Overview of Electronic Nicotine Delivery Systems: A Systematic Review

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Abstract

Context—Rapid developments in e-cigarettes, or electronic nicotine delivery systems (ENDS), and the evolution of the overall tobacco product marketplace warrant frequent evaluation of the published literature. The purpose of this article is to report updated findings from a comprehensive review of the published scientific literature on ENDS.

Evidence acquisition—The authors conducted a systematic review of published empirical research literature on ENDS through May 31, 2016, using a detailed search strategy in the PubMed electronic database, expert review, and additional targeted searches. Included studies presented empirical findings and were coded to at least one of nine topics: (1) Product Features; (2) Health Effects; (3) Consumer Perceptions; (4) Patterns of Use; (5) Potential to Induce Dependence; (6) Smoking Cessation; (7) Marketing and Communication; (8) Sales; and (9) Policies; reviews and commentaries were excluded. Data from included studies were extracted by multiple coders (October 2015 to August 2016) into a standardized form and synthesized qualitatively by topic.

Evidence synthesis—There were 686 articles included in this systematic review. The majority of studies assessed patterns of ENDS use and consumer perceptions of ENDS, followed by studies examining health effects of vaping and product features.

Conclusions—Studies indicate that ENDS are increasing in use, particularly among current smokers, pose substantially less harm to smokers than cigarettes, are being used to reduce/quit smoking, and are widely available. More longitudinal studies and controlled trials are needed to...
evaluate the impact of ENDS on population-level tobacco use and determine the health effects of longer-term vaping.

CONTEXT

Electronic nicotine delivery systems (ENDS), or e-cigarettes, produce an inhaled aerosol instead of smoke, providing an alternative mode of nicotine delivery.\textsuperscript{1–6} The U.S. Food and Drug Administration’s Center for Tobacco Products finalized a rule to regulate ENDS.\textsuperscript{7} Thus, there is a pressing need to identify the pathways by which to manage ENDS and how to strike a balance between potential benefits and harms to public health.\textsuperscript{4,8,9}

Reviews have been published on ENDS in general\textsuperscript{10–21} or on specific topics, including: health effects\textsuperscript{22–58}; impact on smoking cessation\textsuperscript{29,40–43,45,47,48,51,59–73}; product features\textsuperscript{22,39,41–43,45,47,74–77}; potential to induce dependence\textsuperscript{28,45,47,78,79}; consumer perceptions\textsuperscript{26,48,80,81}; patterns of use\textsuperscript{8,26,43,48,51,82–90}; and policies.\textsuperscript{8,48,91–98} Two conducted a bibliometric review of the ENDS literature\textsuperscript{86,99} and 46\% of the reviews were systematic.\textsuperscript{11,13,15,16,22–28,33,34,36,39,46,48,53–58,60,61,66,68,70–75,79–82,85,86,88–90,93,97,100–104} The dramatically changing product landscape warrants frequent updates and synthesis of the rapidly growing evidence to inform prudent practice, policy, and regulation.\textsuperscript{9,105,106} This comprehensive review presents a current synthesis of empirical studies on ENDS across a broad range of topics.

EVIDENCE ACQUISITION

A systematic review of empirical articles on ENDS was conducted via a PubMed search through May 31, 2016 (Appendix Table 1 shows search strategy and eligibility criteria).\textsuperscript{107} Analyses were conducted from October 2015 to August 2016. Included studies (Figure 1) were catalogued into one or more of the following topics:

1. Product Features;
2. Health Effects;
3. Consumer Perceptions;
4. Patterns of Use;
5. Potential to Induce Dependence;
6. Smoking Cessation;
7. Marketing and Communication;
8. Sales; and

Categories 5 and 6 were added to the original protocol\textsuperscript{107} to provide information. Study quality is not presented herein, but will appear in future papers. Figure 2 depicts the number of studies published each year. Appendix Table 2 details coding of articles.
Terminology

The inhalation of ENDS aerosol is referred to as “vaping,” and the inhalation of the smoke from any combustible tobacco product as “smoking.”

EVIDENCE SYNTHESIS

Of 1,634 articles identified through PubMed, 676 were included in the review (Figure 1). An additional ten studies were included through targeted searches or discussion with experts.

