayed from the expected effects of nicotine to the variations found across e-cigarettes [22]. Since there are many components to the e-cigarette, the exposure to cardiovascular toxins may vary. As a result of greater voltage and coil resistance, exposure to harmful chemicals may lead to increased cardiovascular events [22].

Studies have also shown varying impacts on heart rate and blood pressure. Yan and Ruiz [25] conducted a study with 23 participants exposed to either e-cigarettes (tobacco or menthol flavored) or conventional cigarettes (Marlboro) [25]. The authors reported that all participants had increased heart rates when nicotine was present. Conventional cigarettes had the greatest increase in beats per minute (bpm) from baseline and approximately 4% greater than with e-cigarettes. The diastolic blood pressure did display a significant increase, however less so with e-cigarettes. Furthermore, the nicotine concentration in the plasma was significantly higher with conventional cigarettes and continued to remain elevated, compared to e-cigarettes, even one hour after exposure. However, the authors noted that the nicotine delivery for e-cigarettes was dependent on the carriers of the e-liquid with greater amount being delivered with propylene glycol versus glycerin. This variability was believed to be a result of the formers enhanced ability to be vaporized, relative to glycerin [25].

In another study, Farsalinos et al. [26] analyzed the acute effects on myocardial function using echo-cardiography examination on heavy smokers and e-cigarette users [26]. The subjects either used an e-cigarette for 7 minutes, or one cigarette to be finished within ~5 minutes. The authors reported that acute conventional cigarette smoking resulted in a slowed myocardial relaxation, relative to the e-cigarette [26]. Additionally, the systolic blood pressure, pressure-rate, and heart rate were elevated less with e-cigarette usage [26]. Furthermore, much like the findings in the previous study [25], the diastolic blood pressure increased from baseline in both groups [26]. Farsalinos et al. [26] reported short term findings of a less negative impact on myocardial function with e-cigarette use. Despite this, the study was of a small sample size and conducted almost a decade ago and only evaluated short-term use [26].

Vansickel [27] also conducted a study on the acute effect of e-cigarette usage, focusing on heart rate, plasma nicotine levels, expired carbon monoxide, and other subjective effects [27]. The study contained 32 participants exposed to either a 16 or 18mg nicotine e-cigarette cartridge, their regular brand of conventional cigarette, or an unlit conventional cigarette. The participants were instructed to take 10 puffs, with 30 second intervals, from each product in different sessions. The authors reported that participants' using conventional cigarettes had plasma nicotine concentration ~8 times that of baseline when examining its peak five minutes after initial exposure. Conversely, in the e-cigarette and the unlit conventional cigarette group no significant levels of nicotine were observed. Furthermore, the carbon monoxide levels resulting from conventional cigarettes were 3 times above baseline, whereas from the e-ciga-

rette products and the unlit conventional cigarette, no significant levels were observed [27].

Although certain studies have presented data suggesting minimal cardiovascular impact, Espinoza-Derout [28] and colleagues have demonstrated that e-cigarettes with nicotine negatively impact the heart [28]. Mice were exposed to either vapor from an e-cigarette (BluCig PLUS) containing 2.4% nicotine, no nicotine (BluCig PLUS), or saline [28]. Upon completion of the 12-week period, plasma nicotine levels in the mice exposed to the nicotine containing e-cigarette vapor [28,29] were approximately the same as levels found in heavy conventional cigarette smokers (≥18 cigarettes a day). However, no changes in left ventricular dimensions, heart to body ratio, or heart rate were reported [28]. Left ventricular fractional shortening, ejection fraction, and fiber shortening were significantly worse in e-cigarettes with nicotine in comparison to e-cigarettes without nicotine or saline vapor [28]. Furthermore, plaque buildup in the aortic root was observed for mice exposed to the nicotine-containing e-cigarettes, in addition to increased lipid accumulation (intramyocardial) and abnormal mitophagy [28]. Conventional cigarettes have been recognized to cause heart failure and atherosclerosis [30], while e-cigarettes have only recently shown to have this negative impact on the cardiovascular system. More long-term studies are needed to understand its true effect.

