

# BMJ Open Electronic nicotine delivery devices, and their impact on health and patterns of tobacco use: a systematic review protocol

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## ABSTRACT

**Introduction:** E-cigarettes or electronic nicotine delivery systems (ENDS) have recently attracted considerable attention. Among some individuals there is strong debate and a polarisation of views about the public health benefits versus harms of ENDS. With little regulation, the ENDS market is evolving, and new products are introduced and marketed constantly. Rapid developments in manufacturing, marketing and consumer domains related to ENDS will warrant frequent re-evaluation, based on the state of the evolving science. The purpose of this article is to describe a protocol for an ongoing comprehensive review of the published scientific literature on ENDS.

**Methods and analysis:** We will undertake a systematic review of published empirical research literature on ENDS using the National Library of Medicine's PubMed electronic database to search for relevant articles. Data from included studies will be extracted into a standardised form, tables with study details and key outcomes for each article will be created, and studies will be synthesised qualitatively.

**Ethics and dissemination:** This review synthesises published literature and presents no primary data. Therefore, no ethical approval is required for this study. Subsequent papers will provide greater detail on results, within select categories, that represent gaps in the literature base.

## INTRODUCTION

E-cigarettes or electronic nicotine delivery systems (ENDS) have recently attracted considerable attention for several reasons. Compared with combustible cigarettes, these (1) deliver nicotine without combustion, (2) are thought to be less toxic,<sup>1–8</sup> (3) can be used to reduce nicotine craving/withdrawal,<sup>3 9–13</sup> (4) tend to be less expensive<sup>2 3 8 14 15</sup> and (5) can potentially help one quit combustible cigarette smoking/prevent relapse.<sup>1–4 6–8 15–21</sup>

## Strengths and limitations of this study

- This review systematically synthesises studies related to electronic nicotine delivery systems use across a broad range of study designs and outcomes.
- The results of this study may inform future regulatory action and future research studies.
- This review will be limited to English language and peer-reviewed articles.
- Owing to the volume of studies in the literature base, the literature search was limited to one database.

While there is great variability in the design and performance of ENDS within and across brands, characterising features include the use of a battery or other power source, and a heating element that when activated delivers an aerosol mist from a solution most often containing tobacco-derived nicotine, flavourings and other ingredients.<sup>22 23</sup> ENDS typically fall into three categories: disposable 'ciga-like' products, rechargeable 'ciga-like' products and larger rechargeable products (ie, personal vapourisers, tank systems). In addition to physical and performance-related differences, these categories of products differ in price, where they are typically sold, and the type of ENDS users that purchase them.<sup>14 24</sup>

Among some individuals, there is strong debate and a polarisation of views about the public health benefits versus harms from use of ENDS.<sup>25–27</sup> Proponents argue this is a disruptive technology that has potential to speed the demise of the combusted cigarette. From this perspective, ENDS could present an unprecedented opportunity to alleviate the burden of tobacco-related death and disease on a massive scale. Opponents are concerned about minimising unintended



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**Table 1** Electronic nicotine delivery systems systematic review study categories and outcomes

Study category	Outcomes
Product features	<ul style="list-style-type: none"> <li>▶ Product design</li> <li>▶ Nicotine, propylene glycol, flavouring, particulate matter and other toxicant content</li> </ul>
Health effects	<ul style="list-style-type: none"> <li>▶ Effects of:               <ul style="list-style-type: none"> <li>– Nicotine</li> <li>– Tobacco-related toxicants</li> <li>– Non-tobacco-specific toxicants</li> </ul> </li> <li>▶ Impact on:               <ul style="list-style-type: none"> <li>– Cardiovascular system</li> <li>– Lung function</li> <li>– Blood count</li> <li>– Other physiology</li> <li>– Cognition</li> <li>– Abuse liability/addictiveness</li> </ul> </li> <li>▶ Adverse events</li> <li>▶ Cytotoxicity</li> </ul>
Consumer perceptions	<ul style="list-style-type: none"> <li>▶ Awareness</li> <li>▶ Product perceptions</li> <li>▶ Interest</li> <li>▶ Reasons for use</li> </ul>
Patterns of use	<ul style="list-style-type: none"> <li>▶ Ever, current and dual use with other tobacco products</li> <li>▶ Initiation/progression</li> <li>▶ Smoking cessation/reduction</li> <li>▶ Use among various groups: general population, youth, young adults, adults, current smokers, former smokers, never-smokers, etc</li> </ul>
Marketing	<ul style="list-style-type: none"> <li>▶ Advertisement/promotion prevalence and expenditure</li> <li>▶ Claims and depictions</li> <li>▶ Receptivity to advertising/promotion</li> <li>▶ Marketing channels</li> </ul>
Sales	<ul style="list-style-type: none"> <li>▶ Market share/sales volume</li> <li>▶ Retail and online availability</li> <li>▶ Pricing</li> </ul>
Policies	<ul style="list-style-type: none"> <li>▶ Federal, state, local and organisational</li> <li>▶ Existing and proposed</li> <li>▶ Public support for policy</li> </ul>

