A Review of Electronic Cigarettes and Liquid Nicotine Poisoning Exposure Cases in the United States

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ABSTRACT -- Purpose: In 2007, electronic cigarettes (e-cigarette) were introduced as a smoking cessation device. Since then, its sale and marketing has been expanded annually. Concomitantly, there is an increase in the electronic cigarette (e-cigarette) and liquid nicotine exposure cases reported to the United States (US) poison control centers. The purpose of this review is to assess the exposure cases reported to US poison control centers to characterize the adverse health effects of e-cigarette and liquid nicotine use. **Methods:** The PubMed database was searched for e-cigarette and e-liquid exposure reports since 2010. The qualitative analysis was conducted to depict the characteristics related to the incident cases and health outcomes of e-cigarette and e-liquid exposure to support public awareness. **Results:** Since 2010, there was an increase in e-cigarette exposure incidents with ingestion, inhalation, ocular and dermal identified as the commonly reported routes of exposure in both children and adults. The clinical symptoms were well characterized based upon the specific route of exposure. The exposure incidents were categorized into age, sex, type of exposure, symptoms, management site and medical outcome. The children less than 5 years of age were unintentionally exposed followed by both unintentional and intentional exposure in adults. The reported medical outcomes have a range from minor effects exhibiting symptoms that were not bothersome to major effects with life-threatening symptoms, and death. The short-term or acute exposure was mostly associated with mishandling or misuse of the e-cigarette device or e-liquid. The case reports of young adult males who are linked to intensive use of e-cigarettes show lung injury. **Conclusion:** E-liquid and e-cigarette use continue to pose a serious health risk for both adults and children. There is accumulating data of incidents associated with short-term e-cigarette use or intensive use of e-cigarettes. However, monitoring of the long-term health effect of e-cigarettes is needed in order to raise public awareness among young adults.

INTRODUCTION

E-cigarettes were originally introduced as a smoking cessation device in 2003. Since 2007, the use of electronic cigarettes (e-cigarettes) has drastically increased with international patents and easy availability in the United States (US) and other countries. There are over 466 brands of e-cigarettes and 15,586 unique flavors available in the US (1, 2). There was an increase in the number of e-cigarette adult users from 2009 (1.8%) to 2010 (3.4%) (3). E-cigarettes have been the most commonly used tobacco product since 2014 among middle and high school students in the USA (4). Use of e-cigarettes is gaining popularity in the middle and high school adolescents who are either non-smokers -or past/current smokers (5-8). Several longitudinal studies have confirmed the positive correlation between e-cigarette use and the increased risk of initiation of traditional cigarette smoking among middle and high school students who are non-smokers.(3, 7-12). In fact, there was a 10-fold increase from 1.5% in 2011 to 16.0% in 2015 in the consumption of e-cigarettes among high school students (8).

The popularity of the e-cigarette continued to increase due to many reasons including, but not limited to, cost-effectiveness (9), attractive flavors (10), e-cigarette promotion through social media, motivation to help quit traditional cigarettes, ability to conveniently purchase e-cigarettes online and at kiosks in shopping malls, and its ease of use in public places where smoking is prohibited (11-15). The common perception regarding smoking e-cigarettes is that it is less harmful than smoking traditional cigarettes, mostly due to its harmless content which makes using them safer when compared to traditional cigarettes (9). E-cigarettes are not only increasingly

used but are reported to be misused among children, adolescents, and adults (16-18). The data from Monitoring the Future (MTF) survey showed that the perceived risk of regularly vaping e-liquid with nicotine is 41-42% among adults and 35% among 12th graders. The same survey results showed that the perceived risk of occasionally vaping an e-liquid containing nicotine was 19-20% among adults and 18% among 12th graders (19). The US Preventive Services Task Force looked at the perceived risk and reported that there was insufficient evidence to recommend e-cigarettes for tobacco cessation in adults as there was limited and contradictory evidence (20).

The National Poison Data System (NPDS) database and surveillance system is used by the American Association of Poison Control Centers (AAPCC) and the Centers for Disease Control and Prevention (CDC) for public health surveillance to improve the situational awareness for chemical and poison exposures (21, 22). NPDS is the data repository for all the US poison centers and collects information from phone calls to US poison centers. As of September 30, 2022, the AAPCC has reported 4787 e-cigarette and liquid nicotine exposure cases in all age groups (23). There is almost a 20-fold increase in the e-cigarette and liquid nicotine exposure cases reported to poison control centers from 2011 to 2021. These exposure cases are mostly due to the acute exposure to e-cigarettes and was categorized into short-term and intermediate health effects. The purpose of this review is to report the trends in and health effects of e-cigarette and liquid nicotine exposure cases reported to poison control centers in order to characterize the adverse health effects of e-cigarette and liquid nicotine use. These reports provide information on the results of short-term exposure to e-cigarettes and e-liquids. However, there is a lack of data on the long-term health effects of e-cigarette use. In this study, short-term e-cigarette and liquid nicotine exposure cases reported to poison control centers from 2010 until 2022, which were then published in peer-reviewed articles, were reviewed. The author has also discussed the long-term health effects in humans with respect to the route of exposure, symptoms, medical outcomes, and severity of accidental or intentional exposure of e-cigarette and liquid nicotine among adults and young users. So far, there is emerging, but very limited data, on the long-term health effects of e-cigarette use. The need of such data is crucial to bringing awareness to children and young adults.