Another study by Goel et al, focused on the toxic properties of free radicals found in e-cigarette aerosol [31]. Conventional cigarettes are known to have a significant amount of toxic free radicals (reactive oxygen species and reactive nitrogen species) [31]. These can cause oxidative stress, modifying biomolecules and impacting cellular pathways [31,32]. Subsequently, this damage plays an important role in cardiovascular disease [32]. The study specifically focused on short-lived, highly reactive radicals. Subjects took puffs for 5 seconds, with 20 second intervals, for a total of 40 puffs from an e-cigarette. By using electron paramagnetic resonance with spin trapping, short lived free radicals were identified and found to be 10 times greater in concentration than air pollution; however, 100-1000 times less than in conventional cigarettes [31]. The authors highlighted that although e-cigarettes have significantly less free radicals than conventional cigarettes, the comparison between the two should be made with caution, as it does not consider the different nature of smoking patterns between the groups. For instance, e-cigarette smokers typically take longer puffs with a slower flow rate compared to conventional cigarette users [31]. Other factors that could potentially contribute to the free radicals found in e-liquid, may be a result of the wick heating or the type of solvent (propylene glycol versus glycerol). Goel et al. did report finding the generation of free radicals from both of these sources [31].

Stroke

Parekh et al. [33] conducted a cross-sectional survey on the risk of stroke for conventional smokers, e-cigarette users, dual e-cigarette and conventional cigarette users, and e-cigarette users with history of conventional cigarette use [33]. The authors reported that odds of stroke with conventional cigarettes was ~2 times greater than solely e-cigarette users. However, when current dual users were studied, a 3-4 times greater risk versus non-smokers was observed. The findings suggested a potential contribution to increased risk of stroke when e-cigarettes were added to conventional cigarette use. The authors believed there may be a cerebrovascular effect from e-cigarette. Although the study reported a lower risk for solely e-cigarette usage, there was speculation that the data was affected by the population age, as this group tended to be much younger. Parekh [33] also conducted studies to see if there were any differences when switching from sole conventional cigarette use to e-cigarette use with a history of conventional use. They did not see any significant difference and made a cautious conclusion that there is no clear benefit in switching [33].

Another study focused on the impact of nicotine and e-cigarettes on brain glucose levels [32]. To understand nicotine's effect, short-term (1 day) and long-term (5 days) studies were conducted in which neurons were isolated from mice fetuses and treated with nicotine. Both studies showed that the nicotine was not toxic to the neuron but did reveal lowered glucose uptake within an ischemic environment. The long-term group also had lowered GLUT1 expression, a key transporter for glucose utilization in the brain. Furthermore, mice that were exposed to direct inhalation of e-cigarette vapor (BluTM 24mg/mL), 6 times a day, for 7 days had lowered glucose uptake and a significant decrease in both GLUT1 and GLUT3 expression in brain slices. The study did not evaluate the potential effects of other components of the e-liquid, such as the solvent. Ultimately, they attributed the decreased brain glucose utilization to the inhibition of the GLUT1 transporters and expressed concern that chronic e-cigarette use could lead to worsening stroke outcomes and recovery [32].

Pulmonary effect

Vardavas et. al [34] conducted a study to understand the short-term pulmonary effect of e-cigarettes [34]. Thirty participants were instructed to use an e-cigarette for 5 minutes in any manner they chose (i.e., no restrictions on inhalation time and spacing between puffs). This was followed by assessing the effect on lung function via evaluation of exhaled nitric oxide, dynamic lung volumes, and total respiratory resistance. They found a 16% decrease in fractional exhaled nitric oxide (FeNO) after e-cigarette usage. Additionally, an overall increase in flow resistance, using impulse oscillometry, of ~8% at a respiratory resistance of 5Hz and ~9% at respiratory resistance of 10Hz was observed. It was also noted that there was an increase of 18% in peripheral flow resistance relative to baseline. The study was one of the first to find a clear physiologic change because of e-cigarette exposure. They determined that e-cigarette vapor exposure increases oxidative stress, impedance, and peripheral flow resistance [34].