consequences such as unforeseen health hazards related to ENDS, dual use that might undermine cigarette smoking cessation and the possibility that ENDS will attract non-users, including youth and former cigarette smokers.

The ENDS market is evolving, with new products being rapidly introduced and marketed. Currently, there is no independent entity charged with monitoring and regulating ENDS products, but the US Food and Drug Administration (FDA) Center for Tobacco Products (CTP) has proposed a rule to deem ENDS as subject to the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act).<sup>28</sup> Previous reviews have

addressed specific topics, including the health effects of ENDS,<sup>29–48</sup> the impact of ENDS on smoking cessation,<sup>38 49–53</sup> product features,<sup>29 48 54 55</sup> consumer perceptions,<sup>34 56</sup> patterns of use<sup>34 57</sup> and policies.<sup>58</sup> There are also several published comprehensive reviews about the ENDS literature.<sup>59–63</sup> However, rapid development in manufacturing, marketing and consumer domains related to ENDS will warrant frequent re-evaluation, based on the state of the evolving science. The purpose of this article is to describe a protocol for an ongoing comprehensive review of the published scientific literature on ENDS.

## METHODS AND ANALYSIS

### Design

We will undertake a systematic review of empirical research literature published in peer-reviewed journals on ENDS to be updated at regular intervals and on an as-needed basis to inform FDA public comment periods and other policy-relevant information gathering sessions.

### Eligibility criteria

#### Study design

Eligible studies are experimental studies, quasi-experimental studies, observational studies (including case–control, cohort and cross-sectional studies), case reports, case series, qualitative studies and mixed methods studies providing empirical data on ENDS. Potential other sources will be obtained by emailing experts and reviewing reference lists of included articles.

#### Outcome measures

We will accept a broad range of outcomes that will demonstrate the impact of ENDS on individual-level and population-level health. These are listed in [table 1](#).

Published reviews, commentaries, letters to the editor, editorials, practice guidelines, position statements and study protocols will be excluded unless they present original data from the authors. This review will be limited to English language studies published in peer-reviewed journals (not limited to the USA). Preclinical/animal studies will be excluded.

### Search methods

We conducted an initial search in August 2013 using the National Library of Medicine's PubMed electronic database and the following keywords: “e-cigarette\*” OR “electronic cigarette” OR “electronic cigarettes” OR “electronic nicotine delivery”. We did not specify a starting publication date because ENDS are a relatively new class of tobacco products. Since the initial search, we have conducted regular searches to identify new studies on ENDS and added the medical subject heading (MeSH) term “Electronic Cigarettes” that was introduced in 2015 as well as “vape” OR “vaping” to our list of search terms. Searches will be conducted at regular intervals and on an as-needed basis to inform FDA

public comment periods and other policy-relevant information gathering sessions. Reference lists of published literature reviews on ENDS will be screened for additional eligible studies.