METHODS

A search was made using the PubMed database and the Google search engine to ensure the selection was comprised only of peer-reviewed articles related to the health effects and clinical outcomes of e-cigarette exposure cases from the year 2010 until the year 2022. The keywords used included: (electronic cigarette), (poison control center), (United States) AND (electronic cigarette), (e-liquid), (short term exposure) AND (e-cigarette), (long-term health effect), (case reports). The relevant peer reviewed articles were assessed for eligibility after applying the inclusion and exclusion criteria. The inclusion criteria included the studies available for humans, English language, and free-full text. The exclusion criteria included full text not available, *in vivo studies,* and *in vitro* studies, social media reports, non-English language, insufficient data for the outcome and data related to the environment. The structure of the proposed framework for the review is provided in the flowchart (Figure 1).

Toxicity and components of e-cigarette

E-cigarette devices use a liquid mixture (e-liquid) that contains propylene glycol, vegetable glycerin, nicotine, and flavoring. While most research groups have reported nicotine content in commercially available e-liquids to be in the range of 0.3-5 percent (24-28), the discrepancy between the nicotine content labelled on the packaging and the result of chemical analysis done in laboratory studies showed a high percentage of 60-90% of nicotine in free or unprotonated form, which can be readily absorbed. This factor may contribute towards increasing uptake of nicotine by the user. The current report by the CDC on the frequency of e-cigarette use among middle school and high school students is four in 10 frequent users, and one in 4 daily users (19, 25, 27-31). The toxicity of nicotine inhalation includes proliferation of airway smooth muscle and epithelial cells that may contribute to small airway remodeling in COPD (32-34).

The use of flavorings in e-cigarettes has been a focus for marketing, and in 2020-2021, approximately eight in ten middle and high school students reported to use flavored e-cigarettes. In 2022, 14.5% of high school students and 3.3% of middle school students reported using e-cigarettes (4, 35, 36). The flavoring in e-liquids is a mixture of aldehydes such as benzaldehyde in fruits flavor or cinnamaldehyde in cinnamon flavors, diacetyl, acetoin, and acetyl propionyl (37-41). The aldehydes

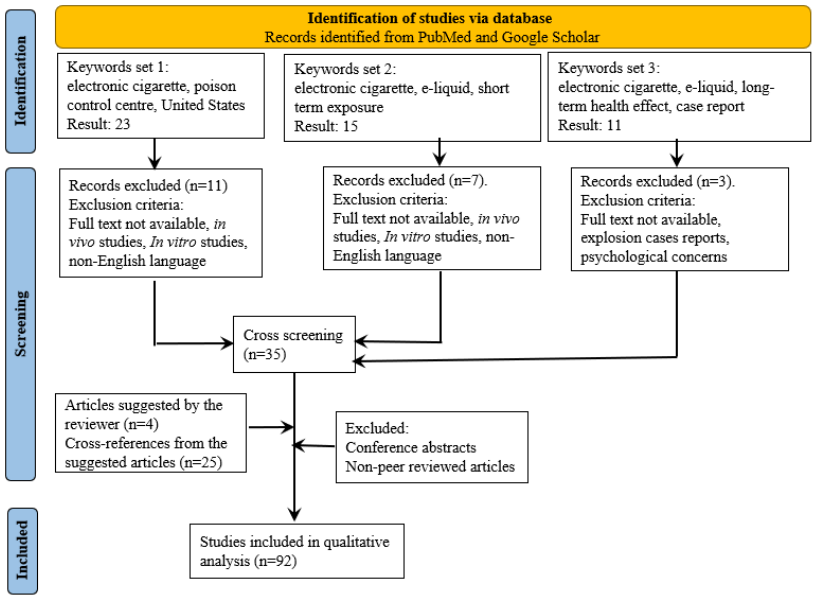

Figure 1. The structure of the proposed framework for the review is provide in the flowchart**.**

are cytotoxic primary irritant of mucosal tissue of the respiratory track and exert chronic respiratory effects. The flavoring chemicals are identified on the Generally Recognized as Safe (GRAS) list for ingestion. There is very limited data on the toxicity of flavoring chemicals that undergo heating, vaporization, and inhalation. There are few in *vitro studies* exploring the effects of e-cigarettes, however, the limitation of these studies is the consideration of factors such as deposition efficiency and puffing regime, that is difficult to extrapolate in the e-cigarette users (37).