Another study conducted by Kleiman [10] evaluated e-cigarette vapor on lung injury in rats [10]. The authors had previously conducted a study to understand the vapors' cardiovascular effects; however, none of the animals experienced any acute respiratory distress. The model of e-cigarette used in that study was no longer available, thus an alternative with a nickel-chromium alloy (nichrome) heating element versus the previous stainless-steel heating element was employed. After exposing rats to e-cigarette vapor using this nichrome heating element for 2 hours, 80% of the rats

experienced clinical acute respiratory distress. Additionally, ~60% of the rats displayed multiple foci of pulmonary inflammation [10].

E-cigarette or vaping associated lung injury (EVALI) has been a growing concern. In February 2020, a dramatic increase in hospitalizations (2,987) and deaths (68) was reported [35,36]. The rise in cases was reported to be linked with tetrahydrocannabinol (THC) and vitamin E acetate in the e-cigarette vapors [36,37]. In a study by Blount and others, vitamin E acetate was detected in over 90% of the bronchoalveolar-lavage fluid samples from the 51 patients with EVALI [37].

Cervellati et al. [38] reported a related finding of increased pro-inflammatory mediators and cytokine release, as a result of humectant in e-cigarette vapor [38]. The study focused on exposure to skin and lung cells. Keratinocytes were more susceptible to conventional cigarette smoke, with a decrease in cell viability and an increase in LDH release. When exposed to the e-cigarette vapor, without flavoring or nicotine, there was no change in cell viability or LDH release. However, vapor with flavoring and nicotine had a rapid loss in cell viability and increased LDH, which was comparable to the conventional cigarette smoke. Furthermore, the authors observed clear morphologic changes as a result of conventional cigarette smoke and potential vacuolization and altered cytoplasmic membranes from the e-cigarette vapor flavoring [38]. Cervellati [38] reported no association between cytotoxicity and the presence of nicotine or humectants in the vapor but did find a correlation to concentration of flavoring chemicals. This was further supported by a study on mice that used e-liquids with flavorings, which resulted in decreased lung glutathione levels and an increase in pro-inflammatory cytokines (IL-6 and IL-8) [15].

Furthermore, Ghosh studied inflammatory markers in bronchoalveolar lavage fluid from non-smokers, smokers, and e-cigarette users, and reported increased levels [39]. This suggested the exposure to e-cigarette vapor may result in inflammation of the lungs, which was further supported by the previous studies [15,38].

Chung [40] and others conducted a study on human and sheep cells to understand the impact on airway epithelial cells with an emphasis on e-cigarette vapor induced airway mucociliary dysfunction [40]. They found a negative impact on volume loss and increased mucus viscosity, with reduced airway surface liquid (ASL) hydration. The impairment in the sheep trachea was observed to be dose dependent, specifically related to nicotine levels.

McGrath-Morrow [41] conducted a study with mice focused on e-cigarette vapor exposure during the neonatal phase and analyzed the impairment in lung growth and systemic uptake of nicotine, post-natal [41]. The mothers and neonatal mice were placed in a chamber and exposed to e-cigarette emissions, either with 0 or 1.8% nicotine, in propylene. Only within the group exposed to 1.8% nicotine did the mice have a decreased KI67 (cell proliferation marker) expression and a greater mean linear intercept (a marker of the separation distance between respiratory surfaces), indicating that there was modest impairment of alveolar growth. Furthermore, in the 0% nicotine exposure group, the mice had an 11.5% decrease in total body weight and the 1.8% nicotine exposure group decreased to 13.3%. The authors reported high mean plasma and mean urine cotinine levels, establishing the systemic nicotine absorption in the neonatal mice. It was suggested that the absorption may also be attributed to nicotine being concentrated in breastmilk [41].