Product Features

There were 75 studies of ENDS products, liquids, and emissions.\(^5,6,108–180\) Ten additional studies were published on methods to analyze ENDS liquids and vapor.\(^181–190\) One study measured hazardous waste potential of ENDS disposal.\(^191\)

Product performance and design—Products comprise a cartridge, heating element, and battery.\(^6,112,156,192,193\) ENDS are available in three main subtypes: disposable “cigalike,” rechargeable “cigalike,” and rechargeable vaporizers (tank or open systems). Larger ENDS devices (i.e., tank/modified) can produce blood nicotine concentrations approaching those of cigarettes, but with a slower absorption rate; higher blood nicotine levels are more common among experienced vapers.\(^145,192–197\)

Liquid/vapor analysis—Mainstream and exhaled ENDS vapor contains ultrafine and fine particulate matter at similar sizes to that of smoke.\(^108,113,121,132,139–142,148–151,162,163\) Some studies found that the amount of particulate matter produced by ENDS is significantly lower than that found in smoke,\(^113,144,148,149\) whereas others found no difference or slightly higher concentrations in ENDS. Because the chemicals in vapor particles differ substantially from those in smoke, it is unclear what these results about size and volume of particulate matter imply about relative harm of ENDS vapor versus smoke.\(^121,132,142,163\)

The ENDS nicotine content in liquid and vapor varies across manufacturers, devices, cartridges, and puff to puff.\(^110–116,122,124,126,128,129,138,143,147,153,159,160,183,184\) Mainstream and exhaled ENDS vapor contains nicotine\(^113,148,150,151\) generally at lower levels than in smoke,\(^113,124,136,144,157\) or at a level comparable to smoking a low-nicotine cigarette.\(^122\) One study suggested nicotine may be detected on surfaces in the home of vapers,\(^127\) but another study found no difference in deposited nicotine on surfaces between homes with vapers and homes without smokers.\(^109\)

Liquids, mainstream, and exhaled ENDS vapor can contain propylene glycol,\(^111,122,125,130,133,148,150,151,184\) vegetable glycerin, additives, and flavorings.\(^148,150,151,155\) Although several potentially toxic constituents have been measured in some ENDS liquid and vapor, including tobacco-specific nitrosamines, heavy metals, and carbonyls (i.e., formaldehyde, acrolein, aldehydes), there are much fewer total constituents at much lower or trace levels when ENDS are used as intended, in non-“dry puff” conditions, than levels observed in smoke.\(^111,113,117–120,123,125,131,134–138,144,146,148,150,151,154,157–159,161,162\)
Summary—There is wide variability in nicotine delivery by ENDS brand, product type, and user profile.\textsuperscript{112,126,153,159} The amount of particulate matter and the chemical composition of vapor are unclear in terms of harms. Some liquids and vapor contain some potentially toxic constituents, but in far fewer numbers and at much lower or trace levels than found in smoke.

Health Effects

There have been 116 articles that examine the impact of vaping on human health\textsuperscript{142,150,162,169,193,195,197–305} and 13 on animal health.\textsuperscript{243,306–317} Studies address physiologic and cognitive effects of vaping, adverse events associated with vaping, exposure to secondhand vapor, and cytotoxicity of ENDS. Specific human biomarkers measured are listed in Table 1.

Physiologic and cognitive effects—Human exposure to some potentially harmful chemicals is significantly lower for ENDS than for cigarettes. Laboratory studies find modest increases in nicotine biomarkers after vaping.\textsuperscript{169,195,197,203,206,209–211,215,222,232,233,239,246,248,264,271,284,300} Vaping has no or minimal impact on other physiologic measures (i.e., exhaled carbon monoxide, complete blood count, body weight),\textsuperscript{142,202,203,230,237,239,242,257,265,272,274,276,282,285,292,303} with improvements in outcomes seen for smokers switching to ENDS, such as reduced blood pressure, improved lung function, and improved disease symptoms (i.e., asthma and chronic obstructive pulmonary disease).\textsuperscript{214,230,273,287} Some studies have examined cardiovascular measures associated with vaping,\textsuperscript{195,197,209,222,226,232,246,248,257,273,300,301} with the majority finding an increase in heart rate,\textsuperscript{195,223,246,248,300} but three finding no change after use.\textsuperscript{209,222,273} Studies measuring cognitive effects of vaping indicate some positive impacts, including improved memory and mood, consistent with a meta-analysis of acute positive benefits of nicotine\textsuperscript{318}; studies also report effects related to withdrawal reversal among smokers.\textsuperscript{207,208,214}

