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## Electronic Cigarettes as Smoking Cessation Tool: Are we there?

Sohini Ghosh, MD<sup>1</sup> and M. Bradley Drummond, MD, MHS<sup>1</sup>

<sup>1</sup>Division of Pulmonary Diseases and Critical Care Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

### Abstract

**Purpose of Review**—Electronic cigarette (e-cigarette) use is rapidly increasing, with many users reporting trying e-cigarettes as a method to quit combustible cigarettes. This review highlights recently published studies assessing the use of e-cigarettes as a tool for cessation of combustible cigarettes.

**Recent Findings**—When evaluating data from four randomized controlled trials and multiple cohort studies, differential association between e-cigarette use and cessation rates was seen. Cessation rates are highest in UK cohort studies and in studies using a multi-faceted approach, such as with the addition of varenicline. The largest evidence base is derived from observational cohort studies. Overall, the current evidence remains too small for conclusive results regarding efficacy of e-cigarettes for combustible cessation. There does appear to be a consistent reduction in daily combustible cigarette use in regular e-cigarette users.

**Summary**—Currently, there are conflicting data which can be used to support or dismiss e-cigarettes as a tool for smoking cessation. As larger population-based studies become available, the potential harms and benefits of e-cigarette will become clearer. In the short term, shared decision making with combustible cigarette users will be imperative when considering e-cigarettes as a smoking cessation tool.

### Keywords

e-cigarette; electronic tobacco products; smoking cessation; nicotine replacement therapy

### Introduction

E-cigarettes, also known as electronic nicotine delivery systems, are battery operated devices which deliver nicotine by heating and aerosolizing a nicotine containing solution. E-cigarettes have three key components: a power source, an electronic heating element, and liquid-containing nicotine cartridge. The liquid in the cartridge contains varying concentrations of nicotine and flavorings in a stabilizing liquid vehicle. When the user activates the heating element, a nicotine-containing liquid aerosolizes and is subsequently inhaled (1, 2). E-cigarettes have been marketed as an alternative to traditional combustible

Corresponding Author/Reprint Request: M. Bradley Drummond, MD, MHS, 125 Mason Farm Road, CB# 7248, Chapel Hill, NC 27599, brad\_drummond@med.unc.edu, Phone: 919-966-7054, Fax: 919-966-5178.

CONFLICTS OF INTEREST

None

cigarettes. E-cigarettes became available in the US in 2007 with increasing awareness and popularity, leading to approximately 15% of US adults in 2014 reporting trying an e-cigarette (1, 3, 4). Current smokers and those reporting recent cessation comprise the largest fraction of e-cigarette users, with approximately 50% of these groups in the US, and 40% in Great Britain reporting use (3–5). Among both current and former smokers the most commonly cited reasons for the use of e-cigarettes were perceived health benefits when compared to combustible cigarettes, followed by assistance with smoking cessation (5). These epidemiological data highlight that e-cigarette users are integrating these devices as a smoking cessation tool. What remains unclear is whether the current state of scientific evidence supports this social phenomenon. The purpose of this review is to summarize the recent literature regarding the efficacy of e-cigarettes to impact smoking cessation. With these data, clinicians, policy makers and e-cigarette users can better understand the potential role of e-cigarettes in smoking cessation.

### Acute Toxicity of E-Cigarettes

Any consideration of e-cigarettes as a cessation tool must incorporate a discussion of the known harms of these devices. Heterogeneity in e-cigarette device design leads to substantial heterogeneity in vapor constituents (2, 6). Vapor analysis of 12 brands of e-cigarettes revealed the presence of many toxic chemicals including carbonyl compounds, volatile organic compounds, carcinogenic nitrosamines and heavy metals (7). These toxins were present at concentrations 9–450 times lower than that seen in cigarette smoke. Recent studies have reported that super-heating of glycol derivatives, achievable with newer higher voltage “tank” devices, increases the generation of potentially carcinogenic carbonyl compounds (8). While the preponderance of data support that e-cigarettes generate toxic compounds at levels less than combustible cigarettes, it is unclear if these levels are below a threshold for harm. Moreover, given the relative infancy of e-cigarette use, it will likely be decades before long-term harm data are available. These uncertainties have been used as evidence by both proponents and opponents of e-cigarettes to support their claims of benefits or harms.

