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The Risk and Safety Profile of Electronic Nicotine Delivery Systems (ENDS): An Umbrella Review to Inform ENDS Health Communication Strategies

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CONTRIBUTION

TA and WM contributed to the conception and design of the study, supervised data collection, contributed to the interpretation of the data, and critically revised the manuscript for important intellectual content. RJ, WL, OJO, TF, and PG performed the literature review, data collection, and review quality assessment. TA, OJO, and ZB performed data cleaning and data meta-analyses. All authors contributed to the interpretation of the data and critically revised the manuscript for important intellectual content. This manuscript was written by TA with input from all coauthors who read and approved the final version.

COMPETING INTERESTS

All authors (except Dr. Eissenberg) certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Dr. Eissenberg is a paid consultant in litigation against the tobacco industry and also the electronic cigarette industry and is named on one patent for a device that measures the puffing behavior of electronic cigarette users, on another patent application for a smartphone app that determines electronic cigarette device and liquid characteristics, and a third patent application for a smoking cessation intervention. The CSTP is supported by grant number U54DA036105 from the National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the U.S. Food and Drug Administration. The content of this message is solely the responsibility of the author and does not necessarily represent the views of the NIH or the FDA.

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Abstract

Objectives: This umbrella review aims to summarize the evidence about electronic nicotine delivery systems (ENDS) risk and safety health profile to inform ENDS health communication strategies.

Data sources and study selection: Six databases were searched for systematic reviews presenting evidence on ENDS-related health effects. Ninety reviews divided into 5 categories were included: toxicity = 20, health effects = 40, role in smoking cessation = 24, role in transition to combustible cigarettes (CCs) = 13, and industry marketing claims = 4.

Data extraction: Findings were synthesized in narrative summaries. Meta-analyses were conducted by study type when appropriate. Quality assessment was conducted using the *Measurement Tool to Assess Systematic Reviews*. The Institute of Medicine's Levels of Evidence Framework was used to classify the evidence into high-level, moderate, limited-suggestive, and limited-not-conclusive.

Data synthesis: We found high-level evidence that ENDS exposes users to toxic substances; increases the risk of respiratory disease; leads to nicotine dependence; causes serious injuries due to explosion or poisoning; increases smoking cessation in clinical trials but not in observational studies; increases CCs initiation; and exposure to ENDS marketing increases its use/intention-to-use. Evidence was moderate for ENDS association with mental health and substance use, limited suggestive for cardiovascular, and limited-not-conclusive for cancer, ear, ocular, and oral diseases, and pregnancy outcomes.

Conclusions: As evidence is accumulating, ENDS communication can focus on high-level evidence on ENDS association with toxicity, nicotine addiction, respiratory disease, ENDS-specific harm (explosion, poisoning), and anti-ENDS industry sentiment. Direct comparison between the harm of CCs and ENDS should be avoided.

Keywords

Electronic cigarette; electronic nicotine delivery system (ENDS); exposure to toxicants; health effects; marketing; communication; combustible cigarette; cessation

INTRODUCTION

Advances in tobacco control have helped curtail combustible cigarette (CC) smoking worldwide, but this progress is potentially compromised by an alarming increase in the use of electronic nicotine delivery systems (ENDS) products.[1, 2] ENDS are now the leading tobacco product among young people in the United States (US).[3, 4] Young people are particularly drawn to ENDS use due to the novelty of the devices, nicotine buzz, flavors, targeted industry marketing, and the perception of their safety.[5–7] ENDS have their own health risk profile including emitting toxic substances, prompting nicotine dependence, and increasing the risk of initiating CC product use.[8, 9] Nicotine exposure has also been found to interfere with healthy brain development among youth, and its influence can remain until

the mid-20s.[10] In addition, while ENDS has shown some promise in helping CC smokers with quitting under controlled randomized clinical trial (RCT) conditions,[11] evidence from observational studies suggests that ENDS use can reduce the likelihood of cessation and increase dual-use.[12–14]

Communication of ENDS risks to young people has been identified by major health and regulatory bodies as a priority strategy to limit ENDS use.[15] It is also aligned with the US Food and Drug Administration's (FDA) statutory obligation, according to the Family Smoking Prevention and Tobacco Control Act.[16] From a consumer rights perspective, communication of product-associated risks is important to: 1) protect consumers from health and safety hazards in the marketplace, and 2) give them adequate information to enable them to make informed choices.[17] In this regard, children are particularly sensitive to deception or exaggerated advertising claims and represent a vulnerable population that needs protection against misleading and false safety claims.[17] Moreover, exaggerating the risk of consumer products beyond the bound of evidence carries the risk of undermining trust in public health measures, hinders their potential benefit to some groups (e.g., smokers in a clinical cessation setting), and opens the door to challenges to these claims. Hence, the development of effective ENDS health messages requires an extensive and robust review of the evidence about the potential harmful and beneficial profiles of these products.