The aerosols, from heating of e-liquids, release toxic compounds including carbonyl compounds (acetaldehyde, acetone, acrolein and formaldehyde) and metals (cadmium, lead, nickel, tin, and copper) that are generated as degradation products (42). The formation of aldehydes such as acetaldehyde and formaldehyde, and acrolein are reported due to the thermal degradation of propylene glycol and vegetable glycerin. The formaldehyde and acrolein form adduct with proteins and DNA thus resulting in the oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, and inflammation (43). The metallic taste reported during vaping is the result of metal particles. The metals, such as chromium, lead, nickel and tin, have been reported to cause in vitro and in vivo toxicity. The metals in e-cigarette aerosol is reported to contribute to the metallic taste in the mouth of the users during vaping. Metal may cause stenosis in humans, and *in vivo* and *in vitro* studies show cytotoxicity, oxidative stress and inflammation in lung and cardiac tissues (44, 45).

The common symptoms reported for e-cigarette exposure cases, specifically in children, included: tachycardia as cardiovascular clinical effect, pallor and erythema/flushing as dermal clinical effect, vomiting, nausea, oral irritation, and abdominal pain as commonly observed gastrointestinal clinical effect, drowsiness, agitation/irritability, ataxia as neurological symptoms, eye irritation/pain and red eye or conjunctivitis as ocular symptoms, and cough/choke as respiratory symptoms (46). E-cigarette users have reported the upper and lower respiratory tract symptoms including, but not limited to, mouth and throat irritation, dry cough, headache, nausea, dyspnea, and vertigo (47, 48). Jankowski et al has reported that the short-term exposure to toxic components of e-cigarettes may change the lung function and oxidative stress thereby leading to symptoms such as cough and shortness of breath, irritation of upper respiratory airways, lung function impairment, and bronchiolitis (29). The pulmonary toxicity, vaping associated lung injury (EVALI), dose-dependent cardiovascular, immunologic, and neuro-developmental effects have also been reported (49).

Study variables of e-cigarette reports

Since 1983, the U.S. poison control centers collects data and monitors exposure case data across the United States, for the purpose of epidemiological

studies related to exposure (47). As the availability and popularity of e-cigarettes has grown in the past few years, the need to monitor potential e-cigarette device and e-liquid exposure cases has also increased. According to the AAPCC, there were 269 e-cigarette and liquid nicotine exposures reported in 2011 and 5360 e-cigarette and liquid nicotine exposures in 2021. As of September 30, 2022, there were 4787 e-cigarette exposure calls listed on the AAPCC database (23).

E-cigarette device and e-liquid exposure have been characterized in different research as the patients age, sex, route of exposure**,** type of exposure source**,** management of incident**,** symptoms**,** clinical outcome, and reason for exposure**.** The route of exposure include ingestion, inhalation, dermal, ocular and/or multiple routes. Ingestion of e-liquids, specifically by children, is reported to be the major cause of e-cigarette exposure followed by inhalation and dermal or ocular both in adults and children. The type of exposure source could be from the e-liquid, e-cigarette cartridge, device or unknown. The management of the incident is either managed on site or managed at the hospital or other. The route of exposure may also define the symptoms, and symptoms may overlap with different route of exposure such as vomiting, and nausea are the common symptoms of ingestion, inhalation, and dermal exposure of e-cigarettes. The other symptoms related to ingestion may include drowsiness, tachycardia, and agitation. The dizziness is commonly seen as inhalation and dermal exposure. The other symptoms of inhalation/nasal exposure include agitation, and headache. The ocular exposure may lead to eye irritation or pain, red eye or conjunctivitis, blurred vision, headache, and corneal abrasion; dermal exposure may also result in headache, and tachycardia. The multiple routes may also cause eye irritation or pain, vomiting, red eye or conjunctivitis, nausea, and cough (16, 50). The reason for exposure could be unintentional, intentional, abuse, misuse, and suicidal attempt (16). The clinical outcome includes no effect, minor effect (drowsiness, first-degree burns, transient cough), moderate effect (isolated brief seizure, gastrointestinal symptoms causing dehydration) or major effect (respiratory failure requiring intubation, repeated seizures, coma) (50). The minor effects are the minimally bothersome symptoms that are limited to the skin and mucus membranes and are generally resolved rapidly with no residual disability or disfigurement (51). The moderate effects are the non-life threatening symptoms that are more prolonged or systemic in nature than minor symptoms with no residual disability or disfigurement with some form of treatment is indicated. The major effects are the life threatening symptoms that result in major disability or disfigurement (52-54).

E-cigarettes and liquid nicotine exposure report data

In 2007, electronic cigarettes (e-cigarette) were introduced to the United States market, since then e-cigarette sale and market has been doubled annually (55, 56). The increase in the sales of e-cigarettes led to the concomitant increase in the e-cigarettes and liquid nicotine human exposure cases reported to United States poison control centers. The US poison control centers added a new, unique code to specifically capture the e-cigarette calls. The e-cigarette exposure calls contain information on the exposure to e-cigarette device and nicotine liquid contained in its cartridge. In just a few years, there was a considerable increase in the e-cigarette exposure calls. From September 2010, there was an increase in 0.3% e-cigarette exposure calls from health care facilities that went up to 41.7% in February 2014. Figure 2 shows the AAPCC.org data with the increase in the number of exposure cases of e-cigarette and e-liquid from 2011 to 2022. AAPCC data is considered preliminary for 2021 and 2022 with the possibility of updating a case by poison center anytime during the year. Figure 2a show a consistent increase in the exposure calls from 2011 until 2014, followed by a slight decrease in phone calls until 2017, noticeable increase in 2018-2019, and a small change in trend thereafter. Figure 2b show the comparison between the pandemic and post pandemic data. There was a increase in the number of e-cigarette exposures from the month of May 2022, when compared to the last two years (2020 and 2021).

