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Heather L. Walsh

*James Madison University*

Audrey L. McMurray

*James Madison University*

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# **Are Electronic Cigarettes the Solution to Smoking Cessation?**

Audrey McMurray and Heather Walsh  
James Madison University, Harrisonburg, VA

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## Clinical Scenario and Clinical Question

**Clinical Scenario:** Mr. Johnson is a 55-year-old male, presenting with a persistent dry cough for the past month. He has smoked one pack of cigarettes a day for the past 30 years, but would like to quit. He has heard from friends that electronic cigarettes work best at helping to quit smoking, and is wondering if this is true.

<b>P</b>	Population	<i>Smokers</i>
<b>I</b>	Intervention	<i>Electronic cigarettes</i>
<b>C</b>	Comparison	<i>Alternate smoking cessation therapies</i>
<b>O</b>	Outcome	<i>Smoking cessation of tobacco use</i>

**Clinical Question:** Among smokers, are electronic cigarettes more effective at leading to smoking cessation as compared to alternate smoking cessation therapies?

### Abstract

*Objectives:* Little is known regarding the effectiveness of electronic cigarettes (e-cigarettes) as therapy to aid in smoking cessation. Many hypothesize that e-cigarettes are equally as effective or more effective than alternate smoking cessation therapies. The purpose of this review was to examine the evidence on effectiveness of e-cigarettes on smoking cessation and quitting behavior as compared to other smoking cessation therapies, or no therapy at all.

*Methods:* Searches were done in PubMed utilizing the terms “electronic cigarettes” and “smoking cessation” [MeSH terms]. In PubMed, the following filters limits were used: published in the last 5 years, human species, English language, and adult (19+ years old).

*Results:* Studies by Biener and Hargraves, Brown et al, and Bullen et al, demonstrated a positive correlation of electronic cigarettes with smoking cessation. However, study by Bullen et al was not statistically significant. Study by Al-Delaimy et al revealed a negative correlation of electronic cigarette use on smoking cessation.

*Conclusion:* These studies demonstrate the inconsistencies that compose the existing research on electronic cigarettes and their role on smoking cessation. Additional research remains a vital factor in determining the effect of e-cigarettes on smoking cessation, as well as an investigation of the safety of these devices.

### Introduction

Smoking is the leading cause of preventable and premature death worldwide. Eighteen percent of adults in the United States smoke cigarettes, and nearly seventy percent of them want to stop.<sup>1</sup> Several nicotine replacement therapies have been on the market since 1984. Some examples include nicotine gum, inhalers, lozenges, nasal sprays, and patches. An alternative nicotine product that has emerged in the last two decades is electronic nicotine delivery systems (ENDS). Of these electronic systems, electronic cigarettes (e-cigarette) are the most popular.<sup>2</sup>

E-cigarettes are battery-operated devices that vaporize nicotine for inhalation. Various designs of e-cigarettes are available. First generation e-cigarettes were made to resemble conventional cigarettes or cigars. The newer generation e-cigarettes are now available in the form of pens, USB (Universal Serial Bus) sticks, or other everyday items. The three main components to an e-cigarette include a cartridge, an atomizer, and a battery. A liquid mixture is stored in the cartridge and comes in various flavors with varying concentrations of nicotine.<sup>2</sup>

Up to 50% of e-cigarettes sales and advertising is conducted online. They are marketed as healthier, more cost-effective, and a more socially acceptable alternative to conventional cigarettes.

Additionally, they are marketed as an effective smoking cessation tool, despite the fact that adequate studies have not been performed to determine the efficacy of e-cigarettes in smoking cessation.<sup>2</sup>

Currently, e-cigarettes lack FDA approval except for those that have been marketed as therapeutic.<sup>3</sup> In 2010, a federal court case, Sottera v. FDA, ruled that the FDA needed to extend its regulations over tobacco products not marketed as therapeutic.<sup>3</sup> As a result, in 2014, the U.S. Food and Drug Administration proposed a “deeming rule,” which would extend its regulatory authority to cover additional products that meet the definition of a tobacco product under the proposed rule: “Tobacco Products Deemed To Be Subject to the Food, Drug & Cosmetic Act (Deeming).”<sup>4</sup> If approved, additional products to be covered would include electronic cigarettes, cigars, pipe tobacco and hookah tobacco among others.<sup>5</sup> Once the proposed rule is approved and final, these additional products would be subject to various federal regulations such as: prohibition on sales to minors, prohibition on free sampling, warning label requirements, and the requirement that tobacco manufacturers register with the FDA and seek the agency’s review of new tobacco products.<sup>5</sup> Of significant note, the FDA would also be able to conduct rigorous scientific review of these new tobacco products to determine their safety and efficacy, as well as their role in tobacco-related disease and death.<sup>4</sup> However, until such time as the rule is adopted, the FDA’s Center for Tobacco Products does not have authority to regulate the sale or use of e-cigarettes as tobacco products, unless marketed for therapeutic purposes.

Since the introduction of e-cigarettes to the U.S. marketplace in 2007, they have sparked significant controversy. Numerous concerns surround the use of e-cigarettes: that e-cigarettes will lead to the renormalization of smoking, promote experimentation among young people, induce harms via secondhand exposure,<sup>6</sup> and encourage dual-use—using e-cigarettes as a supplement rather than a substitute—to be used in environments where conventional cigarettes are prohibited, thereby increasing exposure to toxins and worsening morbidity and mortality rates.<sup>7</sup> Much remains unanswered, but each study serves as a stepping stone to further understanding.

Our purpose for this review is to assess the available evidence on e-cigarettes and their role in smoking cessation so as to better inform the Harrisonburg, Virginia community. In particular, we hope to address the question of many: Are e-cigarettes beneficial to smoking cessation?

## Methods

An initial search using PubMed database was performed in October 2015 using the search terms “electronic cigarettes” AND “smoking cessation” [MeSH terms]. MeSH, or Medical Subject Headings, provides a convenient way to retrieve information when different terms are used for the same meaning. For example, by using “smoking cessation” [MeSH terms], entry terms also included “cessation, smoking,” “cessations, smoking,” and “smoking cessations.” The first search using PubMed database gave 228 results. No duplicates were found. The following filters to narrow the search were then applied: published in the last 5 years, human species, English language, and adult (19+ years old). Once these filters were applied, 69 articles remained. Among quality inspection of the remaining articles revealed studies that were excluded for various reasons. Some studies included pregnant women, subjects with schizophrenia, or other medical conditions that were excluded to better apply it to the general population. Many studies were also systematic reviews that did not show original research. Other studies were excluded due to small sample size. Since electronic cigarettes are fairly new, many studies focused more on the behaviors of smoking electronic cigarettes (e-cigarettes), or the types of individuals e-cigarettes attract most, and not so much on its correlation to smoking cessation. The final four articles were chosen based on the previous criteria and which ones more closely answered the clinical question. See PRISMA flow chart below at figure 1 for the search process in chart form.