In 2018, the US National Academies of Sciences, Engineering and Medicine (NASEM) released a report on the health consequences of ENDS.[8] However, the report included evidence available before August 2017. Since then, there has been a marked growth in scientific evidence about these products. This umbrella review, which is a review of systematic reviews and meta-analyses,[18, 19] aims to systematically update the evidence on ENDS health profile categorized across five domains: toxicity, health effects, smoking cessation, transition to CC, and industry marketing. Results will inform and guide the development of evidence-based health communication strategies for ENDS.

METHODS

Search strategy

The study protocol was registered on PROSPERO (CRD42021241630). We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[20] A comprehensive search was performed using PubMed, MEDLINE, EMBASE, PsycINFO, CINAHL, and The Cochrane Database up to November 2021. We used a combination of terms and keywords related to the scope of this review (e.g., e-cigarette, ENDS, cancer, initiation, cessation) (Supplement A. Table 1).

Inclusion criteria

Inclusion criteria were kept broad to perform a comprehensive assessment of the current state of the evidence. We included all reviews that: 1) met the definition of a systematic review (e.g., thorough search strategy, minimizing bias); 2) published in English, 3) with/without meta-analysis of observational studies and RCTs; and 4) presented evidence on ENDS effects in one or more of the five domains (toxicity, health effects, smoking cessation,

transition to CCs, industry marketing). We excluded reviews that were funded by the tobacco/ENDS industry.

Data screening and extraction

Study selection, quality appraisal, and data collection were performed by 6 reviewers independently and in duplicate using Covidence software.[21] Titles and abstracts were screened to identify potentially relevant articles. Full texts of these articles were assessed for eligibility based on the inclusion/exclusion criteria. Extracted data included: the title, first author, country, publication year, number and design of included studies, outcomes, summary of results (effect size, odds ratios (OR), or relative risk (RR) when applicable), conflicts of interest, and funding source. We resolved all discrepancies by discussion and consensus

Quality assessment

We conducted quality appraisal using the *Measurement Tool to Assess Systematic Reviews* (AMSTAR).[22] A score between 0 and 11 was calculated based on this tool, and the quality of the review was determined low (0–4), medium (5–8), or high (9–11).[23]

Summary measures and synthesis of results

Findings were synthesized separately in narrative summaries. First, two reviewers collected the data independently, then they cross-referenced these data to ensure validity. Second, the authors conducted a narrative synthesis of the reviews. Finally, the authors compiled a list of main outcomes for ENDS based on the data synthesis from all reviews. Where appropriate, ORs from the studies in the integrated systematic review were combined using a random-effects model.[24] Heterogeneity of study effect estimates was assessed by I^2 statistics.[24] All analyses were conducted using Stata V.16.1.

Evidence about potential harmful/beneficial effects was graded into four levels using the Institute of Medicine's "*Levels of Evidence Framework*": high-level, moderate, limited-suggestive, and limited-not-conclusive.[25] Given the preliminary nature of evidence, expert judgment in the evaluation of studies was involved. We performed six meta-analyses to estimate the effect of ENDS on asthma, alcohol use, marijuana use, smoking cessation (RCTs, 67observational studies), and CC smoking initiation. Effect sizes were reported as RR, OR, AOR, or mean differences. When raw data were not available, we used the effect size and confidence intervals to estimate the overall effect for our review using the generic inverse variance method.(25)

Patient and public involvement

No patients were involved, and no patient identifiers were collected.

RESULTS

Study selection and quality assessment

A total of 4582 reviews were identified for title/abstract screening; 3368 remained after exclusion of duplicates; 349 were identified for full-text screening, and 90 reviews were

eligible and included in our review. Eight reviews were included in 2 domains, 1 review was included in 3 domains, and 1 review was included in 3 categories in ENDS health effect. The quality assessment is presented in Supplement A, Tables 2, 3, 4, 5, and 6. Overall, 14% of the included reviews were of high-quality, 30% of medium-quality, and 36% of low-quality. A list of excluded studies can be found in Supplement A. Table 7.

Studies characteristics

Overall, 20 reviews were included in toxicity; 40 in health effects; 24 in smoking cessation; 9 in transition to CCs; and 4 in ENDS marketing. Characteristics of included reviews are shown in Supplement B, sections 1, 2, 3, 4, and 5.