### Study selection

For the first round of review to determine eligibility, one reviewer will screen the article title and abstract for reference to ENDS. Articles that make it through this round will then be reviewed in full text to determine inclusion into one or more of the following categories: (1) product features, (2) health effects, (3) consumer perceptions, (4) patterns of use, (5) marketing, (6) sales and (7) policies. At the point of data extraction, reviewers will confirm eligibility before entering the study's data in the review. If an article is excluded for multiple reasons, only the primary reason for exclusion will be noted. The hierarchy for identifying the reason for exclusion when multiple reasons exist will be as follows: (1) the article was not available in English, (2) the article was not relevant to ENDS, (3) the study included non-human participants or (4) the study did not include original data. The remaining studies will be retained for inclusion in the systematic review. If a study meets the criteria for eligibility in the first round, but does not fit into one of the seven categories listed above, the team of reviewers will meet to discuss whether additional categories should be added to capture emerging themes in the scientific literature.

### Quality assessment

Randomised studies assessing the impact of ENDS on health effects, consumer perceptions or patterns of use will be evaluated using the Cochrane Collaboration tool for assessing risk of bias.<sup>64</sup> For other study designs, we will consider the study's applicability or relevance to the literature and note its limitations.

### Data extraction

Data from included studies will be extracted into a standardised form developed in Microsoft Excel by a number of reviewers (AMG, COC, OG, LT, LK, SWR, SF and ACV), with each reviewer completing data extraction for a given category of studies. The form will contain the following fields: (1) study objective(s); (2) study details/methods (including study design, intervention groups, number of experiments, equipment used, setting, puff conditions and measurement conditions); (3) target population; (4) sample size; (5) products tested, if applicable (including number, type, brand name/model, nicotine content and flavour of products); (6) measures; (7) outcomes; (8) limitations; (9) major conclusions and (10) funding source/author disclosures. During this process, the form will be revised if other relevant information is not captured in these fields. In addition, individual reviewers will identify other categories of the review (eg, product features and health effects) in which the study should be included

based on the outcomes measured in that study. All communications regarding the addition of studies to other categories will be documented on a web-based project management system available to all authors. This will ensure that studies addressing multiple outcomes are captured in all of the relevant sections of the review.

### Data analysis

Following data extraction, we will create tables with details and key outcomes for each study within each category (ie, product features and health effects). In addition, we will qualitatively synthesise studies by outcomes measured and the main results. We intend to publish subsequent papers on select outcomes to address gaps in the literature base. Given the heterogeneity of the included study designs and outcomes, we do not expect to conduct meta-analyses of study results, assess meta-biases or evaluate the body of evidence systematically using a central framework (eg, GRADE). As the evidence base grows, we will re-examine whether there are a sufficient number of similar studies on a single topic to warrant conducting these evaluations.

### ETHICS AND DISSEMINATION

This review synthesises published literature and presents no primary data. Therefore, no ethical approval is required for this study.

### Publication plan

Findings from this systematic evidence review will be disseminated in white papers, policy documents (eg, federal docket submissions), fact sheets and peer-reviewed journal articles.

### STRENGTHS AND LIMITATIONS

This review is unique in three ways. First, whereas most other reviews on ENDS have focused on a particular outcome of interest,<sup>31 35 36 43 50 52 53 56</sup> this review will systematically synthesise studies related across a broad range of study designs and outcomes on an ongoing basis. Second, the review will be updated regularly and in response to opportunities to inform policy and programme decision-making. Third, the review will highlight gaps in the literature to recommend areas for future research in pace with the rapidly evolving tobacco landscape and evidence base.

Limitations of the review include the restriction of eligible studies to those that are peer-reviewed, indexed in PubMed and available in English language. Owing to the volume of studies in the literature base, the search is limited to one database, and a single author conducts the title and abstract review for a given search. While an individual author conducts data extraction for a given category of studies, we have developed a process for identifying studies that should be categorised under multiple outcomes and a team approach to communication to reduce bias in data extraction.

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**Contributors** ACV conceived of the study and assumes overall responsibility for the scientific integrity of the work as a whole. ACV, AMG, COC, OG and LT developed the search strategy, and the inclusion and exclusion criteria. AMG drafted the protocol. ACV, AMG and LK will perform the title and abstract review. All authors will perform data extraction.

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