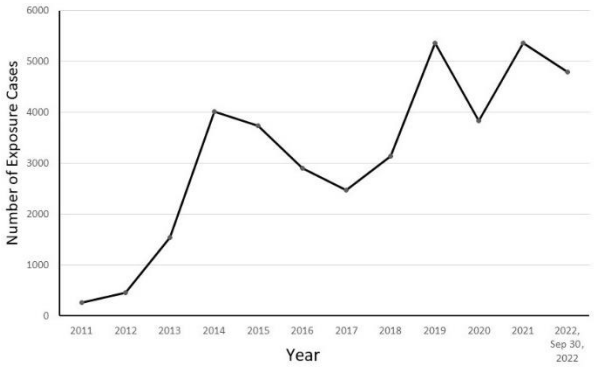

Figure 2a. The e-cigarette and liquid nicotine exposure cases in human population reported to the poison control centers in the Unites States

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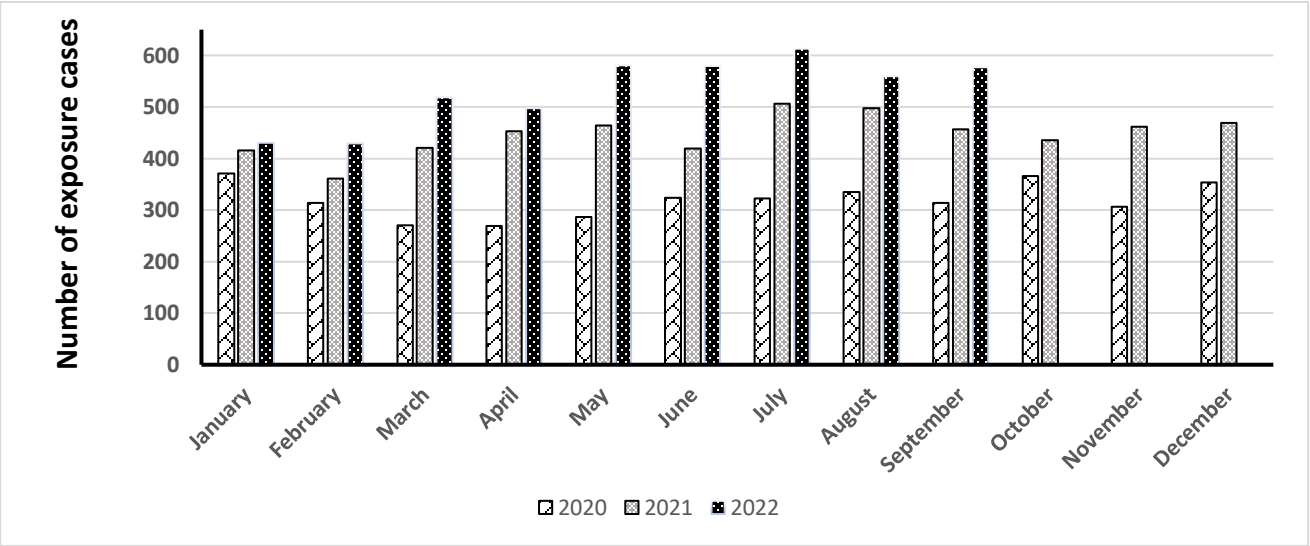

Figure 2b. Comparison of the e-cigarette and liquid nicotine exposure cases for 2020-2022 i reported to the poison control centers in the Unites States

Characteristics of e-cigarette exposure cases

***Route of exposure* (Table 1)**. Ingestion of whole or leaky cartridge and e-liquid contribute to the e-cigarette toxicity in almost 64.8-92.5% in children (50, 5457). The ingestion of e-liquid has been reported to show toxicity among children with unintentional (accidental) exposure. In both children and adult's inhalation accounted for over 9-16.8% exposure followed by dermal (5.9-8%) and ocular (4-8.5%) exposure (53-56). The unintentional exposure in children and adults accounted for 87% with intentional exposure of 5% and unknown exposure of <1% (58). There was also a single suicidal case via intravenous injection reported in the adult category for the liquid nicotine exposure (56). The exposure cases reported from 2010-2014 for all US poison call centers were in the age ranges of 51.10-58% for 0-5 years, 1.9% for 6-10 years, 5.5% for 11-19 years, and 34.70-42% for ≥20 years. The range of exposure reports maybe due to the update of the exposure cases by the US poison control centers during the specific month of the data collection (50, 56). Overall, there were more cases of e-cigarette exposure in children reported to US poison control centers, when compared to reports of adults in 2010-2014.