Summary of findings

A. Toxicity

Twenty reviews, that assessed 968 studies were included in this category (Supplement A. Table 8). Eleven reviews looked at the overall toxicity profile of ENDS (nicotine, carbonyls, harmful chemicals, metals, carcinogens) in e-liquids and aerosols.[26–36] The majority of these reviews indicated that ENDS could not be regarded as safe because they produce several harmful chemicals with known adverse health effects (e.g., glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles).[28–30, 32–34] TSNAs and carbonyls are designated carcinogens according to the International Agency for Research on Cancer (IARC) because they have cytotoxic effects and can alter gene expression.[32, 37]

Five reviews examined nicotine levels in ENDS.[26–28, 32, 35] One review found that nicotine yield from automated smoking machines is less than from CCs.[38] Another review compared levels of nicotine in aerosol from JUUL with other ENDS products and found that JUUL has lower free nicotine in the pod liquid and aerosol compared with other products (5%–6%, 13%–95%; respectively), but a high total nicotine content in the form of benzoate salt.[39]

Two reviews confirmed the presence of hazardous trace metals (e.g., lead, aluminum) in ENDS aerosol, liquid, and human biosamples.[40, 41] Metal levels showed substantial heterogeneity depending on sample type (liquid, aerosol), source of liquid (bottle, cartridge, tank/open wicks), and device type (cig-a-likes, tank). For example, trace metal levels in liquid from cartridges or tank/open wicks were higher than those from bottles, possibly due to coil contact. Notably, metal levels in the biosamples of ENDS users were similar to or higher than the levels found in CC or cigar users.[41] Exposure to these metals is associated with serious adverse effects. For example, lead is associated with an increased risk of cardiovascular and kidney disease and is a major neurotoxicant, particularly for children and the elderly.[42, 43] Exposure to aluminum at high levels can lead to impaired lung function and fibrosis as well as decreased performance in motor and cognitive functions.[44]

Four reviews explored the association between ENDS and carcinogenic biomarkers.[45–47] One review identified six biomarkers that have a strong link to bladder cancer in the urine of ENDS users.[48] Among these, o-toluidine and 2-naphthylamine, which are known to

produce bladder cancer in human and animal studies, were found in ENDS users' urine at 2.3- and 1.3-fold higher levels than never ENDS users. Two reviews indicated that the levels of PAH 1-hydroxypyrene (1-OHP), a carcinogenic biomarker, were significantly higher in ENDS users than in never-users,[49] and their levels did not decrease in CC smokers who switched to ENDS.[50] In a review that was focused on head and neck cancer, most *in vitro* studies demonstrated the cytotoxicity of exposure to ENDS aerosols, with several levels of DNA damage and oxidative stress induced by toxic components.[47]

Two reviews reported that some flavors in ENDS liquids (e.g., vanillin, cinnamaldehyde) could affect cellular function, including phagocytosis and cytokine production in both *in vitro* and *in vivo* studies.[26, 27] A meta-analytic review highlighted the possible correlation of the chemical reactivity of flavor compounds with the toxicant formation in ENDS aerosols.[51]

Three reviews investigated ENDS' environmental emissions.[52–54] All confirmed that ENDS use under real conditions releases toxicants including nicotine, carbonyls, metals, VOCs, and particulate matter (PM) in indoor environments, and that passive exposure to exhaled aerosol from ENDS can lead to adverse health effects.[52–54] For example, compared to background air levels, nicotine in ENDS emissions was 10–115 times higher, acetaldehyde 2–8 times higher, and formaldehyde about 20% higher. Conversely, when compared with CC, smoke levels of heavy metals were generally lower in ENDS aerosol. One review indicated that the total amount of suspended PM emissions were higher in vapor from nicotine-free ENDS (11.6μg/m3) compared to nicotine ENDS (1.2μg/m3).[41]

High-level evidence exists that most ENDS products contain and/or emit toxic substances (e.g., metals, carcinogens) that are capable of causing DNA damage and mutagenesis and that ENDS emissions increase airborne toxicants (e.g., metals), PM, and nicotine in indoor environments compared with background levels.

B. Health effects

Forty reviews, divided into 12 categories, were included in this domain (Supplement A. Table 9).

1. Respiratory disease—Thirteen reviews were included in this category. Six reviews related to "e-cigarette or vaping-associated lung injury" (EVALI) indicated that vitamin E acetate (an additive in some tetrahydrocannabinol-containing ENDS) is the primary, but not only, cause of EVALI. [55–60] Four reviews demonstrated a consistent and strong association between ENDS use and respiratory disorders (e.g., asthma exacerbation) among adolescents and adults.[36, 61–63] In Wills et al., the pooled AOR from 15 studies for the association between ENDS use and asthma was 1.39 (95% CI, 1.28–1.51), and 1.49 (95% CI, 1.36–1.65) for the association between ENDS use and multiple respiratory symptoms. [61] This review also confirmed that exposure to ENDS liquid or aerosol increases levels of pro-inflammatory biomarkers that are relevant to these respiratory diseases in laboratory studies as well.[61] Furthermore, two longitudinal studies showed that ENDS use might predate the onset of asthma.[64, 65] Similar results were reported in another review.[62] We

performed a meta-analysis of these two reviews that included 26 studies; our pooled RR showed an increased risk for asthma (1.13 [95% CI, 1.09–1.18]; n= 2,114,396).

One review indicated that ENDS use could cause nasal mucociliary clearance impairment, [66] while another review found that acute eosinophilic pneumonia had a similar presentation and clinical course to that associated with CC smoking.[67] Finally, one review found that former CC smokers who transitioned to ENDS showed ~ 40% lower odds of respiratory outcomes (e.g., asthma, wheezing) compared to current exclusive CC users.[68] However, this estimate was based on a limited number of epidemiological studies with important limitations.

