Safety and Efficacy of Electronic Cigarettes: A Comprehensive Review of Toxicological and Clinical Evidence

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Introduction

Electronic cigarette (EC) products continue to undergo rapid technological evolution, and findings from earlier-generation devices may not be generalizable to newer models that incorporate higher battery capacity, adjustable voltage systems, and modified aerosolization mechanisms [1]. Variability in device engineering, nicotine formulation, and heating temperature significantly influences toxicant generation and nicotine delivery efficiency, thereby complicating direct comparisons across studies. In addition, marketing strategies, regulatory frameworks, and sociocultural influences differ between countries, contributing to heterogeneous patterns of EC uptake and variable public health consequences [2,3]. The overall impact of ECs must therefore be evaluated within the broader landscape of persistent combustible tobacco availability, widespread dual use of ECs and conventional cigarettes among adults and youth, and shifting perceptions of nicotine risk [2,3].

A comprehensive assessment of EC safety requires examination of toxicant exposure, pharmacokinetic nicotine delivery, respiratory and cardiovascular effects, and real-world patterns of use. Such evaluation is critical for the development of evidence-based regulatory policies aimed at protecting both smokers and nonsmokers, including vulnerable populations such as adolescents and pregnant women, particularly in light of aggressive marketing tactics

employed by the tobacco and vaping industries [4]. Despite widespread promotional claims, current scientific evidence does not conclusively substantiate assertions that ECs are either harmless alternatives to combustible cigarettes or reliably effective smoking cessation tools [5]. Moreover, the potential for EC use to renormalize nicotine consumption and undermine existing tobacco control measures remains a public health concern. To minimize unintended negative consequences on prevention and cessation efforts, EC use should be restricted in environments where conventional smoking is prohibited, and regulatory oversight—including advertising and marketing restrictions—should be comparable to that applied to traditional tobacco products [6].

Keywords : Electronic cigarettes; E-cigarettes; Vaping; Electronic nicotine delivery systems (ENDS); Nicotine delivery; Smoking cessation; Harm reduction

Types of E-Cigarettes

Electronic cigarettes are available in multiple configurations that vary in size, battery capacity, refill mechanisms, and nicotine delivery efficiency [7]. The earliest and simplest format is the disposable e-cigarette, which closely resembles a conventional cigarette and consists of a small battery connected to a prefilled cartridge containing an atomizer and e-liquid, with or without nicotine. These devices are neither rechargeable nor refillable and are discarded once aerosol production declines. Rechargeable e-cigarettes represent the next category; although similar in appearance to traditional cigarettes, they incorporate rechargeable batteries and replaceable cartridges or cartomizers that heat nicotine-containing solutions. Some models regulate puff duration and airflow to improve aerosol consistency and nicotine delivery [8]. More advanced devices include pen-style, medium-sized rechargeable e-cigarettes, which are larger than conventional cigarettes and typically feature higher-capacity batteries and refillable reservoirs such as clearomizers. These often incorporate manual activation switches, allowing users to control puff duration and intensity. The most sophisticated systems are tank-style, large-sized rechargeable devices—commonly referred to as advanced personal vaporizers or “mods.” These devices include high-capacity batteries, refillable tanks, and adjustable voltage or wattage settings, enabling greater customization of aerosol production. Because tank systems can generate higher temperatures and larger aerosol volumes, they may significantly influence nicotine pharmacokinetics and toxicant formation [9]. The considerable variability in device engineering across generations

underscores the necessity for device-specific evaluation in toxicological, pharmacological, and clinical research.

Chemical Constituents

Analyses of cartridge-based e-liquids from several brands have demonstrated poor concordance between labeled nicotine concentrations and actual measured content, raising concerns regarding product standardization and quality control [10]. Simulated e-cigarette use has shown substantial variability in nicotine delivery, with individual puffs containing between 0 and 35 µg of nicotine. At a higher delivery rate of approximately 30 µg per puff, an estimated 30 puffs would be required to achieve the 1 mg nicotine dose typically delivered by smoking a conventional cigarette [11]. Even under optimal conditions, a single puff from the e-cigarette with the highest nicotine content delivered only about 20% of the nicotine found in a puff of a combustible cigarette [12]. Importantly, nicotine exposure from e-cigarettes is strongly influenced by user behavior, including puff duration, frequency, and inhalation patterns. Comparative analyses of UK-manufactured e-cigarette brands revealed that nicotine concentration in cartridge e-liquid was not significantly correlated with the amount of nicotine detected in the generated aerosol, underscoring the critical role of device engineering characteristics—such as heating coil efficiency and airflow dynamics—in determining nicotine delivery, even under standardized puffing protocols [13].