### Randomized-Controlled Trials of E-Cigarettes for Cessation

Currently, there are limited clinical trials to assist health care providers when counselling patients on the role of e-cigarettes as a cessation tool. Four randomized controlled trials (RCTs) have directly studied e-cigarettes usage for smoking cessation (9–12) (Table 1). The largest study was conducted by Bullen and colleagues in New Zealand between 2011 – 2013(11). This study recruited 657 smokers interested in quitting to receive low intensity behavioral support along with either 16 mg nicotine e-cigarette, 21 mg nicotine patch or placebo e-cigarette for 6 months. Biochemically verified abstinence at 6 months was the primary outcome. At 6-months, there was no difference in the biochemically-confirmed smoking abstinence: 7.3% nicotine e-cigarette, 5.8% nicotine patch, 4.1% placebo e-cigarette (nicotine versus placebo e-cigarette  $p=0.44$ ; nicotine e-cigarette versus patch  $p=0.46$ ). Notably, 57% of patients in the nicotine e-cigarette decreased their daily number of cigarettes smoked by at least half compared with 41% of participants randomized to nicotine patch ( $p=0.0002$ ).

The 2013 “Efficiency and Safety of an Electronic Cigarette as Tobacco Cigarettes Substitute” study by Caponnetto and colleagues randomized 300 Italian smokers not interested in quitting to either 1) 7.2 mg e-cigarette for 12 weeks, 2) 7.2 mg e-cigarette for 6 weeks then 5.4 mg e-cigarette for 6 weeks or 3) 0 mg e-cigarette for 12 weeks.(10) After 12 weeks, participants were advised to continue using their e-cigarette if they wished, but no additional cartridges were provided by investigators. Participants were subsequently followed for an additional 40 weeks. At the end of the study period of 52 weeks, overall cessation rates were 11% in the 7.2 mg group, 13% in the 5.4 mg group and 4% in the placebo group ( $p=0.24$  for overall difference). At 52 weeks, 9–12% of smokers in all three groups had reduced their baseline cigarette usage by half with no significant differences between groups.

A 2014 RCT by Adriaens and colleagues randomized 48 smokers who were not wanting to quit to either a control group with no intervention, or to one of two different brands of refillable second generation e-cigarettes with 18 mg nicotine containing solution (12). The primary aim of the study was to evaluate acute cravings over a span of 8 weeks in relation to successful sustained smoking reduction. An e-cigarette group was permitted to use the device for eight weeks, while the control group was asked to avoid e-cigarettes. All groups were followed for six months after the eight-week study. At six months, cessation rates were 19% for the e-cig group and 25% for the control group ( $p$ -value for difference not provided). A total of 60% fewer cigarettes were smoked per day across all groups, however only 23% participants had a >50% reduction in number of cigarettes smoked.

The most recently published RCT by Tseng and colleagues enrolled 99 New York residents (9). After a brief counseling session, participants were asked to reduce cigarette consumption by 50%, and were then randomized in a double-blinded fashion to either nicotine e-cigarette or placebo e-cigarette, and then followed for three weeks. They were not offered other nicotine replacement therapy, and were excluded if already on nicotine replacement therapy. Formal assessment of cessation was not a pre-specified outcome of this study, but no participants reported complete cessation at follow-up. After three weeks there was a significant reduction in cigarettes per day smoked in both groups ( $p<0.001$ ). The odds of achieving at least 50% reduction in users of nicotine e-cigarettes was 3.2-fold greater than placebo e-cigarettes ( $p=0.034$ ).

So how are we to incorporate these data into an assessment of the value of e-cigarettes as a cessation tool? Taken individually or in total, the available RCTs demonstrate that e-cigarettes are no better and no worse than placebo or nicotine replacement as a tool for smoking cessation. However, all RCTs are limited by variable outcome assessments, inadequate sample size, and diverse study populations of smokers. The most recent Cochrane review published in September 2016 found that data pooled from the studies by Bullen and Caponnetto support an effect of nicotine e-cigarettes on cessation when compared to placebo e-cigarettes, but grades the confidence in these conclusion as low given the few trials, low event rates and wide confidence intervals (13). The study by Bullen and colleagues is the only RCT to compare e-cigarettes to standard nicotine replacement therapy, which is the most relevant comparator for clinicians. Unfortunately, the fixed dose nicotine replacement used in that study has been shown to be less effective than dual replacement

approached (i.e., patch and gum) (14, 15). Moreover, the trial design placed the nicotine replacement group at a disadvantage compared to the e-cigarette group, as the nicotine replacement group was given vouchers for patches while the e-cigarette group was directly provided e-cigarettes. It is tempting to speculate that e-cigarettes may have been less effective than nicotine replacement if these study weaknesses were not present. Despite this, Bullen and colleagues should be commended for embarking on a rigorous and relevant comparator design. Study designs comparing established cessation practices should be a focus of future randomized control trials as to obtain the most clinically relevant data.