Adverse events—The total of all tobacco/nicotine exposures reported by the National Poison Data System was 1\% (\(n=10,452\)) of the total calls for household substance single exposures in 2014 (\(N=1,002,495\)).\textsuperscript{266} Within this context, ENDS comprised 29.5\% of all tobacco- and nicotine-related calls (\(n=3,910\)), up from 14.7\% in 2013 (\(n=1,495\)). Cigarettes comprised 43.1\% (\(n=5,714\)) of all tobacco- and nicotine-related calls in 2014 and 57.1\% (\(n=5,817\)) in 2013.\textsuperscript{266,319} Between 2012 and 2015, ENDS accounted for 14.2\% of the nicotine single exposure calls among children aged \(\leq 5\) years, compared with 60.1\% from cigarette exposures and 16.4\% from other tobacco product exposures.\textsuperscript{280}

The Food and Drug Administration received 35 adverse event reports (respiratory symptoms, eye irritation, headache, nausea, sore throat/irritation, dizziness, racing/irregular heart rate) of passive vapor exposure between January 2012 and December 2014.\textsuperscript{258} Other studies report the most common adverse events associated with vaping as mouth and throat irritation, nausea, headache, and dry cough.\textsuperscript{193,199,202,214,217,232,240,249,264,265,288,303,304,320} From 2012 to 2015, there were
92 reported overheating/fire/explosion events in the U.S., and about half resulted in injuries (i.e., thermal burns, lacerations, or smoke inhalation). 291

**Secondhand electronic nicotine delivery system vapor exposure**—Three studies have examined the individual health effects among non-smokers/vapers of exposure to secondhand ENDS vapor, one with machine-generated vapor215,216 and two via human-generated vapor.169,236 Two studies found no difference in cotinine levels following vapor and smoke exposures,215,236 whereas one study found nicotine content present in oral fluid from those exposed to vapor was much lower than from those exposed to smoke.169 One study found no differences in pulmonary function following vapor and smoke exposure,215 but white blood cell count, granulocyte count, and lymphocyte count increased significantly following smoke exposure, whereas vapor exposure did not affect complete blood count.216 Secondhand vapor studies to date show that non-users may be exposed to nicotine in ENDS vapor but the level of exposure is low, and exposure to other compounds also appears very low, or at trace or non-detectable levels when compared with secondhand smoke. It is unclear if any levels are sufficient to be of biological concern to humans. More-definitive studies are needed before conclusions about harm can be made.321,322

**Cytotoxicity**—In cellular studies, exposure to ENDS vapor increased anti-inflammatory processes,275,278 placed oxidative stress on exposed cells,269,279,294,301 and increased cell apoptosis and necrosis.305 Particular ENDS flavors are more cytotoxic than others, but generally most studied ENDS liquids are much less cytotoxic than cigarette smoke extract.213,228,238,250,254,260,295,296,308 In cytotoxicity studies, cinnamon flavor in ENDS was found to be the most toxic (i.e., inhibiting cell survival or inducing cell stress/morphologic change) when comparing flavors.198,247 Most studies find that nicotine levels are not correlated with cytotoxicity.198,213,238,255,260,312 Two studies examined the effect of vegetable glycerin and propylene glycol, frequently found in e-liquids, on various human and animal cells and found that they were not cytotoxic for any cell type.198,297

**Animal models**—Studies performed in animal models show that exposure to ENDS may have some physiologic effects (i.e., reduced weight, oxidative stress, neurobiological changes),243,306,310,312–317 yet these effects are less substantial than those caused by exposure to cigarettes.243,307,310,312–317 Attempts to generalize from animal to human effects are premature without further research on human samples.