Further chemical evaluation comparing aerosols from 12 e-cigarette brands, a conventional cigarette, and a pharmaceutical nicotine inhaler identified measurable levels of toxic and carcinogenic compounds in e-cigarette aerosol. Although the concentrations of these toxicants were generally 1–2 orders of magnitude lower than those observed in cigarette smoke, they were consistently higher than levels detected in the nicotine inhaler, which is an approved nicotine replacement therapy [14]. These findings suggest that while e-cigarettes may reduce exposure to certain combustion-related toxicants, they are not devoid of potentially harmful constituents.Nicotine Absorption Early studies of nicotine absorption in 2010 found that e-cigarettes delivered much lower levels of plasma nicotine than conventional cigarettes, whereas a more recent study demonstrated that more experienced users using their own product who engaged in more puff intervals have nicotine absorption similar to that with conventional cigarettes, perhaps as a result of a combination of characteristics of the devices and user vaping topography. [15] Another study of smokers smoking e cigarettes using a specified protocol found a similar rise in serum cotinine

immediately after use (mean increase, ≈20 ng/mL). Several studies reported that regard- less of nicotine delivery, e-cigarettes can modestly alleviate some symptoms of withdrawal, and participants positively appraised the use of e-cigarettes. [16] In a study comparing the nicotine inhalator and e-cigarettes, the nicotine inhalator delivered an amount of nicotine similar to that in the 16-mg e-cigarette; however, the authors noted that the e-cigarette malfunctioned and did not deliver any nicotine in a third of participants. [17] These results highlight the need for product regulation in terms of drug delivery and effects, as well as device functioning and labeling. [18]

Health Effects

Propylene glycol (PG) and glycerin are the primary base components of e-cigarette liquids. Inhalation of PG may cause eye and respiratory irritation, and prolonged industrial exposure has been associated with central nervous system and behavioral effects [31]. Regulatory and safety agencies have cautioned against inhalation of PG mists due to irritant potential [19]. When heated, PG can form propylene oxide (an IARC Group 2B carcinogen), and glycerol may generate acrolein, a known upper respiratory tract irritant [20].

Reported adverse events associated with e-cigarette use range from mild symptoms such as throat irritation, cough, nausea, and vomiting to serious injuries including device explosions and burns [21]. Short-term pulmonary studies in healthy smokers have shown no significant changes in spirometry after brief e-cigarette use; however, increased dynamic airway resistance (18%) and reduced exhaled nitric oxide (16%) have been observed, suggesting acute airway effects [22]. These findings indicate possible peripheral airway constriction, particularly concerning for individuals with asthma, emphysema, or chronic bronchitis [23].

Comparative studies demonstrate that conventional cigarette smoking causes significant reductions in lung function parameters, whereas active or passive e-cigarette exposure does not produce similar immediate spirometric decline [38]. Additionally, cigarette smoking increases white blood cell counts, reflecting systemic inflammation, whereas short-term e-cigarette exposure has not shown comparable inflammatory biomarker elevation [24]. However, elevated exhaled nitric oxide levels have been reported in users of nicotine-containing e-cigarettes, indicating potential pulmonary inflammation [25].

Some industry-funded risk assessments have concluded that e-cigarette aerosol does not pose significant inhalational health risks [26]. However, methodological concerns, including

failure to detect established carcinogens in cigarette smoke and reliance on occupational exposure threshold limits, limit the validity of these conclusions .Occupational exposure standards may not adequately account for vulnerable populations such as children, pregnant women, or individuals with chronic disease who may be exposed to secondhand aerosol [27].

In summary, while short-term studies suggest that e-cigarettes may have fewer acute pulmonary and inflammatory effects than conventional cigarettes, measurable biological changes occur. Long-term health consequences remain uncertain due to insufficient duration of widespread use [28].

Clinical Trials

Four clinical trials have evaluated the efficacy of e-cigarettes for smoking cessation, although two involved very small sample sizes and three lacked a non–e-cigarette control group [48]. Only one study compared e-cigarettes with standard nicotine replacement therapy (21-mg nicotine patch). Importantly, none of the trials incorporated the intensive behavioral support typically included in pharmaceutical smoking cessation programs [29].