There have also been case reports of e-cigarette induced lung injury [42]. A 46-year-old healthy man with a history of smoking conventional tobacco cigarettes 3 months prior, had switched to e-cigarettes and was vaping 20 times per day, when presented to the hospital. The patient was found to have ground glass opacities in both lungs. After the initial screening, the bronchoalveolar lavage fluid was seen to have a high total cell count of 6% lymphocytes, 57.5% neutrophils, 18.5% eosinophils, and 18% macrophages. Furthermore, the fluid had lipid-laden macrophages. The authors suspect these macrophages were attributed to the glycerin found in e-cigarette vapor. Additionally, swelling of the alveolar septum as well as invasions of eosinophil and neutrophils were observed. There were also macrophages with blackish-brown pigmentation with purulent exudate in the alveolar. This led to a diagnosis of acute alveolitis with intra-alveolar fibrosis (acute interstitial pneumonitis), attributed to e-cigarette usage. The symptoms were quickly relieved with the discontinuation of e-cigarettes and administration of methylprednisolone [42].

Asthma/COPD

Lappas et al. [43] conducted a study to investigate the effect of e-cigarette usage on individuals with mild asthma [43]. Immediately after using an e-cigarette for 5 minutes, there was a sudden decrease in FeNO in both healthy individuals and individuals with mild asthma. However, the individuals with asthma displayed a 2x greater decrease in FeNO. Although the difference in degree of change was deemed insignificant, the levels for individuals with asthma remained lowered beyond the 15-minute mark, whereas in healthy individuals the reduction lasted for less than 15 minutes. Additionally, individuals with asthma had 2x higher baseline impulse oscillometry system values than healthy smokers, when tested for respiratory system total impedance, varying respiratory resistance, and resonant frequencies. The data matched a peripheral obstructive pattern and ultimately Lappas [43] suggested that e-cigarettes have a greater negative impact on the duration and intensity of inflammation and respiratory symptoms on individuals with asthma [43].

Boulay [44] and others had opposing findings when testing for respiratory mechanics and lung function in healthy versus asthmatic patients [44]. They observed no change in lung function when utilizing spirometry or forced oscillation. Additionally, they found no signs of inflammation nor FeNO and serum C-reactive protein levels, between individuals who used e-cigarettes and those who did not. A longitudinal study on tobacco product use also demonstrated no association between the development of new-onset asthma or worsening of asthma symptoms over time, with the use of conventional cigarettes or e-cigarettes [45]. However, they did find, in a cross-sectional analysis, that conventional cigarettes led to poor control of asthma [45]. Another longitudinal study found the odds of developing respiratory disease when switching from con-

ventional cigarette to e-cigarette, was lowered [46]. Interestingly, Bhatta found that dual use of conventional cigarettes and e-cigarettes was more harmful than when either alone [46].

Noël et al. [47] focused on the impact that e-cigarettes had during pregnancy [47]. Pregnant mice were exposed to vanilla flavored e-cigarette vapor with 18mg/mL of nicotine for 20 consecutive days during the gestational period. The exposure to e-cigarette vapor resulted in alterations of the lung transcriptome among the offspring. Additionally, a 7-week-old male mouse developed asthma as a result of in utero e-cigarette exposure. This indicated that e-cigarette vapor has the potential to cause the development of lung disease. The authors also reported that in utero exposure may lead to a lung that is more susceptible to future allergen exposure [47].