**Summary**—Studies on the health effects of vaping indicate no or minimal impact on physiologic biomarkers and some possible acute positive effects on cognition and mood regulation. Adverse events reported by vapers are generally mild and resolve, though there have been serious adverse events reported in some cases. There have been a greater number of poison control center calls related to nicotine exposures from ENDS in recent years, including exposures among children. Calls related to cigarette exposures—where smoking is much more prevalent than vaping—remain more common. Secondhand vape studies show that non-users may be exposed to nicotine in vapor, but at lower levels than when exposed to smoke.
**Consumer Perceptions**

One hundred eighty-eight articles have addressed consumer perceptions of ENDS.\(^\text{145,192–194,214,241,288,299,320,323–505}\)

**Awareness**—Awareness of ENDS has increased among U.S. adults since 2009,\(^\text{323,339,362,378,384,386,388,391,394,395,440}\) with 86.4% of the U.S. population aware of these products in 2013.\(^\text{440}\) Awareness is highest among younger age groups, non-Hispanic white populations, and those with higher income and education.\(^\text{323,370,391,440}\) Most healthcare providers are aware of ENDS.\(^\text{334,336,377,458}\) Awareness of ENDS has increased in other countries over time.\(^\text{326,333,335,359,369,374,380,381,396,414,451,452,460,475,483,494}\)

**Product perceptions**—Generally, ENDS are perceived to be less harmful than cigarettes regardless of the respondent’s tobacco use status.\(^\text{192–194,214,288,325–327,332,335,336,338,353,354,361,369,372,374,382,384,389,390,446,448,449,453–457,461–464,467,471–474,476,477}\) In the U.S. and Great Britain, this belief has eroded over time with more individuals mistakenly believing ENDS are as harmful or more harmful than cigarettes.\(^\text{391,414}\) Studies suggest that ENDS are also perceived as less addictive than cigarettes,\(^\text{367,375,403,446}\) tools that may help users reduce or quit smoking,\(^\text{320,327,330,338,357,374,448,453,455,458,461,464,467,481,483,485,486,488,493,495,499}\) less expensive than cigarettes,\(^\text{335,338,447,455,456,472,499}\) and more convenient or easier to use than cigarettes.\(^\text{335,338,357,400,499}\)

Common ENDS concerns include the lack of research on long-term use,\(^\text{397,399,436}\) absence of regulation,\(^\text{397,399}\) potential harms of use,\(^\text{443,464}\) potential to undermine other tobacco control measures,\(^\text{399,401,480}\) and social stigma.\(^\text{299,402,464,467,477}\)

**Reasons for use**—The most commonly cited reasons for use by vapers include:

1. to address tobacco craving/withdrawal symptoms\(^\text{194,320,353}\) as reported by 67%–79% of adults\(^\text{194}\) and as a smoking-reduction/cessation aid,\(^\text{192,193,214,241,323,324,326,332,337,338,347,350,353,358,369,372,375,376,381,382,389,393,395,422,434,455,456,459,461}\) which was reported by 55%–85% of adults in nationally representative samples\(^\text{323,350,395}\),

2. to evade smokefree policies or avoid disturbing people with secondhand smoke,\(^\text{192,193,214,323,324,326,332,337,338,341,345,347,350,353,358,369,372,374,376,387,389,395,421,426,432}\) as reported by 45%–85% of adults in nationally representative samples\(^\text{323,350,395}\); and

3. because they are perceived as less harmful/less toxic than cigarettes.\(^\text{192,194,323,326,337,338,341,345–347,350,353,358,372,374,375,382,395,422,434,455,456,459,475,483,494}\)
by 45%–75% of adults in nationally representative samples.323,350,395


**Summary**—Awareness of ENDS is high, and most users report using them to aid in smoking cessation, to evade smokefree policies, or because they are perceived as less harmful. Beliefs that ENDS are less harmful than cigarettes have lessened over time.

**Patterns of Use**


**Electronic nicotine delivery system use in the U.S**—National cross-sectional data indicate that ENDS ever and past 30–day use in the U.S. has increased over time, particularly among youth from 2010 to 2014 (Table 2). This is also true for studies based outside of the U.S.329,528,543,592,613,647 However, past 30–day ENDS use among U.S. youth did not change significantly from 2014 to 2015, indicating a slowing in prevalence as reported in both the National Youth Tobacco Survey and the Monitoring the Future survey.640,648 The 2014 National Health Interview Survey showed that ever use of ENDS among young adults aged 18–24 years in the U.S. in 2014 was 21.6%, whereas “every day” or “some days” use in the same age group was 5.1%.610,639 These data also show that ever use and “some days” or “every day” use of ENDS among all adults was 12.6% and 3.7%, respectively, in 2014.610,639 Although young adults were significantly more likely to report ever use of ENDS than older adults, they were not more likely than older adults to be using ENDS “some days” or “every day.”610