A proof-of-concept study conducted in Italy in 2010 enrolled smokers aged 18–60 years who were not intending to quit. Participants were provided Categoria e-cigarettes and instructed to use up to four 7.4-mg nicotine cartridges daily to reduce cigarette consumption . At six months, 68% completed follow-up: 13 participants became dual users, 5 continued exclusive cigarette smoking, and 9 quit tobacco cigarettes while continuing e-cigarette use [. Dual users showed a ≥50% reduction in cigarette consumption (25 to 6 cigarettes/day; P<0.001) . At 24 months, among 23 participants, 5 had quit smoking entirely and 11 maintained significant reductions (24 to 4 cigarettes/day; P=0.003) [53]. However, absence of a control group and use of an early-generation product limit interpretation of efficacy [20].

A similar small study involving 14 smokers with schizophrenia found that 50% achieved a ≥50% reduction in cigarette use at 52 weeks, and 14.3% achieved sustained abstinence . No worsening of psychiatric symptoms was observed . Nevertheless, results are not generalizable due to the small sample size and lack of controls [31].

A randomized quasi-controlled trial compared three groups: 7.2-mg nicotine e-cigarette, nicotine tapering (7.2 mg followed by 5.4 mg), and non-nicotine e-cigarette . All groups demonstrated similar reductions in cigarette consumption (7–10 cigarettes/day at 1 year).

Quit rates at 1 year were modest and not statistically different (4% placebo, 9% low nicotine, 13% high nicotine) . Early quitters tended to maintain abstinence, whereas others continued dual use . Approximately 26% of quitters were still using e-cigarettes at 1 year. Study limitations included absence of a true control group and product variability [32].

Safety

Safety concerns surrounding electronic cigarettes (ECs) primarily relate to aerosol composition, thermal degradation products, nicotine toxicity, and vulnerable population exposure. Aerosol generation temperature varies depending on device design and carrier substances. Glycerol requires higher heating temperatures than propylene glycol (PG), and temperatures exceeding 100°C may produce toxic by-products such as acrolein, a potent irritant of the skin and respiratory tract [33].

Data extrapolated from chronic exposure to theatrical fogs containing PG or mineral oils suggest possible associations with airway obstruction, systemic inflammation, and mild reductions in lung function parameters such as FVC and FEV1 . Acute EC use for five minutes has not consistently demonstrated spirometric changes but has been associated with decreased exhaled nitric oxide (FeNO) and increased pulmonary impedance—potential early markers of airway obstruction . However, PG is widely used as a pharmaceutical carrier (e.g., nebulized medications) without established long-term adverse effects, making the clinical significance of these findings uncertain [34].

Unlike conventional cigarette smoking, which is associated with elevated inflammatory markers and systemic inflammation, short-term active or passive EC exposure has not demonstrated significant increases in white blood cell counts or other acute inflammatory biomarkers [35]. Nevertheless, long-term systemic effects remain unknown.

Nicotine toxicity from refill fluid ingestion is an additional safety concern. Traditional estimates suggest lethal nicotine doses of 40–60 mg [36], although recent toxicological analyses indicate that fatal doses may be considerably higher (0.5–1 g) [37]. Despite uncertainty regarding exact lethal thresholds, accidental ingestion—particularly among children—remains a regulatory concern. The effects of EC use during pregnancy are also unclear [38].

In vitro cytotoxicity studies demonstrate that embryonic and neonatal stem cells are more sensitive to EC refill fluids than adult lung fibroblasts, with flavoring agents implicated as primary contributors to toxicity rather than nicotine, PG, or glycerin alone. Early FDA testing identified tobacco-specific nitrosamines (TSNAs) and diethylene glycol (DG) in some cartridges; DG is associated with significant systemic toxicity [36].

Subsequent analyses confirmed that EC aerosols contain carbonyl compounds (formaldehyde, acetaldehyde, acrolein), volatile organic compounds (toluene, xylene), TSNAs, and heavy metals (cadmium, nickel, lead). Although these substances are generally present at levels 9–450 times lower than in conventional cigarette smoke and often comparable to pharmaceutical nicotine inhalers, their presence underscores that ECs are not risk-free.[40]

Efficacy

Electronic cigarettes (ECs) may serve multiple roles—as smoking cessation aids, nicotine delivery systems, or harm-reduction tools. Harm reduction emphasizes minimizing adverse health consequences rather than achieving complete abstinence. ECs are designed to simulate conventional smoking by delivering aerosolized nicotine in varying concentrations.