High-level evidence exists that ENDS use can exacerbate asthma yet limited-not-conclusive evidence exists that ENDS may cause Chronic obstructive pulmonary disease (COPD), *nasal mucociliary clearance impairment, and acute eosinophilic pneumonia.*

2. Cardiovascular diseases (CVD)—Six reviews reported on the effect of ENDS use on CVD outcomes.[60, 68–72] Three reviews reported that benefits for CVD may be observed when switching from CCs to ENDS.[68, 70, 72] On the other hand, three indicated a possible association between ENDS and CVD.[60, 69, 71] One review demonstrated that ENDS use (with/without nicotine) might result in short-term elevations of both systolic and diastolic blood pressure (SBP, DBP).[69] In another review, most included studies (75%) found potentially harmful effects of ENDS on CVD through inducing sympathetic nerve activation, oxidative stress, endothelial dysfunction, and platelet activation.[71] For example, human studies in this review largely showed increases in heart rate and blood pressure as a result of ENDS use, as well as abnormalities in heart rate variability, suggestive of sympathetic nerve activation. Both *in vitro* and *in vivo* studies showed increased reactive oxygen species production and a reduction in antioxidants after ENDS exposure, constituting an atherosclerotic risk. Importantly, most studies suggest the potential for CVD harm from ENDS use, mainly through mechanisms that increase the risk of thrombosis and atherosclerosis.[71] For example, human studies showed increases in heart rate and blood pressure as well as abnormalities in heart rate variability, indicating sympathetic nerve activation, one of the key neurohumoral mechanisms that are operative in heart failure.[73] In vitro studies reported various measures of arterial stiffness, indicative of endothelial dysfunction, a prognostic of atherosclerosis.[74–77] Platelet hemostatic processes were reported across murine, human in vitro, and human in vivo studies, which can increase thrombotic risk.[74, 78, 79] This review also indicated that studies with conflicts of interest (e.g., related to the tobacco industry) were less likely to identify potentially harmful effects. In another review, ENDS use was linked to some CVD such as atherosclerotic plaque formation and myocardial ischemia.[60]

Despite the absence of long-term exposure-effect studies, we found limited but suggestive evidence that ENDS use increases the risk of CVD.

3. Cancer—Only one review related to head and neck cancer and ENDS use reported the results from two cohort studies, two case-control studies, and one case series.[47] The case series described two patients with a history of chronic ENDS use (20–30 times/day

for 13 years) who developed oral cancers, indicating a possible link between the long-term consumption of ENDS and this type of cancer.[80] Another study was able to identify a known carcinogen (N'-nitrosonornicotine/NNN) in the saliva of ENDS users.[81] In contrast, a cohort study could not identify a higher number of micronuclei, indicators of genomic instability, in ENDS users compared to non-smokers.[82] Another cohort study found no differences in terms of precancerous oral mucosal lesions between ENDS users and former CC smokers. Overall, all included studies were judged as having poor quality with small sample sizes and limited exposure time to ENDS, and they suffered from limitations in their design (e.g., lack of proper control groups, selection bias, not accounting for confounders).

Limited-not-conclusive evidence exists on the link between ENDS use and cancer in the clinical environment.

4. **Passive exposure to ENDS aerosol—**Two reviews reported on the effect of passive exposure to ENDS.[53, 83] The first review reported on two studies (out of four total) that measured biomarkers of exposure to nicotine and other VOCs in biological samples, with conflicting results. While one study showed a statistically significant difference in urinary cotinine between those exposed to ENDS with nicotine compared to ENDS without nicotine,[84] the other study observed no significant difference between the non-users living in homes with ENDS users compared to non-users living in control homes.[85] The second review identified four studies, all with small sample sizes, that directly assessed passive exposure in human volunteers.[83] In one study, salivary and urinary cotinine levels were significantly lower in volunteers from non-smoking control homes than in volunteers exposed to either ENDS or CC smoke, with CC smoke having the highest cotinine levels.[85] In another experiment, serum cotinine and lung function measures were taken for 15 non-smokers who were passively exposed for one hour to CC smoke or ENDS vapor generated by a smoking machine.[86] No difference was found in lung function for the non-smokers passively exposed to ENDS vapor compared with no exposure, but participants' serum cotinine levels were raised comparable to those of volunteers passively exposed to CC smoke. Similarly, inflammatory markers were not affected by passive exposure to ENDS vapor for one hour in another study involving 10 nonsmokers.[87] Only one animal study in this review examined the effect of passive ENDS exposure to either room air (controls) or ENDS vapor (with or without nicotine) for 20 minutes once or twice a day on newborn mice.[88] Results showed that mice exposed to ENDS (with or without nicotine) weighed significantly less than mice exposed to room air only. Mice exposed to ENDS with nicotine also showed impaired lung growth and elevated plasma and urine cotinine levels. Based on these results, the authors concluded that chronic exposure to ENDS among susceptible groups (e.g., infants, children, asthma patients, the elderly, pregnant women) can be a health concern.