Use of ENDS varies by smoking status, with the majority of users being current smokers, followed by former smokers; never smokers are least likely to have tried ENDS.323,333,336–339,342,344,346,348,350,351,354–357,359,361,369,380,381,384,395,396,421,455,461,472,504,527,531,541,543,551,552,561,568 National Health Interview Survey data show that recent former smokers (quit <1 year ago) were more likely to report using ENDS “every day” or “some days” (22.0%) than adults who had never smoked (0.4%), former smokers who had quit for ≥ 1 year (2.3%), or former smokers who quit cigarettes ≥ 4 years ago (0.8%).610,639 Studies show the use of ENDS is correlated with use of other tobacco products,325,362,394,468,509,517,520,524,557,558,584,585,621,649
marijuana," and alcohol. Frequency of electronic nicotine delivery system use—There are an increasing number of studies characterizing frequency of ENDS use, with most studies indicating ENDS are used infrequently (i.e., 1–2 days per month or “rarely”) by the majority of users, and more frequent (e.g., daily) use is higher among recent quitters and current smokers. According to National Health Interview Survey data, recent quitters (<1 year) were four times more likely to be daily ENDS users than current smokers (13% vs 3.5%). In 2014, the National Youth Tobacco Survey added measures of frequency of use in the past 30 days and found that of the 13.4% of high school students reporting any past 30–day ENDS use, 45.4% (or 6.1% of the population) had tried ENDS on 1–2 days, 16.2% (2.2% of the population) on 3–5 days, 12.0% (1.6% of the population) on 6–9 days, 10.9% (1.5% of the population) on 10–19 days, 5.8% (0.8% of the population) on 20–29 days, and 9.7% (1.3% of the population) used ENDS all 30 days. Of the 3.9% of middle school students reporting past 30–day ENDS use, over half (54.5%, or 2.1% of the population) had used ENDS on 1–2 days. Topography—Ten studies examined ENDS user topography. Puff duration and volume are higher for ENDS products than for cigarettes, but flow rate (among experienced vapers) and puff counts (upon initial use in naïve vapers) have been found to be lower than for cigarettes. Higher liquid nicotine concentration has been associated with shorter puffs, but puff velocity shows no effect on nicotine yield. There is significant intersubject variability in puff behavior, suggesting more research is needed to determine the impact of user topography on vapor production and nicotine intake. Summary—Because ENDS is a new and potentially disruptive technology, it is expected that ENDS use has increased in all age groups since their introduction and up until at least 2014. The rate of increase among youth has recently slowed or flattened in 2015. ENDS use is most common among current and recent former smokers, whereas prevalence is low among never smokers and long-term former smokers. Most past 30–day ENDS use among youth in the U.S. consists of use on 1–2 days in the past month. Daily ENDS users are most likely to be recent former smokers. Potential to Induce Dependence The potential of ENDS to induce dependence is considered to be primarily a function of the products’ ability to quickly deliver a rapid and adequate dose of nicotine to the brain of the user, but cigarette smoking is still the most rapid method of nicotine delivery. Twenty-eight studies have examined nicotine biomarkers resulting from vaping. Nicotine delivery is dependent on characteristics of ENDS devices and liquids, such as battery size, device type, propylene glycol/vegetable glycerin ratio, and nicotine liquid concentration, as well as individual user differences (i.e., naïve or not naïve). Five clinical laboratory reports of
experienced vapers indicated ten puffs of nicotine-containing ENDS reliably increased plasma nicotine within 5–10 minutes\textsuperscript{195–197,223,580} in all but one report,\textsuperscript{580} in which plasma nicotine levels significantly lower and reached a peak more slowly than that achieved with ten puffs from a cigarette. Recent assessments with second-generation devices demonstrate that a plasma nicotine concentration similar to that of cigarettes can be achieved after vaping, dependent upon the user’s puff topography\textsuperscript{197} or ENDS liquid nicotine concentration.\textsuperscript{564,580} Whether such levels are routinely achieved by most vapers is unclear.

The immediate reinforcing subjective effects of using a drug that are substantially but not solely a function of dose and speed of nicotine delivery also influence its ability to induce dependence and elicit repeated use.\textsuperscript{651,652} Twenty-four studies have examined the subjective effects of vaping \textsuperscript{193,195–197,199,203,206–209,211,221–223,225,232,239,264,300,303,328,330,335,360,427,429,529,540,653,654,658–660}.