## Cohort Studies of E-Cigarettes for Cessation

Given that conclusive data from RCTs is unlikely to be available in the near future, clinicians may look to data from observational studies to derive conclusions about the role of e-cigarettes for cessation. While these data do not meet the “gold standard” of scientific proof attributed to RCTs, they are informative in that these study designs are more reflective of the real world setting. A recent non-randomized trial from London included offering e-cigarettes to all smokers seeking help from the UK’s Stop Smoking Services (16). E-cigarettes were offered in addition to the standard treatment of behavioral support and medications. Of 100 smokers, 69 opted in for e-cigarette use. In addition to e-cigarette use, 20 participants also opted to use varenicline while 23 opted to use nicotine replacement therapy. Of those who trialed e-cigarettes, 68% reported cessation in the e-cigarette group at four-week follow-up compared with 45% of smokers not using e-cigarettes ( $p=0.06$ ). There was a significantly higher cessation in smokers who used varenicline plus e-cigarette compared to those using e-cigarette alone (85% vs. 54%;  $p=0.03$ ). The higher rates of cessation using a multi-faceted approach suggests that combination therapy which incorporates e-cigarettes with non-nicotine pharmacotherapy warrants additional exploration.

Two large longitudinal cohort studies have examined the association of intensive (i.e., daily) use of e-cigarettes with cessation of combustible cigarettes (17, 18). Brose and colleagues examined surveyed 4064 adult smokers in the UK at baseline and one-year later with a retention rate of 43% at follow up. The authors found an association between e-cigarette use and increased quit attempts (OR 2.11; 95% CI 1.24–3.58;  $p=0.006$ ), but no association between e-cigarette use and cessation (OR 0.62; 95% CI 0.27–1.37;  $p=0.24$ ) (17). Biener and colleagues surveyed 1374 US smokers at baseline and 2–3 years later (51% retention rate) (18). Self-reported one-month cessation rates were 12% for e-cigarette non-users, 9% for non-daily e-cigarette users and 20% for daily e-cigarette users (overall  $p=0.50$ ). In adjusted analyses, compared to non-users, regular e-cigarette users were six times more likely to quit smoking (OR 6.07; 95% CI 1.11–33.2). No association was observed between non-daily e-cigarette use and cessation. These results are consistent with a previously published cohort study of 1549 US smokers which observed that e-cigarette use as baseline was not associated with cessation one-year later (OR 0.71; 95% CI 0.35–1.46;  $p=0.35$ ) (19).

Two UK cohort studies have shown that e-cigarettes are associated with increased cessation of combustible cigarettes (20, 21). Brown and colleagues enrolled 5863 participants in a retrospective cross-sectional study in England evaluating adults who had attempted to quit

smoking within the past 12 months (20). Participants were asked about their number of quit attempts, use of nicotine replacement therapy, use of e-cigarettes and smoking urges. Non-smoking was reported among 20% of e-cigarette users, 10% of nicotine replacement users and 15% of those using no aid. Use of e-cigarettes increased the odds of self-reported abstinence compared with nicotine replacement therapy (OR 2.23; 95% CI 1.70–2.93) or no cessation aid (OR 1.38; 95% CI 1.08–1.76). The association between e-cigarette use and self-reported abstinence persisted after adjusting for potential confounders including age, sex, social grade, nicotine dependence and prior quit attempts. Extrapolated data from this study estimates that 19,000–22,000 long term quitters were generated with the assistance from e-cigarettes (22). Recently Beard and colleagues reported findings from 1200 smokers in the UK Smoking Toolkit Study, a cross-sectional population based survey (21). In 2016, 21% of the cohort reported using e-cigarettes and 18.6% reported successful quit attempts. Self-reported success rates of quit attempts increased by 0.98% for every 1% increase in prevalence of e-cigarette use (95% CI 0.64–1.32%;  $p < 0.001$ ). E-cigarette use during a quit attempt was associated with 0.58% increase in successful quit attempts for every 1% increase in e-cigarette use (95% CI 0.38–0.78%;  $p < 0.001$ ).

The recent cohort studies have yielded conflicting results, with some demonstrating no differential impact on smoking cessation rates, while others have demonstrated efficacy. The cohort studies suffer the limitations inherent in cohort studies, namely observational design without standardized interventions, self-reported outcomes, and low retention rates.

## Conclusions

When assessing the preponderance of available data regarding e-cigarettes and smoking cessation, it is evident that these devices are not clearly superior to approved nicotine replacement therapy or “usual care.” Importantly however, the current data also show that these devices are not clearly *inferior* to approved nicotine replacement therapy or “usual care.” This counterpoint highlights the need for equipoise when evaluating e-cigarettes as a potential cessation tool. Pooled data from the available studies demonstrates no increased serious adverse events related to e-cigarettes for up to two years of follow-up (13). Longer term safety is not known. Although inconclusive, the currently available data informs several realities of e-cigarettes in the cessation landscape:

- E-cigarette use is rapidly increasing and most prevalent among current smokers.
- E-cigarettes are no more or less effective than nicotine replacement therapy for cessation.
- Incorporation of e-cigarettes with varenicline and other non-nicotine pharmacotherapies warrants further investigation.
- Reduction of combustible cigarette use is seen with regular e-cigarette users.
- When compared to combustible cigarettes, e-cigarettes have less acute toxic effects.
- Long term effects of e-cigarettes remain unknown.