Limited-not-conclusive evidence exists on the health effect of passive exposure to ENDS, yet exposure studies clearly show that bystanders are exposed to ENDS-emitted toxicants such as carbonyls, metals, VOCs, PM, and nicotine.

5. Ear diseases—Only one review reported on the effect of ENDS use in otology and indicated that these effects are still largely unknown.[89] In this review, an *in vitro* study indicated that ENDS liquid can induce cytotoxic effects on human middle-ear epithelial cells and reduce their viability from 100% to 32–62%,[90] particularly when nicotine was included in the liquid. This is consistent with animal studies (not related to ENDS) showing that nicotine has a direct deleterious effect on cochlear outer hair cells, with reports of distorted shape, heterochromatic nuclei, and vacuolated cytoplasm.[91] However, data on the clinical implications of nicotine from ENDS in otology in humans do not exist.

Limited-not-conclusive evidence exists on the link between ENDS use and ear diseases.

6. Ocular diseases—Only one review reported on the effect of ENDS use on ocular diseases.[92] The review indicated that ENDS use might induce dry eye,[93] reduce tear film stability,[93] or reduce ocular blood flow.[94] The review further suggested that these effects present both short-term and long-term health risks to the eyes and vision.[95]

Limited-not-conclusive evidence exists on the link between ENDS use and ocular diseases.

7. Pregnancy outcomes—Four reviews reported conflicting results on the effects of ENDS use on pregnancy outcomes.[96–99] Romer et al. indicated that exposure to nicotine in ENDS could cause low birth weight, miscarriage, and stillbirth.[97] Calder et al. indicated that ENDS use has less effect on birthweight outcomes than CC smoking.[96] However, these outcomes were similar to CC smoking in pregnant women who used both ENDS and CCs. Another review of animal studies suggested that exposure to nicotine in ENDS alters DNA methylation, induces birth defects, reduces birth weight, and affects the development of the heart and lungs of the offspring.[98]

Limited-not-conclusive evidence exists on the effect of ENDS use on pregnancy outcomes.

8. Oral health—All three included reviews indicated an increased risk for gum disease and changes to the oral microbiome in ENDS users.[100–102] Results from three reviews on ENDS and oral health suggests that ENDS use might induce mouth, throat, and periodontal symptoms and lead to different lesions including nicotinic stomatitis, hairy tongue, and angular cheilitis.[100–102] Commonly reported mouth symptoms related to ENDS use or direct liquid exposure included dryness, burning, irritation, bad taste, bad breath, and pain.[101] Finally, extensive dental damage as a result of ENDS explosions was reported.

Limited-not-conclusive evidence exists on the effects of ENDS on oral health.

9. Injuries and poisoning—Four reviews reported on traumatic ENDS-related explosion injuries to the skin and soft tissue.[63, 103–105] Burn severity was typically second-degree (35%) or second- and third-degree burns (20%).[103] Three reviews reported on poisoning (accidental, intentional) through the ingestion or injection of ENDS liquid.[63, 104, 106] In some cases, patients mixed liquid with alcohol, methadone, or benzodiazepines.[104] Most of these patients were either found to be dead or were admitted to the emergency rooms with cardiac arrest, respiratory muscle paralysis, or brain death. Other reported

serious injuries included infant death from choking on a flavor cartridge and nicotine overdoses associated with psychotic symptoms (suicide attempts).[104]

High-level evidence exists that ENDS devices can explode and cause burns and that intentional or accidental nicotine poisoning from ENDS liquid can cause seizures, anoxic brain, and death.

10. Mental health—Two reviews reported consistent results warning that vaping may exacerbate mental illness.[60, 107] Becker et al. found that ENDS use is associated with greater depression, suicidality, Attention-deficit/hyperactivity disorder, eating disorders, and stress among adolescents.[107] ENDS use was also associated with sensation seeking among young adults.[107] Sharma et al. indicated that long-term use of ENDS may have a detrimental effect on brain health due to cerebral oxidative stress.[60] Although the longitudinal evidence linking ENDS use to subsequent psychopathology remains limited, this evidence is consistent with existing models of nicotine's effects on the neurodevelopment of young people.[108] It is well established that nicotine adversely affects adolescent neurodevelopment and increases the risk of cognitive and psychiatric disorders.[109] Evidence from animal models also suggests that prolonged nicotine exposure may induce epigenetic changes and increase vulnerability to stress sensitivity and the subsequent development of mood disorders, schizophrenia, and substance use disorders.[110]

Moderate evidence exists that ENDS use is associated with mental health problems among adolescents and young adults.