Medical outcome and severity of e-cigarette exposure. The severity of e-cigarette exposure or medical outcome are based on the identified or projected adverse clinical effects. The clinical symptoms reported for e-cigarette exposure were related to the route of exposure in adults and children. The most common symptoms were related to ingestion with the gastrointestinal (GI) effects. The clinical symptoms included vomiting, nausea, oral irritation, abdominal pain, and diarrhea. The cardiovascular effects reported were tachycardia, hypotension, bradycardia, asystole, and cardiac arrest. The dermal clinical effect reported were pallor, erythema or flushing, and irritation or pain. The neurologic effects included drowsiness/lethargy, agitation or irritability, ataxia, tremor, confusion, seizure, coma, and syncope among children. The ocular symptoms were red eye, and irritation or pain. The respiratory symptoms included cough, cyanosis and respiratory depression and arrest in children and adults (46, 50, 55). The medical outcome was shown as severe medical outcome, admission to healthcare facility, and clinical effects) with a range from no effect (20-46.6%) to major effect (0.1%) (46, 58).

Management site of incident. The management site is described as patients that were managed on site; already at/en route to a healthcare facility (HCF); not referred to HCF; referred to HCF but did not arrive or refused referral; managed at unspecified site; managed either at non-critical care unit or critical care unit or psychiatry unit; treated, evaluated, and released. It was reported by Wang et al that majority (60.9%, 10,565/17,358) of the patients were not referred to a HCF, followed by patients that were treated, evaluated, and released (27.4%, 4752/17,358) in the year 2010-2018 (57).

Sex. The majority of exposure cases reported were in males when compared to females with

unintentional exposure through ingestion followed by inhalation or respiratory intake of e-liquid and e-cigarette. The most common symptoms reported were nausea, vomiting and dizziness with the management of the patient on-site.

E-cigarettes explosion reports

The acute adverse effects associated with e-cigarettes including overheating, explosions, burns, and other injury has been reported earlier (17). There were 69 incidents reported during 2010 to 2019. The burn injury incident was reported to be highest in the adults with the mean age of 25 years or older, followed by the young adults and children. E-cigarette related burns were from leaking e-liquids, battery failures, battery overheating, custom device modification by the e-cigarette users, incompatible or poorly designed devices, the types and quality of batteries or chargers, and the lack of quality control by suppliers (17, 59). The injuries related to e-cigarette-related burns included thermal and chemical burns, with blast injuries to the face, hands, chest, shoulders and thigh or groin (17, 59). E-liquid is identified as a safety hazard, and the FDA has issued a guidance about its compliance policy for reporting vape battery fire or explosion to the FDA and limiting the safety modifications to battery-operated tobacco and other marketed products to address the potential e-cigarette battery-related injury in the users (60).

Long-term health effects of e-cigarettes

The case report of a 23-year-old male using an e-cigarette for four-years and increasing its use over the past several months due to stress and anxiety related to the COVID-19 pandemic, indicated that the vaping history was the etiology of vaping-related clotting phenomena with the central retinal vein occlusion as a medical outcome typically manifested as unilateral vision loss from thrombosis and occlusion of the central retinal vein with thrombophilic risk factor (63). The chronic use of an electronic cigarette has been reported to increase the platelet aggregation, upregulated adhesion receptors, and impaired vascular elasticity, thereby increasing the risk of thrombogenic events. There was a low possibility of COVID-19 infection as the underlying etiology of the central retinal vein occlusion due to the fact that a single COVID-19 testing performed was negative and the repeat antibody testing was not conducted as a follow-up.

The exposure of e-liquid and e-cigarette aerosol is a health hazard for pregnant women and may increase the risk of long-term cardiovascular complications. The onset of asthma due to irritative action on airways may become a long-term health effect of e-cigarette exposure in animals and humans (64, 65). Tumeo et al reported a case of a 15-year-old female with a history of smoking cigarettes, using an e-cigarette and occasional marijuana. The patient case was a typical e-cigarette or vaping product use Associated Lung Injury (EVALI) with a severe dyspnea, and a central ground glass pattern with peripheral sparing with chest CT scanning. The authors concluded in this study that there is a need of an observation for the long-term implications of e-cigarettes (66). Nemeh et al also reported a single case of EVALI in a 16-year-old patient using e-cigarette, nicotine, and tetrahydrocannabinol for 6-8 months (67). A descriptive analysis of EVALI cases in Canada from September 2019 to December 2019 has concluded that factors influencing EVALI in Canada are complex and multifactorial, and the lack of evidence make it important to investigate the long-term health effects of nicotine and cannabis vaping, including the possible influence on susceptibility to infectious diseases (68). A case report of a 17-year-old male with an intensive use of vaping flavored e-liquids and tetrahydrocannabinol showed a severe acute bronchiolitis with hypercapnic respiratory failure and chronic airflow obstruction (69). A case presentation of e-cigarette induced pneumothorax in a 19-year-old male with a history of frequently using the JUUL e-cigarette with nicotine for the past one year in order to quit smoking cigarettes was reported. After getting discharge from the hospital, the patient continued smoking cigarettes and marijuana but discontinued the use of an e-cigarette (70). Overall, the case reports were related to the pulmonary complications of intensive use of e-cigarettes are limited to EVALI, bronchiectasis, eosinophilic pneumonia, pleural effusion, and suspected hypersensitivity pneumonitis, and diffuse alveolar hemorrhage syndrome (71).