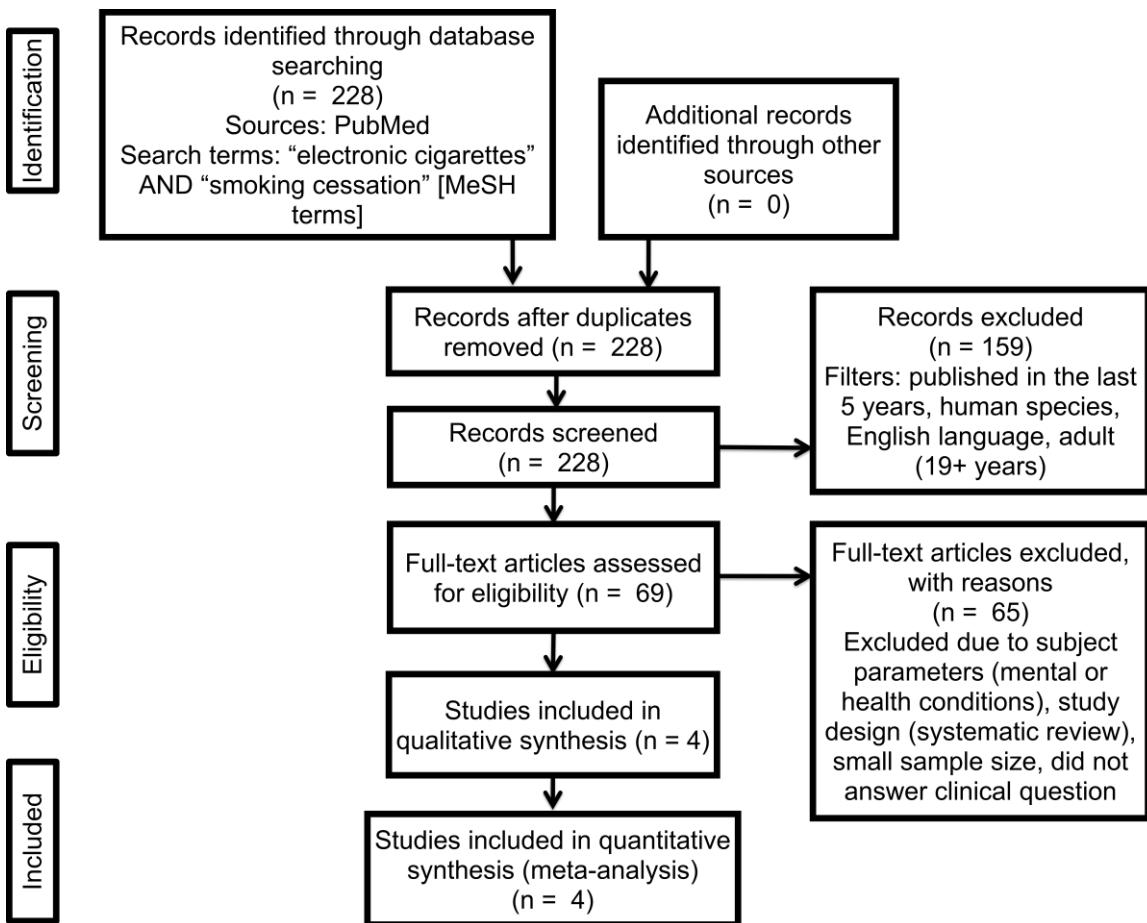


Figure 1. PRISMA flow chart displaying the search terms and inclusion and exclusion criteria used to find final studies for review.

All articles in this critique used odds ratios for statistical analysis, except for Bullen et al. Bullen et al. used the intention-to-treat approach as the primary analysis. Bullen et all. also calculated quit rates, relative risks, and absolute risks for nicotine e-cigarettes versus placebo e-cigarettes. This article then compared treatment groups using  $\chi^2$  tests, with multivariate regression adjusting for other variables. It also addressed per-protocol analysis for the primary outcome of continuous smoking abstinence, in which participants with major protocol violations were excluded, such as withdrawals, failure to follow up, and cross-over treatments. Biener and Hargraves used bivariate tests and logistic regression models to account for gender, age, race/ethnicity, education level, and baseline smoking level. The primary analyses used in article by Al-Delaimy et al. were longitudinal models to predict the outcomes measured at follow up, and multi-variable logistic regression analyses. Brown et al. used  $\chi^2$  tests and one-way analyses of variance (ANOVA)s to assess between different variables, and analysis of covariance (ANCOVA) to test for bias. Results were further investigated using post-hoc Sidak-adjusted  $\chi^2$  tests and t-tests. Logistic regression model was also used in this article. These statistical analyses are discussed in greater detail in the results sections below. All articles in this critique used a 95% confidence interval and a p-value of 0.05.

## Results

## **Study #1**

*E-cigarette use in the past and quitting behavior in the future: a population-based study. Al-Delaimy et al.<sup>8</sup>*

**Objective:** Whether smokers who used e-cigarettes were more likely to quit smoking after 1 year compared to smokers who had never used e-cigarettes.

**Study design:** This study retrieved data from a longitudinal survey called the California Smokers Cohort (CSC). The CSC is designed to investigate different factors that predict smoking cessation behaviors among smokers, both current and former, in California.<sup>8</sup> The study was comprised of data collected from both a baseline survey and a follow-up survey to determine changes in smoking behavior. The smoking behaviors measured included: reduced consumption, quit attempts, and duration of abstinence. The baseline surveys were conducted from July 26, 2011 to April 29, 2012, and the follow-up surveys were conducted from November 6, 2012 to January 16, 2013. Included in the surveys were 1,000 participants, who were residents of California, aged 18-59 years old, and who had smoked at least 100 cigarettes during their lifetime at baseline.

Participants were asked specific questions in order to differentiate factors involving history of tobacco and e-cigarette use. Current smokers included those who smoked cigarettes on at least some days at the time of the survey. Smoking status was categorized according to smoking frequency reported: either every day (daily) or some days (nondaily).<sup>8</sup> Participants were asked if they had heard of e-cigarettes, and were provided with a description of e-cigarettes.<sup>8</sup> If they answered yes, they were categorized by their use of e-cigarettes: have used e-cigarettes, might use e-cigarettes, or will never use e-cigarettes. Nicotine dependence was determined by asking smokers how soon after they woke up did they smoke their first cigarette: smoked within 30 minutes of awaking, or waited 30 minutes or more after waking up.<sup>8</sup> To determine intention to quit, smokers were asked to pick one of four options: never expect to quit, might quit in the future but not in the next 6 months, will quit in the next 6 months, or will quit in the next month.<sup>8</sup> Responders in the first two groups were combined into one category of “no current intention to quit,” and responders in the last two groups were combined into one category of “intending to quit in the next 6 months.” The reason for combining these groups was to increase the stability of the regression model. Sociodemographic characteristics that were included in the model included gender, age, years of education, and ethnicity.<sup>8</sup>

The three outcomes measured included quit attempts, reduction in the numbers of cigarettes smoked, and current abstinence from cigarette use. Self-reported quit attempts were assessed by asking the participants at follow up “during the past 12 months, have you quit smoking intentionally for one day or longer?”<sup>8</sup> Reduction in the number of cigarettes was reported if a smoker’s monthly number of cigarettes was reduced by 20% or more at follow up compared to at baseline.<sup>8</sup> Participants were considered currently abstinent if they reported a duration of abstinence for 1 month or longer.