These studies indicate vaping decreases adverse symptoms related to smoking abstinence (e.g., craving/urges to smoke, irritability)\textsuperscript{197,199,206–208,222,223,330,350,659} and increases ratings of satisfaction/pleasantness.\textsuperscript{195,197,199,222,223,225,335} Though some smokers find ENDS less reinforcing\textsuperscript{195} and satisfying than cigarettes,\textsuperscript{239,344} second-generation devices are more satisfying than first-generation devices.\textsuperscript{330}

There is only one proposed measure of ENDS dependence\textsuperscript{540,661}; however, studies have used many approaches to assessing ENDS dependence and drawing comparisons between products, such as adapting existing scales for cigarette or nicotine dependence or measuring perceived dependence. Approximately one third of former smokers who are daily vapers perceive their dependence on ENDS to be as strong or stronger than their previous dependence on cigarettes.\textsuperscript{193,360,446,662} These studies suggest that the current class of ENDS products may have significantly lower ability to induce dependence than cigarettes, but are capable of inducing some level of satisfaction and dependence, especially when using second-generation (e.g., tank or mod devices with adequate concentrations of nicotine e-liquid/juice).

**Smoking Cessation**

A key question regarding ENDS is their potential role in facilitating smoking abstinence or meaningful smoking reduction. Included study designs and outcomes relevant to smoking cessation and vaping are presented in Appendix Table 3.

Four RCTs show that ENDS are effective in helping some adult smokers to quit or to reduce their cigarette consumption.\textsuperscript{203,653,663–665} In the studies that assessed smoking cessation, rates of cessation in the ENDS study groups were similar to or higher than rates of cessation seen in previous clinical trials of nicotine-replacement therapy (NRT).\textsuperscript{666} Some prospective studies with loosely defined comparison groups report that vaping may be associated with no change or negative correlations with cessation.\textsuperscript{323,393,522,667–670} This stands in contrast to other studies with more-precise measures of how ENDS were used (e.g. duration of use, type of device, use specifically for cessation), which suggest that regular, more intensive vaping can facilitate quit attempts and cessation.\textsuperscript{252,514,516,548} Many longitudinal studies without comparison groups,\textsuperscript{202,232,241,287,288,409,486,536,574,658,671–675} and cross-sectional
studies, suggest that ENDS can help some adult smokers quit or reduce smoking.

The conclusions from the longitudinal and cross-sectional studies reporting negative correlations between those who tried ENDS and smoking cessation have serious limitations, including: selection bias (e.g., smokers who quit by using ENDS were excluded from the sample), inadequate measures of exposure (e.g., ever use in one’s lifetime) to test for a cessation indication, and confounders (e.g., smokers who have repeatedly failed to quit are more likely to try ENDS). This is similar to studies of NRT and smoking cessation in which some observational studies showed negative correlations, whereas >80 RCTs of NRT show strong positive cessation effects. Observational studies with more-robust measures of how ENDS were used (e.g., duration of use, type of device, use for cessation) suggest ENDS can facilitate quit attempts and cessation. More research—especially independent, high-quality RCTs with appropriate measures and control groups—is needed to further determine whether and how ENDS can be an effective cigarette-cessation or -reduction aids.

Marketing and Communication

There have been 74 articles on the marketing and communication of ENDS products. Among noncombustible tobacco products, ENDS advertisements are the most widely circulated. Individuals aware of ENDS report the most common product exposures are through in-person communications, by seeing them at the point of sale, and through online and TV advertisements. Conventions provide manufacturers an opportunity to promote and introduce new products through free samples, celebrity appearances, and branded merchandise giveaways. ENDS are promoted heavily online through ENDS company-sponsored advertisements and users’ social media profiles, with occurrences on YouTube and Twitter. Youth and young adult exposure to TV advertisements for ENDS has increased since 2011. Two RCTs and four cross-sectional studies have shown that tobacco marketing exposure may promote ENDS uptake. Exposure to industry and ingredient warnings is associated with lower odds of intent to purchase ENDS. Several studies have reported the presence of interior and exterior ENDS advertisements at tobacco retail outlets, including one study which found that the ENDS advertisements featured flavored products at the eye level of children. The total expenditure for ENDS advertisements across all media channels is increasing annually, with a 52% increase from 2013 to 2014. Blu eCigs led in total advertisement expenditure until Altria’s MarkTen entered the national market in 2014. Online ENDS advertisements do not account for a large portion of this financial investment. However, this expenditure information is outdated and there is no established method to assess true advertisement expenditures in the current media environment.

