



## Review Article

## Potential health effects of electronic cigarettes: A systematic review of case reports

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## ABSTRACT

The health risks associated with electronic cigarettes (ECs) are largely unknown. The purpose of this systematic review was to evaluate published case reports that deal with health effects attributed to EC use. An Internet search was conducted to identify case reports dealing with the effects of EC use on health. Twenty-six case reports representing 27 individuals (one study contained reports for two individuals) were published between April 2012 and January 2016, and these were grouped into categories of effect according to their health outcomes. Of the 27 individuals, 25 had negative effects subsequent to use or exposure to ECs and their refill fluids, while two reported improvement in chronic immune and gastrointestinal conditions. Three categories of negative health effects were identified: systemic effects, nicotine poisoning, and mechanical injury. Thirteen cases reported EC effects on different systems including: respiratory (6), gastrointestinal or developing intestine of an infant (3), cardiovascular (2), neurological (1), and immune (1). Twelve cases involved nicotine poisoning resulting from accidental ( $N = 3$ ), misuse/abuse ( $N = 1$ ), or suicidal/intentional ingestion ( $N = 8$ ); four of these involved children and three resulted in adult fatalities. Two cases reported mechanical injury caused by an EC battery explosion. Most case reports show that the health of children and adults can be negatively affected by EC products and that if death does not occur, negative effects can be reversed. Data further indicate that EC use can cause negative health effects in previously healthy individuals and exacerbate pre-existing conditions.

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## 1. Introduction

Electronic cigarettes (ECs) are battery-operated devices that heat a liquid containing propylene glycol and/or glycerin, nicotine, and flavorings to produce an aerosol which users inhale (Trtchounian and Talbot, 2011; Grana et al., 2014). In spite of their rapid rise in popularity and worldwide sales, the effects of EC use on short and long-term human health are poorly understood. Because EC aerosol contains fewer chemicals than conventional tobacco smoke, EC are often considered a safe alternative to cigarettes. However, EC are not without health risks.

Information linking EC use to health effects has been gained mainly from short-term *in vitro* studies with cultured cells and *in vivo* experiments with human subjects (Pisinger and Døssing, 2014). *In vitro* studies have shown that cytotoxic effects vary among EC refill fluids (Bahl et al., 2012), some flavor chemicals (such as cinnamaldehyde) have toxicity at the concentrations used in EC (Behar et al., 2014a,b; Lerner et al., 2015), and stem cells are more sensitive than differentiated adult lung cells to EC products (Bahl et al., 2012; Behar et al., 2014a). Recent studies have further shown that EC aerosols induced DNA strand breaks and reduced cell survival *in vitro* (Yu et al., 2016). EC aerosols also reduced endothelial barrier function in cultured lung microvascular endothelial cells and increased inflammation and oxidative stress in mice (Schweitzer et al., 2015; Sussan et al., 2015). Most *in vivo* studies have involved experiments with human subjects, and these were recently reviewed (Pisinger and Døssing, 2014). An infodemiological study of online forums found 405 different health-related effects (78 positive, 326 negative, 1 neutral) attributed by users to EC (Hua et al., 2013). Of recent concern is the finding that a high percentage of EC refill fluids contain toxicants such as diacetyl and diethylene glycol (Westenberger, 2009; Varlet et al., 2015; Allen et al., 2015), and EC aerosols contain formaldehyde-hemiacetals, ultrafine particles, and metals (Jensen et al., 2015; Williams et al., 2013, 2015). The EC industry is making hundreds of new EC models and thousands of flavors of e-liquids or refill fluids available to consumers (Zhu et al., 2014; Tierney et al., 2015). Although many of these flavors are considered safe for ingestion by the Flavor Extracts Manufacturers Association (FEMA), their inhalation safety has not been established by FEMA (Hallagan, 2015).

Additional information on EC health effects can be gained from case reports on EC users who present to physicians with symptoms attributed to EC use or exposure. The number of case reports that appears in the peer-reviewed literature has reached a critical mass and is currently worth mining to gain further insight into the positive and negative health effects appearing in EC users. The purpose of this study was to systemically collate and analyze the existing case reports linking EC use to health outcomes and to identify categories of health effects related to EC use.

## 2. Methods

This review follows the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines for conducting systematic reviews. The flowchart for the systematic review is represented in Fig. 1.

### 2.1. Search strategy

An Internet search using the keywords or phrases: “electronic cigarette”, “e-cigarette case reports”, “e-cigarette case studies”, and “e-cigarette nicotine poisoning case reports” was carried out in PUBMED, MEDLINE, and general internet search engines. Additional

searches with the keywords followed by year were used (*i.e.* “e-cigarette case report 2012”). References in case reports or other related peer-reviewed literature also contributed to gathering literature.

### 2.2. Inclusion criteria

Case reports and reviewed abstracts dealing with health effects attributed to EC use or exposure were included. At a minimum, the cases reporting systemic effects needed to: (1) clearly discuss the patient’s symptoms upon presentation and (2) be reported and diagnosed by healthcare professionals.

Similarly, cases reporting nicotine poisonings or mechanical injuries needed to provide information concerning the context of EC use and/or summarize health impacts on the patient documented by a healthcare professional.

### 2.3. Exclusion criteria

Case reports or abstracts that reported on EC use or EC products without direct correlation to health effects were excluded from the study. Reports that dealt with health effects caused by liquid nicotine unassociated with EC were not included.

### 2.4. Identification and selection of case reports

The search strategy identified 49 articles that attributed health effects to EC use or EC products. Twenty-two of these consisted of original case reports and abstracts that matched search criteria for articles dealing with health effects attributed to EC use or exposure. Nineteen were in the peer-reviewed literature and five were reviewed abstracts (one of these presented two individual cases). The authors agreed on the inclusion criteria for case reports and reviewed conference abstracts that contained sufficient details on health effects related to EC for inclusion in the Results section. The general search yielded 27 articles and news reports that were not included in the evaluation; however, five of these which relate to death and serious illness as well as two regarding perception of EC use during pregnancy are included in the Discussion section. In addition, examination of reference lists in case reports and articles (Ruokolainen et al., 2015; Kim and Baum, 2015) that cited case reports yielded four reports for inclusion (Eberlein et al., 2014; Schipper et al., 2014; Bartschat et al., 2015; Gupta et al., 2014). These literature references also yielded one additional case that reported that adverse health effects associated with liquid nicotine not found in the online search (Kivrak et al., 2014). This case was confirmed to be linked to EC use by correspondence with the original authors (Kivrak et al., 2014).

## 3. Results

### 3.1. Overview of case reports

Of 26 case reports for 27 individuals identified in the Internet search, 25 individuals experienced negative health effects and 2 reported positive or improved outcomes attributed to EC usage (Table 1). The case reports came from 10 countries and included pediatric and adult populations ranging in age from newborn (1 day old) to 70 years old. Most users who experienced health effects were adults (male  $N = 15$ ; female  $N = 7$ ) and five were children. A few case reports dealt with EC users who were former smokers ( $N = 3$ ) or quit smoking for one month or more ( $N = 3$ ). Three deaths were associated with EC use. The case report cohort included 13 individuals with pre-existing health conditions (eight

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