Adjusted odds ratios were calculated and logistic regression analyses of each of the three different outcomes were performed. Odds ratio represents the odds of an outcome occurring given an exposure to something. For example, the odds of quitting smoking when exposed to e-cigarettes. Logistic regression is a method for analyzing data that has one or more independent variable that determines an outcome that is dichotomous (ex: yes/no). The main predictor, or independent variable was the use of e-cigarettes, which was determined by the respondents who answered to “will never use e-cigarettes” and “have used e-cigarettes.” Those who reported that they “might use e-cigarettes” were excluded from the analyses since they may overlap with both groups. The outcomes measured that participants responded yes or no to are shown below in the study results.

**Study results:** Table 1 demonstrates the significant demographic differences among e-cigarette users by displaying the odds ratios. Female smokers were more likely than males to report ever using e-cigarettes.<sup>8</sup> Non-Hispanic whites were more likely than other ethnic groups to ever report using e-cigarettes.<sup>8</sup> Daily smokers were more likely than nondaily smokers to every use e-cigarettes. Other variables were not significantly associated with e-cigarette use.

Demographic	Odds ratio	Confidence interval (95%)
Female smokers	1.66	1.18 - 2.35
Non-Hispanic whites	2.8	1.3 - 6.05
Daily smokers	2.01	1.26 - 3.22

Table 1. Demographics most likely to use e-cigarettes.

Figure 2 represents the frequency of the 3 outcomes divided into the two categories “ever used e-cigarettes” and “will never use e-cigarettes.” There was a positive association between using e-cigarettes and making a quit attempt at follow-up, but this did not prove statistically significant.<sup>8</sup> Use of e-cigarettes, compared to never using e-cigarettes, was associated with a statistically significant lower likelihood of decreasing cigarette consumption by 20% or more during the 1-year period.<sup>8</sup> Smokers ever using e-cigarettes were significantly less likely to be abstinent at follow-up compared to smokers reporting never using e-cigarettes.<sup>8</sup> These conclusions are validated by the odds ratios shown in Table 2.

In this study, e-cigarette use was significantly associated with a failure in smoking cessation and being less likely to reduce their cigarette consumption. Even though e-cigarette users were more likely to attempt quitting, this was not statistically significant.

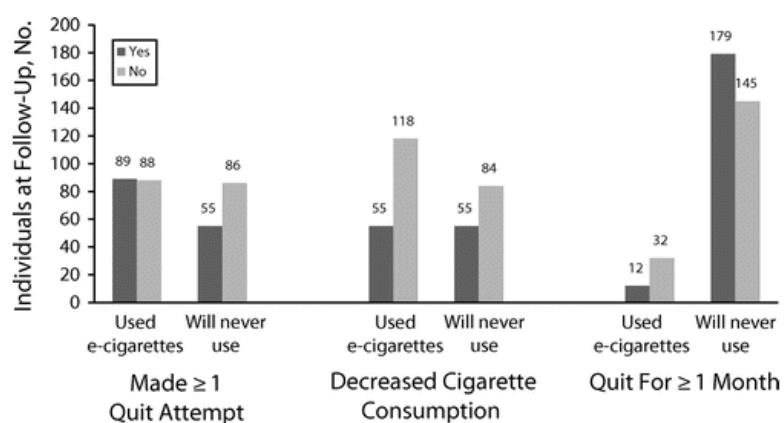


Figure 2. Cigarette quit attempts, decreased cigarette consumption, and abstinence for 1 month or more at follow-up, by use of e-cigarettes.

Outcome measured	Odds ratio	Confidence interval (95%)
Quit attempt	1.15	0.67 - 1.97
Decreased cigarette consumption	0.51	0.30 - 0.87
Abstinence (quit for ≥ 1 month)	0.41	0.186 - 0.93

Table 2. Odds ratios and confidence intervals of the three outcomes measured.

**Study critique:** This study had many advantages and disadvantages. One positive thing this study did was that it avoided some selection and recall biases of cross-sectional studies since it was prospective. Smokers were interviewed at baseline, followed for 1 year, and then re-interviewed

with the same questions regarding their smoking behavior.<sup>8</sup> The study also attempted to increase validity by assessing consistency of e-cigarette use across both baseline and follow-up time points and by excluding inconsistent reports that could cause overlap between categories.<sup>8</sup> Even though clinical trials and experimental studies are generally more favorable for measuring efficiency and efficacy of cessation therapy, they rarely reflect true behavior and cessation in the general population, which is what this study attempted to do.<sup>8</sup> This study also adjusted well for any major confounding variables. Other advantages to this study were that it took place in the United States and used a fairly large sample size.

A limitation to this study was that it did not address any exclusion criteria, so it is much more difficult to know whether or not their population relates to the population of smokers in Harrisonburg, Virginia. Also, smokers were not asked if they tried using e-cigarettes in their last successful quit attempt, which may have skewed the data.<sup>8</sup> In 2010, when the survey questions were developed, e-cigarettes were still limited in use and were not yet known to be associated with quitting, which may have also affected the results of the survey.<sup>8</sup> Another disadvantage to this study was that it only compared e-cigarettes with no e-cigarettes, but did not compare any other forms of smoking cessation interventions, such as nicotine replacement therapies like nicotine patches or gum. Lastly, this study was a survey, and follow up was 1 year after baseline, which could allow for significant recall bias of reported data. With a whole year in between surveys, participants may have trouble recalling important information. It is also possible that with self-reported data, participants may respond in a way to make them look as good as possible, and may under-report their smoking habits since it may be deemed inappropriate. They may be unwilling to respond accurately for various reasons.

## **Study #2**

*A Longitudinal Study of Electronic Cigarette Use Among a Population-Based Sample of Adult Smokes: Association With Smoking Cessation and Motivation to Quit. Biener and Hargraves<sup>7</sup>*

**Objective:** The purpose of this study was to determine whether e-cigarette use increases smoking cessation and/or if e-cigarettes have a negative effect on quitting smoking and motivation to quit.