11. Addiction—Two reviews were included in this category.[26, 27] The first found that behavioral effects related to nicotine addiction are regularly seen in ENDS users and that dual use of ENDS and CCs generate more addiction to nicotine than exclusive ENDS use.[26] Nicotine in ENDS liquids is a well-understood compound with known central and peripheral nervous system effects associated with a high risk of addiction.[8] The second review indicated that most commercial ENDS products contain nicotine.[27] In a large-scale population-based sample, depressive symptoms were associated with ENDS use and their nicotine concentration.[111] In addition, inhaled vaporized nicotine via ENDS was shown to increase heart rate (HR), arterial stiffness, and flow resistance, and in another study to decrease microcirculatory endothelial-dependent function, increase arterial stiffness, and increase BP, HR, and plasma myeloperoxidase in users.[112]

High-level evidence exists that the use of ENDS with nicotine results in symptoms of nicotine dependence.

12. Substance use—Four investigated the association between ENDS use and other substance use including alcohol, marijuana, and illicit drugs (e.g., cannabinoid, cocaine, heroin).[113–116] Results indicated a strong association between ENDS and alcohol use (OR 6.62 [5.67–7.72]), binge drinking (OR 6.73 [4.50–10.07]), and marijuana use (AOR 4.29 [3.14–5.87]) among adolescents ENDS users compared to nonusers.[113–115] Similar, but lower results were reported among young adults (OR 2.30 [1.40–3.79] for marijuana) and adults (OR 1.57 for alcohol and 2.04 for marijuana; $p<.05$). Chadi et al. included

three longitudinal studies suggesting that ENDS use typically predates the use of marijuana.[117–119] While the number of these studies was small, these findings yield high clinical relevance to substance use disorders among young people.[120] One review investigated the risk of ENDS as a drug delivery system for illicit drugs and found that almost 40% of ENDS users had used them to vape recreational drugs, with cannabis being the most common (18.0%).

For alcohol use, our pooled OR from 2 reviews of observational studies assessing the association of ENDS use with alcohol use was 3.72 (95%CI = 2.03 – 6.83) with substantial heterogeneity among studies (Chi2 = 189.61, I^2 = 97%; p < 0.0001). For marijuana use, our pooled OR from 2 reviews of observational studies assessing the association of ENDS use and marijuana use was 2.89 (95%CI = 1.61 – 5.19) with substantial heterogeneity among studies (Chi2 = 41.15, I2 = 93%; p < 0.0001).

Moderate evidence exists on the association between ENDS use and alcohol and marijuana, particularly among youth.

C. ENDS' effect on smoking cessation

Twenty-four reviews were included in this category (Supplement A. Table 10). Thirteen RCTs meta-analysis reviews indicated that ENDS use is effective in smoking cessation (compared to NRT or placebo),[121] while 5 reviews suggested the opposite.

We conducted a subgroups meta-analysis based on several control groups (NRT, ENDS without nicotine, placebo). The pooled RR was 1.20 (95% CI, 1.12–1.29) for five meta-analyses comparing ENDS with NRT, 1.35 (95% CI, 1.18–1.56) for five meta-analyses comparing ENDS with nicotine vs. ENDS without nicotine or placebo, and 1.15 (95% CI, 1.05–1.26) for two meta-analysis reviews comparing ENDS with NRT and/or placebo as control. There was moderate but not significant evidence of heterogeneity among subgroups (Chi^2 = 6.06, p = 0.11, I^2 = 50.5%). However, based on three systematic reviews of observational studies reporting on ENDS association with smoking cessation, our pooled RR for abstinence was not significant (0.96, 95% CI, 0.86–1.08).

Three other reviews reported that ENDS use among CC smokers was associated with a 22.5% to 80% reduction in CCs smoked per day.[122–124] However, one review reported that the risk of relapse was two-fold higher among former CC smokers who were ENDS users than non-ENDS users.[125] One review was focused on pregnant women and found that abstinence rates in pregnant women who were ENDS users vs. non-users were not different.[96]

High-level evidence shows that ENDS use is associated with increased smoking cessation in RCTs, in contrast to evidence from observational studies showing that ENDS use increases risk of relapse and impedes smoking cessation.

D. Transition to combustible cigarette smoking

Eight reviews were included in this category (Supplement A. Table 11). Our meta-analysis indicated that ENDS use is associated with CC initiation, with ORs varying from 2.1 to 6.6.

Our pooled RR from six meta-analyses of RCTs and observational studies for the ENDS transition to CC among adolescents was 1.61 (95% CI, 1.55–1.67).

High-level evidence exists that ENDS use increases the risk of CC initiation among youth and young adults.

E. Industry marketing

Four reviews indicated that exposure to ENDS industry marketing increased favorable ENDS perceptions and experimentation among youth and young adults.[126–129] (Supplement A. Table 12). ENDS shops were more likely to be concentrated near college and university campuses and were targeting non-Hispanic Whites with high or median incomes.[128] ENDS marketing recall was strongly associated with lower harm perceptions, and greater intention to use or use of ENDS. In contrast, exposure to ENDS warnings was associated with a lower intention to purchase ENDS.[129]

High-level evidence exists that ENDS marketing targets youth and young adults, and exposure to marketing among these age groups decreases ENDS harm perceptions and increases intention to use and use of ENDS.