Commonly marketed as alternatives to cigarettes, ENDS advertisements often make claims, such as being an effective smoking-cessation aid. The most common claims advertise ENDS as a healthier alternative to cigarettes.
Sales

There have been 30 articles addressing the sales of ENDS products. The ENDS market is expanding and accessible to consumers through internet vendors and in most tobacco outlets. Field observations of tobacco retail outlets have found that more than half of tobacco retailers sell ENDS. One study found no significant relationship between retail availability and neighborhood demographics, but another study indicated a greater likelihood of ENDS retailers in communities with higher median incomes. One cross-sectional survey of adults found that frequent (weekly/daily) vapers were significantly more likely to purchase over the Internet than infrequent (monthly or less) vapers. Studies assessing online retailers found inadequate age verification methods, with one study reporting a 93.7% rate of successful youth purchases without age verification. ENDS products can be sold at an estimated 200%-400% markup in vape shops. Information is limited on the impact of pricing on ENDS sales, with one study indicating that vapers are two to three times more sensitive to price than smokers, and several studies finding that ENDS are substitutes for cigarettes as cigarette prices increase.

Policy

There have been 51 articles focused on ENDS and policy. Eleven studies described ENDS policies enacted at the local, state, and country level; others addressed proposed city policies, university policies, public and stakeholder opinion of ENDS policies, the unmet research needs of state and community tobacco control practitioners regarding ENDS, implementation and enforcement of ENDS policies in hospitals, and policies related to vaping on American transit systems.

Seven studies examined the impact of policies (e.g., smokefree indoor air laws) on interest, demand, or use of ENDS. One study found that in the event of a menthol cigarette ban, 15.1% of menthol smokers would switch to menthol ENDS. Four studies examined the impact of state-level ENDS policies and potential areas of ENDS regulation on tobacco use, suggesting that a ban on ENDS may increase demand for cigarettes.

DISCUSSION

This review highlights several major findings. First, ENDS are a heterogeneous and evolving product category, with variation in physical factors that can influence vapor production (e.g., tank style, battery power, temperature). E-liquids contain various combinations of nicotine, flavors, and carriers. These factors affect nicotine delivery, appeal, and ease of product use and underscore the degree to which individual preferences may play a role in use patterns. Second, detectable levels of some potential toxicants have been found in ENDS liquids and
vapor, but studies of actual human exposures are few. Although it is difficult to estimate the precise difference in harmful exposure of vaping compared to smoking, experts have concluded that ENDS are substantially less harmful than cigarettes\textsuperscript{267} and toxicant exposures are derived both from far fewer chemicals and at much lower levels or trace levels, estimated to be one fourth to one ninety-fifth those of cigarette smoke.\textsuperscript{125,237,321,322} Third, ENDS can produce mild adverse reactions (e.g., irritation, nausea) in some users; poisonings via misuse and unintended exposure have also been documented.\textsuperscript{266} Fourth, as expected for a novel product, vaping experimentation increased rapidly since being introduced in the U.S.\textsuperscript{509,510,610,807–809} and abroad,\textsuperscript{329,369,414,528,543,647,810} particularly among youth, but in 2015 in the U.S. use appears to be leveling off. ENDS uptake trends have coincided with significant reductions in smoking prevalence to record lows among youth and adults.\textsuperscript{509,510,807–809} The majority of vaping in all age groups occurs among current smokers and recent studies also show that the prevalence of daily vaping is very low in both youth and adults.\textsuperscript{504,610,633}\textsuperscript{514,516,548,610} Fifth, RCTs and population-based studies with more-precise exposure measures show that ENDS are at least as effective as NRT in helping some smokers to quit or reduce their smoking\textsuperscript{1,321,322} and may reach more smokers at scale than NRT\textsuperscript{1,321,322} Finally, various ENDS policies (e.g., inclusion in smokefree indoor air) have been implemented in many jurisdictions,\textsuperscript{779} but there has been little evaluation of the impact of these policies on behavior.