**Study Design:** The sample for this study consisted of a subset of respondents to a survey given to 5,000 individuals living in the Dallas/Fort Worth, Texas and Indianapolis, Indiana metropolitan areas in 2011 and 2012. The original survey investigated individual's receptivity to snus, a form of smokeless moist powder tobacco, which had been readily available in those two areas for some time. Of the 5,155 respondents to that original study, 1,374 individuals gave permission to be re-contacted, forming the sample population for this study. Follow up surveys were conducted between January and March of 2014, totaling three years to be addressed by researchers.

At baseline, the time of the original survey, all respondents reported being cigarette smokers. Smoking status was then assessed at follow-up with the question, "Do you now smoke cigarettes every day, some days or not at all?" If the response was "not at all," the subsequent question was asked: "About how long has it been since you last smoked cigarettes on a regular basis?" The researchers defined smoking cessation as at least one month of abstinence from cigarettes.<sup>7</sup>

Motivation to quit smoking was also assessed. At baseline, participants were scored on a 3-point scale as to their readiness to quit. If still smoking at follow-up, participants were scored again, but as to their degree of intention to quit. If a participant intended to quit within 30 days, he/she received a score of 3. Within 6 months, a 2; and if not within 6 months, then a score of 1.

To address e-cigarette usage, respondents were asked at baseline if they had "ever heard of electronic cigarettes, also known as e-cigarettes?" If the answer was yes, they were then asked whether or not they had used e-cigarettes even once, and if so, how many times within the last 30

days. To assess the degree of e-cigarette usage, additional questions were asked at follow-up. Those who had not heard of electronic cigarettes at baseline, were asked again at follow-up whether or not they had heard of e-cigarettes. For all respondents who had reported ever trying e-cigarettes by follow-up were asked how often they currently used e-cigarettes: everyday, some days, or not at all. From this information, the respondents were then grouped into three different levels of usage intensity. "Intensive use" was defined as daily use for at least one month. "Intermittent" was defined as using once or twice but not daily for a month or more and then the last category was "Non-use/trial" (no more than two times).<sup>7</sup>

Demographic covariates included age, gender, education level, and ethnicity. Cross tabulations were run on these demographics to determine their relationship to smoking intensity and smoking cessation. Logistic regression analyses were done to control for demographics and level of smoking at baseline to determine how e-cigarette intensity predicted smoking cessation.<sup>7</sup>

Lastly, respondents were questioned about their reasons for both starting and stopping use of e-cigarettes. This information reveals potential adjustments that can be made for future e-cigarette designs so as to accommodate consumer preferences and provides basis for future studies to ensure that users are trying e-cigarettes under accurate pretenses.

**Study Results:** Of the 1,374 participants, interviews were conducted with 695 of them yielding a retention rate of 50.6%. At baseline, awareness of e-cigarettes was high (89.4%), and was universal (100%) at follow-up. Trials of e-cigarettes also greatly increased from 22.3% at baseline to 70.4% at follow-up. At follow-up, 23% of those interviewed were categorized as intensive users of e-cigarettes, 29% as intermittent, 18% had used once or twice, and the remaining 30% had still not tried e-cigarettes even once. Through bivariate analyses, (a method used to simultaneously analyze the association between two different variables), it was shown that intensive users were more likely to be heavy smokers and to be minorities.<sup>7</sup> Table 3 demonstrates how certain demographics correlated to e-cigarette use.

		Non-use/trial (n = 364) % (CI)	Intermittent use (n = 220) % (CI)	Intensive use (n = 111) % (CI)	Total (N = 695) % (CI)	p
Gender						
Male	398	45.8 (30.1, 62.3)	47.6 (21.3, 75.4)	84.1 (59.9, 94.9)	55.2 (40.3, 69.2)	.06
Female	297	54.2 (37.7, 69.9)	52.4 (24.6, 78.7)	15.9 (5.1, 40.1)	44.8 (30.8, 59.7)	
Age group (y) at baseline						
18–30	90	12.3 (5.0, 27.1)	8.6 (3.1, 21.8)	30.9 (8.6, 68.1)	15.5 (7.6, 29.1)	.42
31–49	197	50.9 (34.3, 67.3)	47.6 (20.0, 76.7)	48.6 (20.2, 77.9)	49.4 (35.3, 63.5)	
50–65	408	36.8 (23.1, 53.0)	43.8 (19.6, 71.4)	20.5 (7.1, 46.5)	35.1 (24.2, 47.7)	
Education at baseline						
< BA	529	67.5 (51.1, 80.6)	45.7 (20.7, 73.2)	72.8 (45.1, 89.7)	62.5 (47.4, 75.5)	.27
≥ BA	165	32.5 (19.4, 48.9)	54.3 (26.8, 79.3)	27.2 (10.3, 54.9)	37.5 (24.5, 52.6)	
Race/ethnicity						
Minority	121	19.6 (10.6, 33.5)	16.5 (6.0, 38.0)	53.8 (25.2, 80.1)	26.6 (15.5, 41.8)	.02
White/non-Hispanic	572	80.4 (66.5, 89.4)	83.5 (62.0, 94.0)	46.2 (19.9, 74.8)	73.4 (58.2, 84.5)	
Heavy smoker, baseline						
Yes	240	20.6 (11.4, 34.4)	28 (11.3, 54.2)	68.2 (40.3, 87.2)	33.9 (21.6, 48.7)	.01
No	448	79.4 (65.6, 88.6)	72 (45.8, 88.7)	31.8 (12.8, 59.7)	66.1 (51.3, 78.4)	
Smoking cessation						
Quitter	130	12.4 (5.1, 26.9)	8.5 (2.4, 25.9)	20.4 (7.3, 45.5)	13.1 (7.3, 22.3)	.5

<sup>a</sup>Non-use/trial = never used or used one or two times; intermittent use = used more than twice but not daily for 1+ months; intensive use = used daily for 1+ months.

<sup>b</sup>Ns are unweighted; percentages are weighted. CI = 95% confidence interval.

<sup>c</sup>Includes only those continuing to smoke.

Table 3: Relationship of sample demographics to degree of e-cigarette usage.

Of the 695 respondents interviewed, 13.1% reported being abstinent from cigarette smoking for at least one month at follow-up. Intensive users made up the greatest part of that 13.1% with 20.4% of them reporting abstinence. Of intermittent users, 8.5% reported abstinence, and 12.4% of the non-users/triers reported abstinence. Through bivariate testing, these differences were not shown to be significant. Logistic regression models (data analysis with one or more independent variables with only two possible outcomes), however, demonstrate that intensive users of e-cigarettes were 6 times more likely to be abstinent at one month than those who had used only one or two times, or not at all.<sup>7</sup>

In the assessment of motivation to quit smoking, it was found that intermittent users were nearly 6 times as likely to expect that they would still be smoking at one year compared to non-users/triers (OR: 6.04; 95% CI = 1.49, 24.38).<sup>7</sup> Intensive users, however, showed no difference to the non-users/triers in their expectations for likelihood of smoking at one year.