Smoking cessation

E-cigarettes have been considered for use as a smoking cessation device under the perception that it can help with reducing the craving for tobacco and withdrawal symptoms, and ultimately lead to the avoidance of using tobacco completely [2]. In a cross-sectional study by Shahab et al. [48] the authors focused on evaluating the impact of long-term use of nicotine replacement therapy (NRT) and e-cigarette in both dual users (e-cigarette with conventional cigarette or NRT with e-cigarette) and previous conventional cigarette smokers (currently using e-cigarette only or NRT only) [48]. The study utilized biomarkers from samples of saliva and urine to analyze the toxicant levels to assess the participants risk of developing diseases. The subjects were predominantly young white males with a high school education, with most having been smoking since late teens. Shahab reported that participants exclusively using e-cigarette or nicotine replacement therapy had similar nicotine levels as with cigarette-only smokers. This indicates that regardless of the device, users sought out similar levels of nicotine. Furthermore, Shahab [48] reported less carcinogens and toxicants in both NRT and e-cigarette, relative to conventional cigarette [48].

Nelson et al. [49] conducted a cross-sectional study to further understand the long-term use (more than 6 months of use) of e-cigarette and NRT [49]. The study groups included e-cigarette and NRT users that were either ex-smokers (previously used tobacco products) or current smokers (current use of tobacco products). Compared to NRT users, e-cigarette users were reported to have more nicotine consumption and minimal delay before using the product in the morning. Nelson and others reported increased cravings for specifically ex-smokers using NRT. According to ex-smokers who are current long-term users of the e-cigarette, they believe it is better at controlling withdrawal symptoms than NRT [49].

Similarly, a cross-sectional study by Etter [50] found data supporting e-cigarette's effectiveness for decreased cravings [50]. The author found that participants felt definite relief of cravings when they used e-liquids with nicotine. Etter [50] also reported a possible correlation of relief in craving with only the mint flavoring, whereas other flavors did not show this. Furthermore, the author found participants modifying their e-cigarette device to increase the vapor level by increasing the voltage. Since some participants did find craving satisfaction with e-cigarette use, the changes to meet these cravings by increasing vapor level may have actually led to increased addiction [50].

A randomized controlled trial by Bullen et al. [51] focused on comparing e-cigarettes (16mg nicotine concentration) to nicotine patches (21mg nicotine concentration) for smoking cessation [51]. When participants were evaluated for 6 months with intention-to-treat, those that were able to abstain from conventional cigarette usage were 5.8% when using patches, 7.3% use e-cigarettes, and 4.1% with placebo e-cigarettes. The modest efficacy of the e-cigarette, with and without nicotine, suggested the possible benefit of e-cigarettes as a smoking cessation device [51].

Another short-term study was conducted to investigate e-cigarette use for conventional cigarette cravings [52]. The participants were first instructed to use either an e-cigarette or a conventional cigarette of their own choice. Then within each group, participants were asked to take 10 puffs with 30 second intervals between each puff. Blood samples and subjective measures were taken at 5, 15, 30, and 45 minutes, post first puff. At the 60-minute mark, the participants were instructed to again take 10 puffs with 30 second intervals between each with blood samples and subjective measures being taken at the 5-, 15-, 30-, and 45-minute post the 1st puff. After analyzing the results from usage of e-cigarettes with 16mg nicotine concentration (Hydro and NPRO), the author reported that the device was not able to decrease the participants' craving until 5 minutes after the repeated round of use. However, when the participants utilized their own conventional cigarette brand, they had an immediate decrease of cravings post use. Because the e-cigarette was not able to reach comparable nicotine levels to conventional cigarettes, they subsequently did not have comparable decreased cravings [52].

Farsalinos et al. [53] conducted a cross-sectional study with interviewed patients that successfully used e-cigarette solely as a smoking cessation device. All participants in the study were successful utilizing either second or third generation e-cigarettes [53]. The author reported that 42% of the participants included in the study successfully quit smoking in the first month and 19.8% in the first day. Furthermore, 30.6% achieved cessation with the addition of other medical methods. To further understand participant usage patterns, they reported 74% of participants had used nicotine concentrations >15mg/mL, while 16.2% of the participants had to increase the nicotine concentration levels to remain abstinent from smoking. When participants were interviewed after ~8 months of e-cigarette usage, these participants had reported a decrease from their initial nicotine concentration intake. Additionally, side effects were mild and minimal, they included throat irritation, cough, and gastrointestinal discomfort. The authors also reported less e-cigarette dependence relative to conventional cigarettes. The study demonstrates the critical role e-cigarettes, with high nicotine concentration, can play in smoking cessation [53].