Nicotine delivery from ECs varies widely across brands. Analyses show that a single cartridge may contain between 0.5–15.4 mg of nicotine, typically delivered within 150–180 puffs [76]. However, 15 puffs (approximately equivalent to one conventional cigarette) generally deliver substantially less nicotine than a tobacco cigarette (0.025–0.77 mg vs. 1.54–2.60 mg). This variability reflects differences in device design, user behavior, and aerosol generation.[41]

Survey data suggest high self-reported cessation benefits. Among current EC users, 63% reported quitting smoking, and 95% of former smokers attributed cessation to EC use. Reported benefits included improved breathing, reduced cough and throat irritation, and assistance with quitting. In individuals with prior failed quit attempts, EC use was associated with cigarette reduction in two-thirds of participants, temporary abstinence in nearly half, and sustained abstinence in approximately one-third at six months. More frequent EC use was associated with higher abstinence rates. Notably, reduced craving has been observed even with nicotine-free ECs, indicating that behavioral and sensory cues play an important role in smoking dependence [42].

Prospective studies further support modest reduction effects. In a six-month study of smokers not intending to quit, 32.5% achieved a ≥50% reduction in cigarette consumption, and 22.5% maintained abstinence at 24 weeks. In a 12-month randomized controlled trial of 300 participants, 23% reduced smoking by half at 12 weeks, though only 14.5% maintained reduction at 52 weeks; the overall quit rate at one year was 11%. Although differences from placebo were not statistically significant, these outcomes are comparable to some nicotine replacement therapies (NRTs). A post-hoc non-inferiority analysis suggested that ECs may be at least as effective as nicotine patches in certain contexts.[43]

The Impact of e-Cigarettes on Lung Function

Beyond potential carcinogenic risks, the respiratory effects of e-cigarette (EC) use warrant careful evaluation. The primary aerosol constituents—propylene glycol (PG) and glycerol—are chemically similar to theatrical fogs.[44] Acute exposure to PG for one minute in healthy individuals has been associated with a small but statistically significant reduction in FEV1/FVC (2%, $P = 0.049$), although changes in FEV1 and FVC alone were not statistically significant. Longitudinal occupational studies of theatrical fog exposure have demonstrated approximately 5% reductions in adjusted FEV1 and FVC among workers with closer proximity to fog-generating machines, suggesting potential chronic airway effects. While these findings cannot be directly extrapolated to EC use, they raise concerns regarding similar aerosol exposures.[45]

Short-term studies in EC users provide mixed results. In healthy smokers, five minutes of EC use increased total respiratory impedance, airflow resistance, and peripheral airway resistance, accompanied by reduced fractional exhaled nitric oxide (FeNO), indicating possible acute airway inflammation and oxidative stress. However, in a controlled crossover study evaluating active and passive EC exposure among smokers and never-smokers, no significant changes were observed in FEV1 or FEV1/FVC following EC exposure. In contrast, conventional cigarette smoking produced a significant acute decline in FEV1/FVC (7.2%, $P < 0.001$) [26-49].

Overall, available evidence suggests that ECs produce smaller acute impairments in lung function compared to combustible cigarettes. Nevertheless, studies are limited by small sample sizes and short exposure durations. Long-term respiratory and cardiovascular

outcomes remain unknown, emphasizing the need for continued surveillance and standardized regulatory oversight [50].

Conclusion

While regulatory discussions have largely focused on the toxicological profile of e-cigarettes and their potential role in smoking cessation, the rapid expansion of the e-cigarette industry—supported by aggressive marketing strategies reminiscent of mid-20th-century tobacco advertising—raises significant public health concerns. In many countries where traditional tobacco advertising is prohibited, e-cigarettes continue to be promoted through television, radio, and digital platforms, potentially normalizing nicotine use and indirectly reinforcing cigarette smoking behaviors.

Theoretically, complete substitution of combustible cigarettes with e-cigarettes could reduce exposure to harmful combustion-related toxicants and lower disease burden. However, real-world evidence suggests high rates of dual use, inconsistent cessation outcomes, and increasing uptake among adolescents and young adults. Many users report motivations such as circumventing smoke-free policies or reducing cigarette consumption rather than achieving full cessation, which may prolong nicotine dependence rather than eliminate it.

Of particular concern is the rising prevalence of e-cigarette use among youth, including individuals who have never smoked conventional cigarettes. Nicotine exposure during adolescence poses risks to neurodevelopment and increases susceptibility to long-term addiction. Persistent dual use may ultimately sustain low-level cigarette consumption for extended periods, potentially diminishing any anticipated harm-reduction benefits and contributing to an increased overall public health burden.

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