Additional information at follow-up was obtained pertaining to respondents' reasons for starting and stopping e-cigarettes, if applicable. Table 4 shows the results of those survey questions.

	Triers <sup>a</sup> (n = 163) % (CI) <sup>b</sup>	Intermittent use (n = 219) % (CI)	Intensive use (n = 111) % (CI)	Total (N = 493) % (CI)	p
<b>Most important reason for starting e-cigarette use</b>					
Use where smoking is not allowed	5.0 (1.9, 12.7)	8.6 (2.5, 25.9)	2.4 (0.5, 10.1)	5.6 (2.5, 12.2)	.33
To avoid exposing others to tobacco smoke	12.0 (3.3, 35.1)	28.1 (5.0, 74.2)	4.4 (0.6, 25.2)	16.1 (4.2, 45.7)	.21
To cut down on smoking	0.6 (0.2, 1.3)	5.8 (1.5, 19.8)	5.9 (1.2, 23.5)	4.5 (1.7, 10.9)	.33
To quit smoking	46.5 (25.0, 69.4)	46.0 (20.4, 73.8)	65.9 (38.8, 85.5)	52.6 (35.1, 69.6)	.49
Health	8.1 (2.1, 26.4)	1.8 (0.4, 6.8)	15.8 (4.8, 41.1)	8.0 (3.5, 17.3)	.08
	Triers <sup>a</sup> (n = 138) % (CI)	Intermittent use (n = 73) % (CI)	Intensive use (n = 16) % (CI)	Total (N = 227) % (CI)	p
<b>Very important reasons for stopping e-cigarette use<sup>c</sup></b>					
Taste	35.0 (16.7, 59.1)	8.1 (2.4, 24.5)	0.3 (0, 2.7)	23.9 (12.1, 41.9)	.01
Did not feel like tobacco cigarettes	28.2 (12.7, 51.5)	52.8 (22.2, 81.5)	21.1 (2.2, 76.1)	36.3 (20.9, 55)	.30
Bad for health	29.3 (12.3, 55.2)	16.7 (4.0, 49.1)	1.3 (0.2, 9.4)	23.5 (11.3, 42.7)	.32
Did not like look/feel	17.5 (4.7, 47.9)	0.0 (0, 0.2)	0.5 (0, 5.6)	10.6 (2.8, 33.1)	.00
Did not give enough vapor	6.2 (2.4, 15.1)	23.2 (5.9, 59.2)	0.7 (0.1, 4.5)	11.8 (4.5, 27.5)	.07
Too expensive	33.9 (14.9, 60.1)	5.9 (0.9, 31.0)	0.2 (0, 2.4)	22.5 (10.2, 42.6)	.02
Did not work well	22.3 (8.7, 46.1)	12.3 (2.2, 47.3)	18.6 (1.7, 74.8)	18.7 (8.4, 36.3)	.71

CI = confidence interval.

<sup>a</sup>Triers = used one or two times; intermittent use = used more than twice but not daily for 1+ months; intensive use = used daily for 1+ months.

<sup>b</sup>Ns are unweighted, percentages are weighted. CI = 95% confidence interval.

<sup>c</sup>Questions asked only of former e-cigarette users who were smoking at follow-up.

**Table 4:** Reasons for stopping and starting e-cigarettes.

The information provided in Table 4 is more relevant for design adjustments in future e-cigarettes as well as user beliefs that need to be verified through further research.

**Study Critique:** There are several limitations to this study. Most obvious, is that this study is observational. Observational studies lack randomization and risk influence by known or unknown confounding variables. Next, is that the survey format spanned three years of respondents' lives, allowing potential and significant recall bias. Another limitation is the 50% retention rate, which suggests unknown bias.<sup>7</sup> Also, the parameter for "intermittent use" is poorly defined. It includes those who have used e-cigarettes for less than one month, but also those who have used e-

cigarettes for more than six months—just not daily for one full month (intensive user definition). This extensive definition may not produce true findings due to the variability in users within the same category. Another limitation is that intensities of e-cigarettes used were not reported. Without consistency in nicotine concentration across e-cigarettes used, it is impossible to draw direct conclusions about e-cigarette use and cessation. The concentration of nicotine may have been more influential in leading to abstinence and reduction of withdrawal symptoms than diligent use of the product. Another limitation is that this study's sample came from two metropolitan areas. This restricts generalizability to the nation as a whole and to rural areas, such as Harrisonburg. Finally, this study did not biochemically verify reports of abstinence. Biochemical verification could have been accomplished by exhaled breath carbon monoxide measurements. This would be difficult to do in a large population study, however, it allows for falsification of information.

Although there are several limitations, there are also strengths to this study that deserve mentioning. While an observational study, it does accurately illustrate how e-cigarettes are being used and under what pretenses. This is valuable information as e-cigarettes are still considered a somewhat novel product. Another significant advantage to this study is that it was performed in the U.S. which allows for more accurate comparisons to our community. Another strength is that the observations covered three years during a time that awareness of e-cigarettes was high. Lastly, this study used one month point prevalence abstinence—a high standard at which to measure cessation.<sup>7</sup>

### **Study #3**

*Electronic cigarettes for smoking cessation: a randomized controlled trial. Bullen et al.<sup>9</sup>*

**Objective:** To assess whether nicotine-containing e-cigarettes are more effective at leading to smoking cessation than nicotine patches. Non-nicotine placebo e-cigarettes were included to perform a blind comparison of e-cigarettes.

**Study design:** This study was a randomized controlled trial performed in Auckland, New Zealand. The first randomization occurred on September 6, 2011, and the last follow-up was on July 5, 2013.<sup>9</sup> Inclusion criteria included: age 18 or older, had smoked at least ten cigarettes a day for the past year, and wanted to stop smoking. Exclusion criteria were pregnant and breastfeeding women, those using cessation therapies or a cessation program, cardiovascular events within the previous 2 weeks, and those with significant comorbidities. Participants were recruited via community newspapers, underwent a prescreening for inclusion/exclusion criteria, and were then mailed study information and consent forms. The study was approved by the Northern X Regional Ethics Committee and the Standing Committee on Therapeutic Trials approved the use of e-cigarettes, because sales of e-cigarettes are not permitted in New Zealand.<sup>9</sup>

Participants' degree of nicotine dependence was determined by the Fagerström test for nicotine dependence (FTND). A score of 1 to 4 indicates a low to moderate dependence, whereas a score of 5 to 8 or more indicates moderate to high nicotine dependence.<sup>10</sup>