Interpretations of the currently available data regarding e-cigarettes for cessation differ widely by medical and regulatory bodies (23–27). The Public Health England (PHE) has issued a statement encouraging the use of e-cigarettes for smokers who could not, or would not, quit smoking tobacco (28, 29). PHE supported the reduced harm approach by providing an estimate of e-cigarettes being 95% safer than cigarette smoking (28). Additionally, Action on Smoking Health, UK's public health charity which focuses on eliminating the harm caused by tobacco, has denounced the notion that e-cigarettes act as a gateway drug to cigarette use (29). This is in contrast to the recommendations from US regulatory bodies including the US Preventive Services Task Force and Centers for Disease Control and Prevention (CDC), recommending against the use of e-cigarettes for cessation given insufficient data (24, 30). These discrepant messages, derived from assessment of the same body of data, only contribute to the confusion for clinicians, smokers, and e-cigarette users. It is possible that these differing regional guidelines will provide a natural experiment at the global level regarding the impact of e-cigarettes on cessation, as is currently being observed with the recent UK publications (20, 21).

In summary, regarding e-cigarettes for smoking cessation, are we there yet? The simple answer is no. However, researchers, policy makers and e-cigarette users must re-assess what level of evidence will get us there. Definitive RCTs will continue to be difficult to design, will require replication and may never give a conclusive answer to individuals without equipoise on this issue. Cohort studies, while convenient, will also lack definitive findings. Long term studies, required to understand harms of e-cigarettes, will not be forthcoming in the near future. Meanwhile, e-cigarette use by tobacco smokers as a cessation tool is likely to continue to increase. As shared decision making is becoming the new standard of care for medical treatments, it is imperative to engage e-cigarette users in the scientific process. Researchers should engage e-cigarette users to ensure appropriate study designs which replicate real-world use, perhaps abandoning rigid RCTs for rigorous population-level cohort studies. Clinicians' discussions with users should include clear explanations of the certainties and uncertainties surrounding e-cigarettes. It is our practice to recommend approved cessation therapies (e.g., nicotine replacement therapy, varenicline) for individuals inquiring about e-cigarettes. Only if patients have failed these therapies, or are unwilling to try them, do we then discuss e-cigarettes as a bridge to complete cessation. Policy makers should embrace equipoise when interpreting the potential benefits and harms of e-cigarettes. As the scientific knowledge about e-cigarettes and cessation accumulates, all stakeholders should balance the uncertainty of unknown harms of e-cigarettes with the known harms of continued combustible cigarette use.

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## Abbreviations

<b>CDC</b>	Centers for Disease Control and Prevention
<b>CI</b>	Confidence interval
<b>E-cigarette</b>	Electronic cigarette
<b>OR</b>	Odds ratio
<b>RCT</b>	Randomized-controlled trial

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**KEY POINTS**

- Randomized controlled trials have not demonstrated that e-cigarettes are an effective cessation tool
- Cohort studies have yielded conflicting results, with some demonstrating that e-cigarette use is associated with enhanced cessation
- Reduction in daily combustible cigarette use is seen with e-cigarette use, but does not relate to increased cessation
- Researchers, users and policy makers should maintain equipoise when assessing the efficacy of e-cigarettes for cessation given conflicting data

Table 1

Randomized Controlled Trials for E-cigarette use

Author, Publication Date, Country	Study Population	Sample Size	Intervention/Comparison	Trial Length (weeks)	Cessation Outcomes Measured	Cessation Prevalence
Bullen <sup>11</sup> Sept 2013 New Zealand	Smokers wanting to quit	657	16 mg E-cig Placebo E-cig 21 mg Patch	24	Biologically verified cessation	16 mg E-cig: 7.3% Placebo E-cig: 4.1% 21 mg Patch: 5.8%
Caponnetto <sup>10</sup> June 2013 Italy	Smokers not wanting to quit	300	7.2 mg E-cig 7.2 to 5.4 mg E-cig Placebo E-cig	52	Self-reported cessation	7.2 mg E-cig: 11% 7.2 to 5.4 mg E-cig: 13% Placebo E-cig: 4%
Adriaens <sup>12</sup> Oct 2014 Belgium	Smokers not wanting to quit	48	18 mg E-cig Combustible cigarette	32	Biologically verified cessation	18 mg E-cig: 19% Combustible cigarette: 25%
Tseng <sup>9</sup> Feb 2016 United States	Smokers wanting to reduce daily cigarettes	99	4.5% E-cig Placebo E-Cig	3	Biologically verified cessation	4.5% E-cig: 0% Placebo E Cig: 0%