Limitations

A strength of this review is its synthesis of a broad range of study designs and outcomes related to ENDS. Limitations include that eligible studies were restricted to those that are peer reviewed, indexed in PubMed, and available in English language. The authors did not quantify the risk of bias of the evidence given the size and heterogeneity of the sample of included studies. Though bias is possible, the authors used a process for identifying studies categorized under multiple outcomes and regular team communication to reduce bias in data extraction. The summary of studies on patterns of ENDS use is limited to U.S. data; however, a manuscript is in progress to synthesize these studies in depth, including studies conducted in other countries and other topics relevant to vaping patterns (e.g., devices, flavors, and brands).

CONCLUSIONS

There are a number of factors to consider when synthesizing the results. First, ENDS products are highly variable. A standardized method is needed to characterize products with respect to nicotine and toxicant delivery and their potential harms, both relative to smoking and relative to no use (absolute harm). Second, the field lacks consistent definitions of types of users and patterns of use, which complicates the interpretation of research findings. Third, many studies have small sample or cell sizes and employ convenience samples, raising concerns about selection bias, unmeasured confounders, low statistical power, and limited generalizability to draw firm national public health or policy conclusions. Fourth, there exist gaps in the current evidence base, including longitudinal data and data on reasons for vaping and use trajectories (including polytobacco use and use of cessation aids) that may help to explain population impacts and changing trends.\textsuperscript{8} Fifth, caution must be exercised when
drawing conclusions from in vitro, or cellular, studies because effects on cells cannot be readily extrapolated to human harms.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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Figure 1.
Flowchart of studies included in the ENDS systematic review.
*Total number of articles combined across categories exceeds the total number of unique articles because many fit into multiple categories.
ENDS, electronic nicotine delivery system
Figure 2.
Number of included articles by year.
\(^a\)2016 accounts for publications through June 1, 2016.
### Table 1

<table>
<thead>
<tr>
<th>Biomarkers Measured by Outcome Assessed in Published ENDS Studies</th>
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<td>Body weight\textsuperscript{292}</td>
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<td>Motor performance\textsuperscript{302}</td>
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ENDS, Electronic nicotine delivery systems
Table 2


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<tr>
<th></th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
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<tr>
<td>Youth</td>
<td>3.3%(^a)</td>
<td>6.8%(^b)</td>
<td>8.0%(^a)</td>
<td>19.8%(^b)</td>
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<tr>
<td>Middle school students</td>
<td>1.4%(^b)</td>
<td>2.7%(^b)</td>
<td>3.6%(^b)</td>
<td>10.1%(^b)</td>
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<tr>
<td>High school students</td>
<td>4.7%(^b)</td>
<td>10.0%(^b)</td>
<td>11.9%(^b)</td>
<td>27.3%(^b)</td>
<td></td>
</tr>
<tr>
<td>Young adults (aged 18–24)</td>
<td>6.9%(^b)</td>
<td>4.1%(^b)</td>
<td>7.8%(^b)</td>
<td>21.6%(^b)</td>
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<tr>
<td>Adults (aged 18+)</td>
<td>6.2%(^b)</td>
<td>8.1%(^b)</td>
<td>8.5%(^b)</td>
<td>12.6%(^b)</td>
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<tr>
<td><strong>Past 30-day use of ENDS</strong></td>
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<tr>
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<td>1.1%(^b)</td>
<td>2.1%(^b)</td>
<td>3.1%(^b)</td>
<td>9.3%(^b)</td>
<td>13.2%(^b)</td>
</tr>
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<td>1.1%(^b)</td>
<td>1.1%(^b)</td>
<td>3.9%(^b)</td>
<td>5.3%(^b)</td>
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<td>13.4%(^b)</td>
<td>16.0%(^b)</td>
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<tr>
<td>Young adults (aged 18–24)</td>
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<td>d</td>
<td>0.9%(^b)</td>
<td>b</td>
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<tr>
<td>Adults (aged 18+)</td>
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<td>d</td>
<td>1.9%(^b)</td>
<td>b</td>
<td>b</td>
</tr>
</tbody>
</table>

\(^a\) Data not reported in recent Centers for Disease Control and Prevention reports or in the published literature but are publicly available.

\(^b\) Data not yet available in the published literature.

\(^c\) Sample size too small to estimate past 30-day ENDS in young adults before 2012–2013.

\(^d\) Annual estimates unavailable; estimates were collapsed over two-year intervals (2010–2011 and 2012–2013) due to small sample size.

ENDS, electronic nicotine delivery systems