PLEASE TICK (✓) ONE BOX FOR EACH QUESTION		
How soon after waking do you smoke your first cigarette?	Within 5 minutes 5-30 minutes 31-60 minutes	<input type="checkbox"/> 3 <input type="checkbox"/> 2 <input type="checkbox"/> 1
Do you find it difficult to refrain from smoking in places where it is forbidden? e.g. Church, Library, etc.	Yes No	<input type="checkbox"/> 1 <input type="checkbox"/> 0
Which cigarette would you hate to give up?	The first in the morning Any other	<input type="checkbox"/> 1 <input type="checkbox"/> 0
How many cigarettes a day do you smoke?	10 or less 11 - 20 21 - 30 31 or more	<input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3
Do you smoke more frequently in the morning?	Yes No	<input type="checkbox"/> 1 <input type="checkbox"/> 0
Do you smoke even if you are sick in bed most of the day?	Yes No	<input type="checkbox"/> 1 <input type="checkbox"/> 0
<b>Total Score</b>		
<b>SCORE</b>	1- 2 = low dependence 3-4 = low to mod dependence	5 - 7= moderate dependence 8 + = high dependence

*Figure 3: Fagerström Test for Nicotine Dependence.*

Six-hundred fifty-seven individuals met criteria and were randomized by computerized block randomization in a 4:4:1 ratio to nicotine e-cigarettes, nicotine patches, or placebo e-cigarettes. Nicotine patches were chosen as the alternative therapy because they are the most popular NRT product in New Zealand and because they have few known adverse effects.<sup>9</sup> Stratifications by ethnicity (Māori; Pacific; or non-Māori, non-Pacific), sex (male or female), and level of nicotine dependence ( $>5$  or  $\leq 5$  FTND) were also done. Participants to use e-cigarettes were masked as to whether or not they received the nicotine containing e-cigarettes or the placebo version. After randomization, further baseline information was obtained including education status, smoking and quitting history, quitting self-efficacy, medication, withdrawal symptoms and stage of addiction, and behavioral dependence.<sup>9</sup>

At baseline, an analysis of the e-cigarettes to be used in the study was performed. E-cigarettes with nicotine contained 10-16 mg nicotine per mL, and the placebo e-cigarettes contained no nicotine. Mid-way through the study, an analysis of the vapor was also performed. This analysis showed that 300 puffs from one nicotine e-cigarette delivered 3-6 mg nicotine, which is equivalent to smoking between one and five tobacco cigarettes.<sup>9</sup>

Participants allocated to the patch group were sent exchange cards in the mail redeemable for patches from community pharmacies.<sup>9</sup> Instructions were included to use the patch daily, starting 1 week before until 12 weeks after their chosen quit day. Vouchers were also supplied to patch group participants to cover dispensing costs.<sup>9</sup>

Participants in both e-cigarette groups were given an e-cigarette, spare battery and charger, and cartridges (with the nicotine content masked). These participants were likewise instructed on proper use of the device and informed to begin use 1 week before until 12 weeks after their chosen quit day.

Participants of all three groups were referred to Quitline—a telephone hotline to help smokers quit. At baseline, members of Quitline contacted participants to offer telephone-based behavioral support.<sup>9</sup> Quitline helped researchers to monitor usage by providing reports from information obtained by callers who accepted support at baseline. Participants who declined assistance from Quitline were still able to access support from a text message service, Txt2Quit.

The primary outcome to be measured was continuous smoking abstinence. The study's definition of abstinence allowed for use of  $\leq 5$  cigarettes. Abstinence was self-reported at 6 months after quit date and biochemically verified by testing for carbon monoxide concentrations in exhaled air (< 10 ppm).<sup>9</sup> Participants were reimbursed for transportation costs to facilities where testing took place.

Several secondary outcomes were assessed at 1, 3, and 6 months post quit day. These included: continuous abstinence, proportion of 7 day point prevalence abstinence (not a single puff from a tobacco cigarette in the past 7 days), number of tobacco cigarettes smoked per day, proportion of participants reducing tobacco smoking, time to relapse to tobacco smoking, number of patches or cartridges used, use of other cessation treatments, withdrawal symptoms, stage of addiction, smoking latency, and adverse events.<sup>9</sup>

The sample size of 657 participants translated 80% power, with a two-sided  $p = 0.05$  (tests statistical significance in both directions of the probability distribution—whether test statistic is in the top 2.5% or in the bottom 2.5%, given a  $p = 0.05$ ). These values conveyed a 10% absolute difference in quit rates between the e-cigarette group and the patch group (Table 5), and a 15% difference between the nicotine e-cigarette group and the placebo e-cigarette group (Table 6).<sup>9</sup> The primary outcome was analyzed via an intention-to-treat approach (participants lost to follow-up or with an unknown smoking status were assumed to be smoking). Quit rates, relative risks, and absolute risks were calculated for nicotine e-cigarettes versus patches, and for the two e-cigarette

groups. Treatment groups were then compared using  $\chi^2$  tests. A  $\chi^2$  test is used to determine heterogeneity/homogeneity are present among study groups. A per-protocol analysis was also performed for the primary outcome (participants with major protocol violations were excluded). Tests for heterogeneity were also conducted on certain subgroups (ethnicity and sex) to assess for consistency of effects. And lastly, Kaplan-Meier curves were used to analyze time to relapse.<sup>9</sup> A Kaplan-Meier curve in this case, maps out participants and their point to relapse, onto time. This provides an idea of how long others may relapse with the given treatment.

	Nicotine e-cigarettes (n=289)	Patches (n=295)	Difference $\chi^2$ p value	Relative risk (95% CI)
<b>Continuous abstinence</b>				
1 month	23.2%	15.9%	0.03	1.46 (1.04 to 2.04)
3 months	13.1%	9.2%	0.12	1.44 (0.90 to 2.33)
6 months (primary outcome)	7.3%	5.8%	0.46	1.26 (0.68 to 2.34)

Table 5: Continuous smoking abstinence; e-cigarettes versus patches.

	Nicotine e-cigarettes (n=289)	Placebo e-cigarettes (n=73)	Difference Fischer's exact p value	Relative risk (95% CI)
<b>Continuous abstinence</b>				
1 month	23.2%	16.4%	0.21	1.41 (0.81 to 2.46)
3 months	13.1%	6.8%	0.14	1.92 (0.78 to 4.70)
6 months (primary outcome)	7.3%	4.1%	0.44	1.77 (0.54 to 5.77)

Table 6: Continuous smoking abstinence; nicotine e-cigarettes versus placebo e-cigarettes.

**Results:** Overall loss to follow-up was 22%: 17% in the nicotine e-cigarette group, 27% in the patches group, and 22% in the placebo e-cigarette group. Verified continuous abstinence at 6 months post quit day was highest in the nicotine e-cigarette group (7.3%), followed by 5.8% in the patch group, and 4.1% in the placebo e-cigarette group.<sup>9</sup> Sample size calculated prior to the study was based on optimistic estimates of abstinence, thus a lack of statistical power forced inability to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes. However, the 13 weeks of nicotine e-cigarette use did result in increased smoking abstinence at 6 months compared with the patch or placebo e-cigarette groups.<sup>9</sup> Analyses stratified by sex and ethnicity showed no significant differences in primary outcomes suggesting similar findings would be found if applied to other ethnic groups.