Risks as a Smoking Cessation Alternative

Socioeconomic

Although conventional cigarettes are more harmful than e-cigarettes, due to the popularity among youths, the number of users has

grown [54]. Fadus et al. [54] reported that e-cigarette use among youths was 15 times greater in 2018, compared to 2011. E-cigarette devices, such as JUUL, have created sleek designs and enticing flavors that attract the youth population [54]. Sweet flavors often appeal to young adults and have led to this early use [55]. There is growing concern that e-cigarettes may be a gateway to conventional cigarette use as well as cannabis use [54].

Pokhrel [56] and others conducted a cross-sectional study to understand the association of e-cigarette marketing with young adults' understanding of e-cigarettes [56]. The study surveyed 307 college students and found that 90% of participants were exposed to e-cigarette advertising and 43% had used e-cigarettes. The authors reported high responsiveness to e-cigarettes being considered not as harmful as conventional cigarettes. Pokhrel [56] suggested that exposure to marketing and the openness to the belief that e-cigarettes are less harmful, resulted in increased use of e-cigarettes for this demographic [56].

Gorukanti [57] surveyed 9th and 12th grade students to understand the perspective of adolescents towards e-cigarettes [57]. Approximately 40% of the 786 participants felt that e-cigarettes were less harmful than conventional cigarettes and believed the devices were designated for smoking cessation. Furthermore, the authors reported that those that vaped were more likely to claim e-cigarettes only expel water with no tar, help with smoking abstinence, and are cleaner, and safer compared to conventional cigarettes. The authors suggest adolescents have knowledge of e-cigarettes, but the positive attitudes were concerning and may require educating to combat misconceptions [57].

Another factor that may dictate e-cigarette usage is the cost of e-cigarettes. Gorukanti et al. [57] reported 54.42% of 9th and 12th grade students believed e-cigarettes were too expensive [57]. Pesko [58] and others conducted further research with 8th, 10th, and 12th grade students, and observed that a 10% increase in pricing for disposable e-cigarettes was correlated with an ~10% decrease in demand and an ~18% decrease in number of days e-cigarette users would vape [58]. The authors suggested that raising prices or taxes could be a potential solution to the decreasing adolescent users [58].

COVID-19

When the COVID-19 pandemic began, e-cigarette usage among adolescents and young adults became an additional concern and potential risk factor [11]. Gaiha et al. [11] conducted a cross-sectional survey and reported that compared to participants that never smoked or vaped, participants with an e-cigarette use history were 5 times more likely to test positive for COVID-19. The likelihood increased to 7 times greater when participants used both conventional cigarettes and e-cigarettes. More strictly, the participants were reported to also be ~5 times more likely to experience COVID-19 symptoms if they smoked or vaped in the last 30 days prior to infection [11].

The increased risk of COVID-19 may be attributed to increased angiotensin-converting enzyme 2 (ACE-2) [59]. ACE-2 is a critical binding site that allows entry of the virus into the cells [59]. Conventional cigarettes have been identified to increase this binding site through facilitating nicotine receptors [59]. Russo further supported this finding that nicotine can increase ACE-2 expression [60]. McAlinden et al. [59] believe that vaping may bring about similar effects due to e-cigarettes containing nicotine [11].

Farsalinos et al. [61] had a differing argument as the author aggregated data from 11 cases from China and the United States. They suspected that antagonists may be used to change ACE-2 expression and keep SAR-CoV-2 from entering the cell [61]. Therefore, the authors believe smoking may actually have a protective role in this scenario [61]. Although this may be a possibility Leung et al. argue that the inflammation from SAR-CoV-2 is still concerning in patients with a smoker status [62].