DISCUSSION

The retrospective study by Chatham-Stephens et al from September 2010 through February 2014 analyzed the frequency of electronic cigarette exposure and characterization of the adverse health effects associated with e-cigarettes (56). Across the United States between 2010 and 2014, there was an increase in the e-cigarette exposure calls with a trend related to the increase of cigarette exposure calls in summer months. There was an increase in the

Table 1. E-cigarettes and liquid nicotine exposure cases reported to the United States poison control centers reports.

Reference	Date range	Single/ multiple states data	Total case report	Total case report (0-5 years or as mentioned)	Case report (%)	Total case report (6-19 years)	Case report (%)	Total case report (≥20 years)	Case report (%)	Type of exposure/ reason of exposure	Route of exposure	Symptoms	Management of incident	Medical outcome	Sex (%)
(55)	2010-2012	single state		14 (8 months-8 years)	n/a	n/a	n/a	n/a	n/a	cartridge taste exposure.	ingestion, inhalation	transient cough with a pre-existing viral infection.	emergency and other	n/a	n/a
(55)	2010-2012	single state		n/a	n/a	n/a	n/a	21 (≥19 years)	n/a	swallowing whole cartridge or leaky cartridge.	ingestion, dermal, ocular	nausea, vomit, cough, chest pain, confusion, palpitation, dizziness, transient irritation.			
(56)	2010-2014	all states	2405	n/a	51.1	n/a	n/a	n/a	n/a	n/a	ingestion> inhalation>	vomiting, nausea, and eye irritation.	n/a	n/a	n/a
(56)	2010-2014	all states		n/a	n/a	n/a	42	n/a	42	single case of suicide by iv inj. Of liquid nicotine.	ocular> dermal		n/a	n/a	n/a
(58)	2009-2014	single state	225	119	53	13	6	93	41	unintentional > intentional> unknown	ingestion> multiple> inhalation>dermal> ocular	vomiting, nausea, headache, ocular irritation, dizziness, and lethargy.	on site> en/route to HCF> referral by poison center >unspecified site	no effect> minor effect> moderate effect.	Female>Male> unknown
(61)	2010-2013	all states	1700	717	42.2	n/a	n/a	466 (20-39 years)	27.4	accidental in children.	ingestion, inhalation, topical exposure.	n/a	n/a	minor effects	n/a
(46)	2012-2015	all states		4128	14.2	n/a	n/a	n/a	n/a	unintentional	ingestion> dermal> inhalation> ocular> other> unknown	cardiovascular dermal, gastrointestinal, neurological, ocular, respiratory and other symptoms.	on site, HCF, non-critical care unit, critical care unit	no effect >minor effect> moderate effect> major effect.	Male> Female> unknown
(50)	2010-2014	all states	5807	3341	58	108 (6-10 years) 314 (11-19 years)	1.9 (6-10 years) 5.5 (11-19 years)	2001	34.7	Unintentional: e-cigarette device and e-liquid.	Ingestion> inhalation> ocular> multiple routes> dermal> ear> parenteral	5% or above: vomiting, nausea, drowsy, tachycardia, agitation, headache, eye irritation, pain, red	HCF, non-HCF	Minor effect> moderate effect> major effect.	Male> Female

Table 1 continues…

												eye, blurred vision, corneal abrasion, and cough.			
(62)	2010-2015	Single state	98	57	58.2	n/a	n/a	30	30.6	unintentional	ingestion> inhalation> ocular> dermal> parenteral> other	symptoms related to the route of exposure.	on site> patent en route to/in HCF> referred by HCF	no effect= minor effect> moderate effect.	Male> Female
(54)	2012-2017	All states	8269	3146 (1 year), 6940 (<3 years)	83.9 (<3 years)	n/a	n/a	n/a	n/a	unintentional	ingestion of liquid nicotine.	symptoms related to the route of exposure. Rare severe clinical effects: coma, seizure, respiratory arrest, cardiac arrest.	HCF> enroute/in HCF	minor effect> moderate effect> major effect	Male> Female
(57)	2010-2018	all states	17,538	11,250	65	525 (5-11 years) 596 (12-17 years) 1443(18-24 years)	3 (5-11 years) 3.4 (12-17 years) 8.3% (18-24 years)	2667 (>25 years)	15.4 (>25 years)	unintentional	ingestion> dermal> inhalation> ocular>other	vomiting, nausea, ocular irritation, conjunctivitis, or red eye were common symptoms. Among children >5 years old, vomiting, coughing, or choking, and drowsiness or lethargy were common symptoms. were common symptoms.	not referred to HCF> HCF noncritical unit> critical care unit> psychiatric facility.	no effect> minor effect> moderate effect> major effect.	Male> Female> unknown
(59)	2010-2018	all states	69	2	2.9	8 (12-17 years) 20 (18-24 years)	11.5 (12-17 years) 29 (18-24 years)	30 (>25 years)	43.5 (>25 years)	n/a	body part: face> leg/thigh> hand> shoulder/ chest/genitals	superficial burn> 2nd-3rd degree burns> burns, not specified> oral burns	treated, evaluated, and released > not referred> admitted to hospital> refused referral or did not arrive at HCF	moderate effect> minor effect> major effect.	Male> Female