Initially, quit rates for all three groups were high, but by 50 days into the study, most participants had relapsed.<sup>9</sup> Time to relapse in the nicotine e-cigarette group was more than twice as long as the time of those in the patch group (35 days vs 14 days). Cigarette consumption decreased by two more in the nicotine e-cigarette group than in the patch group. 57% of nicotine e-cigarette participants reduced their daily cigarette count by at least half at the 6 month mark, compared to 41% in the patch group.<sup>9</sup>

Significant variability in treatment adherence resulted among the three groups. At one month post quit day, 78% of nicotine e-cigarette users, 82% of placebo e-cigarette users, and only 46% of patch users were still using the allocated treatment product. At the 6 months, those numbers had dropped even more with 29% of nicotine e-cigarette users, 35% of placebo e-cigarette users and only 8% of patch users were still using the allocated treatment.<sup>9</sup>

Perceptions of e-cigarettes remained fairly consistent throughout the 6 months. At 1 month, 88% of nicotine e-cigarette users and 92% of placebo e-cigarette users stated that they would recommend the product in use to a friend attempting to quit. Only 56% of patches users stated that they would recommend their allocated product.<sup>9</sup> At 6 months, the numbers were 85%, 88% and 40%, respectively.

At 6 months, differences in results of the intention-to-treat analysis and the per-protocol analysis were minimal. Additionally, there was no significant difference in adverse events between study groups, nor was an association found between adverse events and the study product.<sup>9</sup>

**Study Critique:** The primary strength to this study is the use of rigorous measurements taken to eliminate bias including: inclusion/exclusion criteria, prescreening, randomization, stratification, and consistency across treatment groups.

This study also had several limitations. First, is the fact that it was performed in New Zealand. This presents concerns over generalizability to our community due to cultural and environmental differences. Second, is the lack of statistical power due to the sample size originally calculated. There was also significantly greater loss to follow-up and withdrawal rate in the patch group than in either of the e-cigarette groups. Perhaps some participants allocated to the patch group chose to participate in the study because they wanted to try the novel e-cigarette devices, but then lost interested when allocated to the patch group.<sup>9</sup> Another reason for this could be due to the fact that patches have been available much longer. Prior attempts or failed attempts with the patch could have de-incentivized participants from diligent use of the patch during the trial.<sup>9</sup> This study also did not give explanation as to why a 4:4:1 ratio was used to separate the different groups of participants. The much lower amount of individuals in the placebo group as compared to the nicotine e-cigarette or patches groups may have resulted in non-comparable data. Another limitation to consider is that nicotine delivery was not efficient (as was more common in the earlier e-cigarette models). Additionally, the e-cigarette cartridges used actually contained less nicotine than was labeled. It was also found that the e-cigarette users consumed on average just over one cartridge per day which correlates to a nicotine delivery of only 20% of the nicotine obtained from cigarette smoking.<sup>9</sup> Use of newer e-cigarette models with higher concentrations of nicotine should be incorporated into future studies based on the limitations shown in this study.

#### **Study #4**

*Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Brown et al.<sup>6</sup>*

**Objective:** The purpose of this study was to assess the effectiveness of e-cigarettes on smoking cessation compared with nicotine replacement therapy (NRT) bought over-the-counter (OTC) and unaided quitting in the general population of smokers who are attempting to quit.

**Study design:** This study consisted of cross-sectional household surveys of adults in England conducted monthly between July 2009 and February 2014.<sup>6</sup> The study compared the self-reported abstinence rates of smokers trying to quit who used e-cigarettes only with those who used NRT bought OTC only, or without any therapeutic aid. The surveys were designed to help provide information about smoking prevalence and behavior in England.<sup>6</sup>

Each month, a new representative sample of 1,800 adults, 16 years or older, were selected via random sampling. These representatives completed a face-to-face computer-assisted survey with a trained interviewer. The samples were nationally representative in socio-demographic aspect and proportion of smokers.<sup>6</sup>

Data was used from survey respondents who smoked either cigarettes or another tobacco product daily or occasionally at the time of the survey or during the 12 months prior to the survey.<sup>6</sup>

Included in this data were individuals who made at least one quit attempt in the preceding 12 months. The data included individuals who used either e-cigarettes or NRT bought OTC during their most recent quit attempt, and an unaided group.<sup>6</sup> The study defined “unaided” as those who had not used any of the following: e-cigarettes, NRT bought OTC, a prescription stop-smoking medication, or face-to-face behavioral support.<sup>6</sup> Exclusion criteria included: those who used e-cigarettes or NRT bought OTC together, a prescription stop-smoking medication, or face-to-face behavioral support.

Five-thousand eight-hundred sixty-three individuals that participated in this study made a quit attempt in the previous year. Four-hundred sixty-four had used e-cigarettes (7.9%), 1,922 had used NRT bought OTC (32.8%), and 3,477 had used no aid to cessation (59.3%).<sup>6</sup>

The study addressed the important confounding variable of nicotine dependency by asking two questions. First, time spent with urges to smoke was assessed by asking participants: “How much of the time have you felt the urge to smoke in the past 24 hours?” Not at all (0), a little of the time (i), some of the time (ii), a lot of the time (iii), almost all of the time (iv), all of the time (v).<sup>6</sup> Next, strength of these urges was measured by asking: “How strong have the urges to smoke been?” Slight (i), moderate (ii), strong (iii), very strong (iv), extremely strong (v).<sup>6</sup> For participants who responded “not at all” to the first question, the answer to the second question was coded as “0.”

Other factors that were assessed included demographics of age, sex, and social grade, number of quit attempts in the last year prior to the most recent attempt, time since the most recent quit attempt was initiated, whether smokers had tried to quit abruptly or gradually, and the year of the survey.<sup>6</sup>

Associations between the use of different quitting methods and confounding variables were assessed using  $\chi^2$  tests and one-way analyses of variance (ANOVA)s for categorical and continuous variables.<sup>6</sup> ANOVA tests for mean differences based on a dependent variable (ex: tobacco cigarette abstinence). To test for any bias, an analysis of covariance (ANCOVA) was used to examine whether the difference in strength of urges to smoke in smokers versus non-smokers depended on the method of quitting.<sup>6</sup> A logistic regression model was also used. The outcome measure was self-reporting non-smoking compared with smoking, and the effect measure was use of e-cigarettes compared with either NRT bought OTC or no aid.<sup>6</sup>