Lipoid pneumonia

Likewise, there were increasing concerns with case reports of lipoid pneumonia [63]. Viswam et al. [63] had reported on a 34-year-old woman with a 3-month history of feeling breathless and coughing with white sputum and streaked blood. The patient also had decreased appetite, weight loss, and night sweats. She was an ex-cigarette smoker that had been vaping for 3 years. On admission, the patient was in respiratory failure. There were no significant findings after clinical examination and hematological test had returned with thrombocytopenia (which the patient had previously). Furthermore, on admission, the patient had bilateral infiltrates in the mid and lower zones as well as diffuse ground-glass infiltrates with a mesh like pattern. Due to the patient's respiratory failure, she was empirically treated with steroids (prednisolone 40mg), which improved her oxygen saturation levels. The authors attributed the lipid findings in the patient's lung because of the vegetable glycerin from the e-liquid and subsequently diagnosed her with lipoid pneumonia. The patient was instructed to stop vaping and encouraged to use other nicotine replacements. Unfortunately, the patient was non-adherent. There was an initial improvement, and the patient was kept on prednisolone for 18 more months. Upon follow up, she had minor improvements in spirometry parameters [63].

Another case reported by McCauley et al. [64] was with a 42-year-old woman with previous dyspnea, productive cough and fever [64]. The patient had started vaping 7 months prior and concurrently experienced respiratory symptoms. When lab tests were conducted, the patient had a white blood cell count of 18x103. Other lab values were unremarkable, except the chest radiograph showed multifocal bilateral opacities. The scan also revealed similar ground glass pulmonary opacities with interlacing lines. The patient also had a cell count of 8% lymphocytes, 1% eosinophils, 43% monocytes, and 48% neutrophils. The bronchoalveolar lavage showed lipid-laden macrophages and the patient was diagnosed with exogenous lipoid pneumonia from e-cigarette usage. The author attributed the cause to the patient's exposure to glycerin-based oils in the e-cigarette vapor. When the patient stopped vaping, symptoms improved. A follow up chest radiograph was normal and pulmonary function displayed no significant impairment [64].

Flavoring

Flavorings found within the e-liquid may be a contributing factor to adverse health effects of e-cigarettes. Farsalinos et al. [65]

conducted a study to further understand the harm that sweet flavorings may impose focusing on diacetyl and acetyl propionyl [65]. Diacetyl is known for having a butter flavor that is safe to consume [66] but may result in decreased respiratory function when inhaled. Acetyl propionyl is commonly a substitute, however if used by companies claiming products are diacetyl free, however itself may cause similar harm. E-liquids were evaluated in an aerosolized state using high performance liquid chromatography. Farsalinos [65] reported ~70 % of the samples contained both diacetyl and acetyl propionyl. Furthermore, 47% of the samples with diacetyl would hypothetically expose users to levels greater than the National Institute for Occupational Safety and Health's acceptable safe limit, with half of these samples being five times greater. Similarly, 41% of samples with acetyl propionyl contained levels above the safe limit, with half being more than 5x greater. The authors suggested that consumers are significantly exposed to these chemicals, but they can be easily removed or replaced to reduce potential user harm [65].

Allen et al. [7] further supported these previous findings [7], establishing the presence of diacetyl in ~80% and acetyl propionyl in ~45% of the various flavored e-liquids tested [7]. Additionally, Allen [7] identified acetoin in ~80% of the e-liquids. This itself is problematic, as acetoin has been associated with respiratory harm [7].