DISCUSSION

The main purpose of this umbrella review was to summarize and comprehensively review the current evidence on the health profile of ENDS to guide the development of evidence-based health communication messages. Below, we summarize this evidence according to domain and level of evidence.[25] We also try to synthesize this evidence into practical recommendations on how to frame impactful and balanced ENDS-related health risk messages. A set of potential messages based on available evidence are presented in to help other researchers and health-related bodies further develop and test evidence-based messages about the ENDS health profile.

For ENDS toxicity, we found high-level evidence that most ENDS products contain toxic substances (e.g., metals, carcinogens) that are capable of causing DNA damage and mutagenesis, and that ENDS emissions increase airborne toxicants (e.g., metals), PM, and nicotine in indoor environments compared with background levels.[32, 34, 36, 53, 130, 131] For ENDS health effects, we found high-level evidence that ENDS devices can explode and cause burns and that intentional or accidental liquid poisoning can cause seizures, anoxic brain injury, or death.[63, 104, 106] We also found high-level evidence that ENDS use exacerbates asthma, and that nicotine in ENDS can cause addiction. In addition, despite the limited clinical evidence about the effect of ENDS use on cancer risk, studies from human genomic and animal studies have consistently shown that ENDS use may be carcinogenic. For example, exposure to ENDS aerosol induces DNA damage and impairs DNA repair in human and animal lung and bladder cells.[132, 133]

Regarding ENDS' effect on smoking cessation, our meta-analysis demonstrated high-level evidence that ENDS use as a therapeutic intervention is associated with increased smoking cessation in RCTs when delivered in a clinical and tightly controlled setting.[134]

In contrast, ENDS as consumer products in real-world observational studies were not significantly associated with smoking cessation,[134, 135] and several such studies show the opposite; ENDS use impedes smoking cessation.[125] Observational studies of these outcomes are more important to their regulation as a consumer product, consistent with the *Tobacco Control Act,* which requires the FDA to consider the risks and benefits of new tobacco products to the population as a whole.[135–137]

We also found high-level evidence that ENDS use increases the risk of CC initiation among youth and young adults.[138–141] Our meta-analysis is consistent with prior umbrella review summarizing the evidence on CC uptake following ENDS use in non-smokers.[142] Finally, there was high-level evidence that exposure to ENDS industry marketing among youth decreases ENDS harm perceptions and increases intention to use and use of ENDS.[39, 126, 128, 129] Evidence was moderate for ENDS association with mental health and substance use, and limited-not-conclusive for cardiovascular, cancer, ear, ocular, and oral diseases, and pregnancy outcomes.

Implications for research

Although data are expanding progressively, additional research is needed to assess the full spectrum of ENDS health effects. In particular, the direct health effects of exposure to ENDS have not been studied adequately, and data on the long-term risk of ENDS use are absent. Hence, further research is needed to establish the risk and safety profiles of ENDS with consideration of the wide variety of ENDS products (e.g., power output, construction materials, design features, liquid constituents), their pattern of use (e.g., daily, less frequent use), and different segments of the population (e.g., children, pregnant women, cancer patients, people with acute or chronic medical conditions). Additionally, more thoroughly designed prospective cohort studies that take place over longer periods and with larger sample sizes are necessary to gauge accurately the short- and long-term health-related risks of ENDS. More animal and cell studies are needed to explore the mechanism of action between ENDS and the risk of various diseases.

Implications for ENDS health communication

Overall, we have presented strong evidence that ENDS users inhale an array of toxic chemicals similar to those found in CC cigarettes smoke and known to cause serious diseases (lung disease, nicotine dependence). Yet there is a lack of comparative quantitative assessments and appraisals of the clinical importance of exposure levels related to ENDS compared to CC smoking, both short- and long-term. Here we suggest several strategies to overcome this gap in our knowledge and advance ENDS-related health communication based on the current level of evidence. First, ENDS communication now can focus on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma, ENDS-specific harm (explosion, poisoning), and anti-ENDS industry sentiment. Second, messages that highlight ENDS-specific harm (e.g., explosion, poisoning, addiction) have the potential to capture attention and motivate behavior change because they are serious and specific to ENDS.[143, 144] Third, an important group for communicating ENDS-related risks is dual and poly tobacco users, many of whom adopted ENDS to either quit smoking

or reduce their harm. Mounting evidence suggests that compared to exclusive CC smoking, dual use carries additional rather than less risk, particularly among high-risk populations for smoking (e.g., children, pregnant women).[96] By increasing the opportunity to be exposed to toxicants and nicotine from both products, CCs and ENDS, dual users can be at higher risk of tobacco health effects and dependence.[145] Evidence suggests that compared with cigarette smokers, dual users are at higher risk of heart problems,[146, 147] lung disease,[61, 65] cancer,[148] and nicotine dependence.[149, 150] Fourth, to preserve scientific credibility, public health groups need to convey evidence-transparent messages without inferring causality based on associations or cross-sectional data. Care will need to be taken in crafting statements that accurately communicate the complex and evolving science on ENDS health risks. Finally, avoiding direct comparison between the harm of CCs and ENDS is highly recommended given the uncertainty about this information, mainly because of the variation in ENDS types/generation, nicotine content, the high prevalence of dual/poly tobacco use, and the scarcity of standardized comparative studies.