**Study results:** Quitting method did not differ by sex or number of quit attempts in the past year, however, quitting method did change based on age, social grade, time since the quit attempt started, cigarettes per day, smoking less than one cigarette per day, the measures of nicotine dependence, and whether the attempt had begun abruptly.<sup>6</sup> Those who used either e-cigarettes or no aid were younger than those using NRT bought OTC, and those using e-cigarettes held a higher social grade compared to those who used NRT bought OTC or no aid.<sup>6</sup> The quit attempts of e-cigarette users were less likely to have begun more than 6 months previously than those using NRT bought OTC or no aid.<sup>6</sup> Those using NRT bought OTC smoked more cigarettes per day and scored higher on all measures of nicotine dependence compared to the other two groups.<sup>6</sup> Those using no aid were more likely to attempt to quit abruptly and smoke less than one cigarette per day compared to the other two groups.<sup>6</sup>

Odds ratios in Table 7 demonstrate that e-cigarette users were more likely to be abstinent than either those using NRT bought OTC or those who used no aid. Those who reported having used an e-cigarette in their most recent quit attempt were more likely to report continued abstinence compared to those who used NRT bought OTC or nothing.<sup>6</sup>

This study suggests that e-cigarettes may prove to be an effective and efficacious aid to smoking cessation.<sup>6</sup> It addresses that the associated harms are minimal, e-cigarettes contain low levels of carcinogens and toxicants, and no serious adverse events have been reported.<sup>6</sup>

Method of therapy	Odds ratio	Confidence interval (95%)
E-cigarettes vs NRT bought OTC	2.23	1.70-2.93

E-cigarettes vs no aid	1.38	1.08-1.76
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Table 7. Odds ratios and confidence intervals on e-cigarettes compared to NRT bought OTC and no aid for smoking abstinence.

**Study critique:** This study demonstrated some major strengths and weaknesses. A strength of this study is the use of a large representative sample. It was also helpful that the study began tracking the use of e-cigarettes as a smoking cessation aid during a time when e-cigarettes were only an emerging research issue.<sup>6</sup> Another strength of the study was that it allowed a comparison between different interventions, specifically e-cigarettes versus NRT bought OTC versus no aid in cessation. Lastly, this study took place over a 12-month period, giving the subject's body enough time to adjust to their smoking cessation intervention and have a potentially greater effect on their urge to smoke.

One limitation of this study is that it is a survey, which creates recall bias since the data was self-reported and involved recalling the previous 12 months. This made it difficult to adjust for all of the potential confounding variables. Also, surveys may show association, but never causation. Another limitation was that abstinence was not measured biochemically, and may have caused some smokers to report abstinence when it may not have been true. Another limitation to this study was that NRT bought OTC and e-cigarettes both represent heterogeneous categories and can be quite variable. For example, NRT bought OTC could mean a variety of things, such as gum, patch, nasal spray, etc. Likewise, e-cigarettes come in a variety of different nicotine concentrations. This variability among the interventions may affect the reliability of the data. Another limitation is that this study was done in England, which may not accurately represent the demographics of the population in rural Harrisonburg, Virginia. The differences in smoking cultures between England and Harrisonburg necessitate caution when considering application of associations reported in this study. Another disadvantage to this study is that interviewers selected those who were most likely to be available to participate, and that the study never reported a response rate.

## Discussion

Study by Al-Delaimy et al revealed a positive association with e-cigarette use and making a quit attempt at follow-up, but it did not reach statistical significance. Use of e-cigarettes was statistically significant for a negative association with decreased cigarette consumption and abstinence. Therefore, a history of e-cigarette use was significantly associated with cessation failure rather than success.

Study by Biener and Hargraves showed that intensive e-cigarette users were six times more likely than non-users/tries to report that they quit smoking. Among intensive users of e-cigarettes, there was shown to be a significantly increased rate of sustained abstinence.

Study by Bullen et al revealed that e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events. Mean cigarette consumption decreased more in the nicotine e-cigarettes group than the patches group. In the nicotine e-cigarette group, there was an increased smoking abstinence at 6 months compared with use of patches or placebo e-cigarettes, but these differences were not statistically significant.

Study by Brown et al demonstrated that those who use e-cigarettes were more likely to be abstinent than those who used an NRT product bought OTC or no aid to cessation.

In summary, three studies concluded that e-cigarette use was most effective in smoking cessation. However one of those three studies was not statistically significant, and the fourth study revealed that e-cigarettes had a negative effect on smoking cessation. The inconsistency of these results cannot allow for arrival at a definite conclusion to the clinical question, and results are unreliable due to several limitations. The outcomes being measured and the alternative therapies

that were investigated vary across the four studies. These differences made it difficult to compare results and to draw distinct conclusions.

Clinical application to our Harrisonburg community is limited by these studies as well. The studies performed in England and New Zealand cannot be directly extrapolated to populations in the United States due to cultural and geographic differences. The studies performed within the United States lack statistical value due to the fact that they were both observational studies in survey format which introduces the potential for significant recall bias. Lack of randomization and unknown confounding variables are two examples of limitations that can accompany observational studies leading to unfounded conclusions about cause and effect relationships and correlations between study groups. Harrisonburg, Virginia has just over 50,000 people and nearly 20% of the population is Hispanic.<sup>11</sup> To confidently apply the findings of any study on electronic cigarettes to those within our somewhat rural community, demographics specific to our community would need to be addressed.

## Conclusion

Some analysts predict that electronic cigarette sales will surpass conventional cigarette sales within a decade.<sup>9</sup> That is a daunting consideration as so much remains unknown about electronic cigarettes. The number one reason that individuals attempt use of electronic cigarettes is to quit smoking. Unfortunately, studies have not yet been able to yield consistent results to answer that question. Additionally, the chemicals found within e-cigarettes have not been evaluated to determine adverse effects on individual users or to those indirectly exposed. Some of these chemicals include acetaldehyde, benzene, formaldehyde, nicotine, among many others, some of which are suspected carcinogens. Diethylene glycol has also been found in some e-cigarettes, which is a component of anti-freeze and considered toxic to humans.

From our analysis of these four articles, certain elements became apparent to us that should be included in further investigations of electronic cigarettes. These include: randomized controlled trials, use of electronic cigarettes with nicotine content more comparable to that of conventional cigarettes, biochemical verification of abstinence, standardized definition of "abstinence" across studies, larger sample sizes, and studies conducted over longer periods of time.

Based on the research found, electronic cigarettes should not be the first method recommended to help patients quit smoking. In regards to the question our hypothetical patient, Mr. Johnson, asked, we cannot be sure if e-cigarettes are the most effective therapy yet. Since these devices are not FDA approved and their safety cannot be guaranteed, other forms of smoking cessation therapies that have been proven to work should be recommended instead. This includes counseling, behavioral therapies, nicotine replacement therapies (both over-the-counter and prescription), prescription non-nicotine medications, or no aid.

Electronic cigarettes have been marketed in the United States since 2007. Until further studies are conducted, perhaps our greatest source of understanding will manifest with time.

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