exposure cases in 0-5 years old children with almost 51.1% followed by young adults with a potential lack of data from the health-care providers and the public that might not have reported all e-cigarette exposures to poison control centers. In 0-5 years of age children, there were increasing cases of ingestion exposure. Weiss et al reported that the majority of exposures among patients of age 5 years or younger were due to ingestion of e-liquid when left unsupervised. Wang et al reported on the e-liquid exposure in children and adults to the Poison Control Centers in the United States from the year 2010 towards 2019 resulting in ocular toxicity due to the mishandling of the e-cigarette products (72). Exposures among patients 20 years and older were mainly unintentional and happened due to the malfunction of the e-cigarette cartridge which resulted in ingestion of e-liquid during vaping (62). The ocular route of exposures in 20 years and older were due to the patients mistakenly using the e-liquid as eye drops or accidently spraying e-liquid in the eye. The ocular exposure occurs when the patients were refilling the e-cigarette. The intentional misuse such as deliberate ingestion or intravenous injection of e-liquid has also happened (62). Vakkalanka et al reported that the majority of exposures to e-cigarette devices and components occurred in children 5 years of age or younger due to accidental exposure, and that the calls to poison control centers have dramatically increased since 2010 (61). In adults, the moderate effect included seizure or vomiting causing dehydration, and major effects included respiratory failure, hypertension, drowsiness, seizure, confusion, dystonia, hallucinations, electrolyte abnormality, and renal failure. In children, the major effects were reported to be cyanosis and respiratory arrest, or nausea, vomiting, seizure, and coma due to ingestion of e-liquid. The health effects in adults could also include dysrhythmia, hypotension, tachycardia, fever, acidosis, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels between 100 and 1000 international units per liter (IU/L), seizures, and cardiorespiratory arrest (50). Therefore, based upon the route of exposure, there could be a multiple set of health effects that were reported to the poison control centers.

E-liquid exposure is common not only in the children and adults with significant toxic responses but has been reported in the suicidal case incident (58). The study by Wang et al demonstrated that the annual number of e-cigarette exposure cases initially increased in 2014 and then decreased each year until 2017, followed by the increase in 2018 accounting for a 25% increase. The majority of the cases were reported in children under the age of 5 followed by children aged 5–17 years and young adults aged 18–24 years. Exposure to e-liquid containing a high quantity of nicotine led to life-threatening symptoms or serious medical outcomes. The reason for annual declines in e-cigarette exposure cases between the years 2015 and 2017, and an increase in 2018 could be due to the development of new tobacco products (57). Hughes and Hendrickson reported that the majority of the pediatric (72%; 139/193) and adult (61%; n = 44/72) exposure cases involved e-liquid refill containers or fluid (72). The route of exposure in children was mainly ingestion of refill liquid. Seventy-one specific products/brands were identified with nicotine concentrations ranging from 0 mg/mL to 60 mg/mL with one product containing 3000 mg in a single bottle. A variety of flavors were identified, including several with names that may be attractive to toddlers or adolescents.

The study by Govindarajan et al reported that the states that did not had the preexisting law requiring child-resistant packaging for liquid nicotine containers had more cases of exposure in children and there was a significant decrease in the mean number of exposures after the federal child-resistant packaging law went into effect (54). The researchers also concluded since 2015 there was a decline in the pediatric exposures to liquid nicotine which may, in part, be attributable to legislation requiring child-resistant packaging and greater public awareness of risks associated with electronic cigarette products.

The limitation of data for e-cigarette acute exposure is mainly due to the vast variety of commercially available e-cigarette device designs, pattern of use, and variability in the commercially available aerosolized solutions. (73). According to a survey querying e-cigarette users, consumers perceive the e-cigarettes as a safe and cheaper alternative to quitting smoking and helping in withdrawal symptoms during quitting of smoking (74, 75). There is a growing body of evidence that e-cigarettes are not a harmless alternative to traditional cigarettes, and that there is an emerging trend among youth and adults (76). The meta-analyses of clinical trials and observational studies assessed the association between e-cigarettes and traditional cigarette smoking among adults and concluded, among smokers, that the e-cigarettes are associated with significantly less quitting (77). The acute e-cigarette use may lead to increases in the blood pressure, thereby causing endothelial dysfunction

and increased vascular and cerebral oxidative stress (78). The 2019 data from Monitoring the Future (MTF) survey indicated the perceived risk of occasionally vaping an e-liquid with nicotine was reported to be 19-20% among adults and 18% in 12th graders. The regular vaping nicotine was reported to be 41-42% among adults and 35% among 12th graders (79).