Legitimate concerns have been voiced that health risk messages for ENDS can lead to unintended consequences such as reducing their appeal among smokers who can benefit from ENDS for smoking cessation.[151] These concerns need to be weighed against the massive uptake of ENDS use among young people, and the emerging evidence that while ENDS health risk messages can motivate users to quit, they do not encourage CC smoking, and may instead discourage smoking.[143] In addition, such potential effects can be mitigated by promoting ENDS within clinical and smoking cessation treatment settings for those unable to quit or reduce their harm otherwise.[152] Most health authorities (e.g., CDC, FDA) agree that "*ENDS are possibly a less harmful alternative for current smokers to quit; however, they are not for people who have never smoked.*" From a consumer rights perspective, while non-smokers should be protected from the marketing of addictive and potentially harmful ENDS, CC smokers who use ENDS to quit also have the right to be informed about the risks associated with ENDS use, that no ENDS devices are FDA-approved as smoking cessation aids, and that the heterogeneity among ENDS devices and liquids is so great that, even if an ENDS was approved for smoking cessation, that approval for that device/liquid combination cannot generalize to other device/liquid combinations within the ENDS product class.

Limitations

This umbrella review has several strengths and limitations that should be acknowledged. The main strength of this review includes the use of a comprehensive and rigorous methodology including a broad search strategy, as well as extraction of data and assessment of the risk of bias and quality by several independent reviewers. Furthermore, prioritizing a wide scope of systematic reviews in five domains allowed the inclusion of a large amount of research evidence covering a variety of ENDS-related health effects, while at the same time narrowing that research into easy-to-distinguish risk/benefit domains for health communication purposes. As for the limitations, first, given the wide scope of the review and inclusion of various study designs, meta-analyses of RCTs were not possible for some domains. In addition, the included reviews used numerous diverse approaches for conceptualizing, operationalizing, and measuring the outcomes of interest.

This heterogeneity significantly limited the ability to synthesize and compare study results. Also, the heterogeneity of ENDS as a product class, with varying device characteristics, liquid constituents, and user-controlled features (e.g., power output), as well as the swift evolution of ENDS products is a challenge that has yet to be addressed fully in the studies reviewed here. Therefore, instead of grading the evidence from meta-analyses only, we focused on a portion of the available evidence when needed.[153] Second, given the wide scope of our review, it was impossible to identify articles that were included in multiple reviews. However, by their nature, umbrella reviews lead to loss of detail and redundancy as some individual studies are included in multiple reviews. Third, some health effects may have been found in multiple studies, but there has not been a review of these studies. Fourth, all included reviews did not include industry-funded studies except one review (Pisinger et al., 2014) that reported that 26 out of their 76 included studies were influenced by manufacturers of ENDS.[32] Finally, we completed our search in November 2021; therefore, the primary studies and reviews published after this date were not included.

Conclusions

This umbrella review provided the most up-to-date evidence on ENDS use health risk and safety profile. This evidence will inform the development of impactful messages for ENDS health communication and indicate important tracks for studies needed to assess the full spectrum of ENDS health effects. ENDS messages can currently be centered on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma exacerbation, ENDS-specific harm (explosion, poisoning), and anti-ENDS industry sentiment. Given the variation in ENDS products and the high prevalence of dual/poly tobacco use, ENDS communication needs to convey evidence-transparent messages and avoid direct comparisons between the harm of CCs and ENDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known on this topic?

- Communication of ENDS risks to young people has been identified by major health and regulatory bodies as a priority strategy to limit ENDS use.
- The development of effective ENDS health messages requires an extensive and robust review of the evidence about these products' harmful and beneficial potential.

What this study adds

- This umbrella review summarized the evidence about ENDS health profile into five domains: toxicity, health effects, role in smoking cessation, role in the transition to CCs, and ENDS industry marketing clams.

How this study might affect research, practice or policy

- ENDS messages can currently be centered on high-level evidence related to ENDS association with toxicity, nicotine addiction, asthma exacerbation, ENDS-specific harm (explosion, poisoning), and anti-ENDS industry sentiment.
- Avoiding direct comparison between the harm of CCs and ENDS is important given the uncertainty about this information, mainly because of the variation in ENDS types/generation, nicotine content, the widespread dual and poly tobacco use, and the scarcity of standardized comparative studies.