Muthumalage et al. [67] investigated the cellular bodies response of various flavoring chemicals found in e-liquids [67]. They exposed monocytic cells, MM6 and U937, to diacetyl, acetyl propionyl, cinnamaldehyde, acetoin, o-vanillin, maltol and coumarin to evaluate cytotoxicity. They reported decreased cell viability when U937 cells were exposed to cinnamaldehyde and o-vanillin. MM6 cells experienced cell death and significant reduction of cell viability from only cinnamaldehyde with a dose-dependent cytotoxic effect. Furthermore, various flavorings were evaluated in regard to their IL-8 response. These showed an increased response resulting in enhanced oxidative stress. It was concluded that cinnamaldehyde, o-vanillin, and acetyl propionyl were the most toxic of the flavorings studied. Additionally, the authors reported a significant increase of H_2O_2 equivalents when mixing more than one flavoring, suggesting a further increase in cytotoxicity, relative to only one flavoring being present [67].

Additionally, Muthumalage [67] investigated the impact of varying JUUL pod flavors on lung epithelial cells and monocytes [67]. They reported that flavors of Cool Mint and Crème Brulee had significantly increased levels in cell free ROS. Furthermore, Cool Cucumber, Classic Menthol, Just Mango, and Caffé Latte flavors had increased mitochondrial superoxide generation, with Classic Menthol inducing cell death in ~8% of the cells. The authors also reported increases in IL-8 cytokines in 16-HBE (human bronchial epithelial cells) and monocytes U937, when exposed to those pod flavors, in addition to in prostaglandin E2. Epithelial barrier dysfunction, due to decreased membrane voltage when exposed to Crème Brulee as well as decrease in membrane resistance when exposed to Cool Cucumber. Additionally, flavorings caused DNA damage in the lung epithelial cells [67].

Conclusion

Since the release of e-cigarettes in 2004 as a potential smoking cessation device, the updates to designs and e-liquids have enticed adolescents and young adults. More non-smokers and younger individuals are using e-cigarettes [6], which has drawn concern and awareness regarding the sparsity in research and regulations on these devices.

E-cigarettes are marketed as less harmful than conventional cigarettes, and this claim is supported by studies which report significantly less cancer, cardiovascular, stroke, and respiratory risk [13]. However, while many studies acknowledge the relative decrease in harm of the device, they report evidence of potential harms and encourage more long-term research and regulations. E-cigarettes have been reported to contain carcinogens in the vapor, which result in an increase in inflammatory markers, oxidative stress, and DNA damage. Additionally, some of the harm from e-cigarette usage is a result of the nicotine found in e-liquids, which increases blood pressure, pressure rate, heart rate, and glucose uptake [26]. There have also been reports of respiratory harm with cases of EVALI, linked to THC, vitamin E acetate, decreased glutathione levels, and increased symptoms for individuals with asthma.

Despite these concerns over the harms associated with e-cigarette usage, there are benefits to e-cigarettes as a smoking cessation device. It has been reported to be better at controlling withdrawal and has comparable nicotine levels with NRTs. There has also been reported smoking abstinence success when utilizing the device. However, the hesitancy in using the device for smoking cessation is attributed to concerns of addiction, because individuals often increase vapor levels to meet their cravings. More studies are required to compare e-cigarettes to NRTs to determine their validity as a non-inferior option for smoking cessation.

E-cigarette regulations on device elements, usage, and accessibility could result in safer use. Certain flavorings have been shown to increase harm, such as menthol e-liquid, which increases bladder cancer risk compared to unflavored e-liquids [20]. Changes to delivery (voltage and coil resistance) of the aerosol can significantly alter exposure to harmful chemicals. Thus, regulating the heating element could provide a safer user experience, as nichrome heating elements have been shown to cause acute respiratory distress in mice [10]. Lastly, studies have suggested that price increases may reduce demand and thus usage of e-cigarettes in adolescent users [58].

Although more than two decades have passed since the introduction of the e-cigarette, it is clear that more data to establish its safety is required. With more than 466 e-cigarette devices recorded in 2014 and 15,500 e-liquids in 2017, combined with the rise in users–especially younger and smoking naïve-it is imperative that more data is collected, and evidence-based guidance is provided for ensuring safe usage and long-term health outcomes [68,69].

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