However, there is a limited amount of published data showing the safety of e-cigarette solution and e-liquids, and inhalation of vapor. The vapor generated from e-cigarettes includes cytotoxic substances such as carbonyls including formaldehyde, acetaldehyde, acrolein and propionaldehyde. The toxic compounds including N-nitrosamines, volatile organic compounds such as toluene, benzene, inorganic compounds such as nickel, cobalt, chromium, lead, nicotine, and particulate matter have been reported (19, 78, 80), while the e-cigarette liquid contains nicotine, propylene glycol and glycerin (80, 81). The tobacco specific nitrosamines were found in nicotine containing e-cigarette vapor. The e-liquid contained nicotine, propylene glycol and glycerin which are known to produce ocular irritating effects. The propylene glycol is metabolized to potentially toxic compounds like lactate and propionic acid (82), which need further study and analysis. There is a considerable amount of data regarding the adverse acute or short-term effect of e-cigarette use on the cardiovascular system due to oxidative stress and endothelial dysfunction (43). The short-term health effects of e-cigarette use in healthy smokers were reported to cause marked impairment of endothelial function and an increase in arterial stiffness (83). The long-term cardiovascular health effects of e-cigarettes are limited and controversial. The chronic exposure of mice to e-cigarette vapor for 8 months reported to exert arterial stiffness or endothelial dysfunction in isolated vessels (78). This observation was similar to the acute exposure of rats to e-cigarettes containing nicotine, as there was a decrease in their endothelial function. A systematic review and meta-analysis reported that e-cigarettes should not be labelled as a safe product as there is evidence of impaired endothelial function in the cardiovascular system (84).

The use of e-cigarettes by adolescents has substantially increased since 2016. The flavoring in the e-cigarettes serves as one of the factors leading to an increase in the e-cigarette use among youth. The public health agencies do not have any policy that prohibit or regulate the restrictions of selling the flavored e-cigarettes which are popular among adolescent and young adults (85). The increasing use of vaporized cannabis such as tetrahydrocannabinol (THC) is concerning in the youth as there is available evidence that youth using nicotine through vaporizers are more likely to subsequently use cannabis through e-cigarettes (86, 87). The risk of using nicotine may serve as a risk factor for subsequent cannabis vaping (88). An increased attention towards the youth trend is needed as cannabis legalization is continuing across the USA.

CONCLUSIONS

Overall, there was an irregular trend of e-cigarette exposure case reports to AAPCC, as there was an increase in the e-cigarette exposures between the years 2010 and 2014 (3742 case reports) followed by the decreasing cases in the years between 2015 and 2017, and then a 25% increase was observed in 2017 (2320 cases) and in 2018 (2901 case reports). Approximately two-thirds (64.8%) of all cases were in children under age five, and 14.7% were in children aged 5–17 years or young adults aged 18–24 years. The ever-evolving tobacco use made the continued surveillance of e-cigarette poisoning exposures important. The continuous monitoring may aim at preventing e-cigarette poisoning. Generally, males have been reported to have more exposures than females. The study conducted by Kamboj et al reported that the frequency of exposure in children for the e-cigarette and nicotine liquid is increasing (46), and the children exposed to e-cigarettes are more likely, 5.2 times, to be admitted to a health care facility than children exposed to cigarettes.

There is a report of an adult suicide death in the USA associated with e-liquid. There are other health outcomes with adults developing cardiac arrest and seizures following intravenous injection of e-liquid (89). The intentional ingestion of nicotine solutions in e-liquids can rapidly cause seizures, paralysis, respiratory arrest, and cardiovascular collapse. Devices refilled with a fatal number of nicotine-containing solutions called e-liquid could lead to serious morbidity or mortality (89). Small children are especially susceptible to nicotine exposure due to the e-cigarette users at home (90) leading to unintentional exposure. The unintentional exposure is accidental ingestion of the attractively-flavored solutions in liquid nicotine solution bottles that are not childproof (58). The most popular concentration of nicotine liquid is 20 ml in a bottle of 18mg/ml (90)

which may lead to the oral toxicity. With the increase in popularity in young people in the United States, the increasing number of cases reported to poison centers may be correlated with the rise in the number of e-cig users, and therefore there is a need of regulatory action to address the risk of e-cigarette liquid exposure that may contribute to changing this trend. The increased use of e-cigarette in the last few years, high concentration of nicotine liquid, lack of information on other chemicals in the e-liquid, and missing child-resistant containers are the factors responsible for the safety concerns in the public health (91). There are upcoming studies in the different organ systems including cardiovascular, pulmonary, and immune system in respect to the exposure of e-cigarettes. Although there are reported exposure calls to United States poison control centers regarding the acute and short-term ocular and dermal toxicity, yet there is a very limited amount of published data on exposure to e-cigarette vapor and e-liquid (82, 92). There is a need to track long-term adverse effects of using the e-cigarettes, as there is limited data for human exposure with intensive use of e-cigarettes. There is a need for prevention strategies that include public awareness, education and additional regulation of appropriate product storage, warning labels, knowledge about the modifications of e-cigarette devices, e-liquid and e-liquid container and good packaging for making it less accessible to children. The public health efforts are needed to control flavoring in the e-cigarettes and attractive advertising that are directed at the young users.

CONFLICTS OF INTEREST. None to declare.

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