The Efficacy and Safety of Electronic Cigarettes as a Tobacco Cessation Product

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The Efficacy and Safety of Electronic Cigarettes as a Tobacco Cessation Product

Abstract

**Background:** Tobacco smoking or secondhand smoke exposure is the leading cause of preventable death in the U.S. Between 2000 and 2004, an estimated 442,100 deaths were attributable to smoking in the United States. Products exist that can increase cessation rates and reduce this risk. E-cigarettes have gained popularity for smoking cessation/reduction and mitigation of withdrawal effects while still continuing to have a "smoking experience". Research investigating the efficacy and safety of electronic cigarettes is limited. This systematic review is a summary of applicable studies regarding the efficacy and safety of electronic cigarettes as a tobacco cessation product.

**Methods:** An exhaustive medical literature search was performed using Medline-OVID, CINAHL, and Health Reference Center-Academic using the keywords: electronic cigarette, e-cigarette, and e-cigarette. The included articles were assessed for quality utilizing GRADE. A search of the National Institute of Health (NIH) clinical trials website was performed to detect currently registered trials.

**Results:** Three studies meeting inclusion criteria were included in this systematic review. All studies reported increased cessation rates without significant adverse effects. The first study, a randomized controlled trial with 657 participants, lacked statistical power to detect difference. The second study, a randomized control design study with 300 participants demonstrated statistical significance. The third study, an observational study with 40 participants, reported results that could be due to chance.

**Conclusion:** E-cigarettes have been shown to increase cessation rates without significant adverse effects. However, quality of the e-cigarette was inconsistent. There is no regulatory oversight to guarantee safety in the U.S. Evidence is insufficient to properly assess the benefits and harms of e-cigarettes. There is a lack of evidence to support routinely recommending the use of electronic cigarettes for smoking cessation at this time. Further randomized controlled studies are in progress.

**Keywords**

Electronic Cigarette, e cigarette, e-cigarette, tobacco, cessation, efficacy

**Subject Categories**

Medicine and Health Sciences

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The Efficacy and Safety of Electronic Cigarettes as a Tobacco Cessation Product

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Biography

Leza Hayes is a resident of the State of Oregon. She attended Concordia University in Portland, OR and majored in Business Management and Communications. After completing her undergraduate degree, she worked on the business side of healthcare as both an office manager for a private medical practice and as the Executive Director for the Oregon Association of Naturopathic Physicians as well as the clinical side of healthcare as a Certified Nursing Assistant 2 in a long-term care setting.
Abstract

**Background:** Tobacco smoking or secondhand smoke exposure is the leading cause of preventable death in the U.S. Between 2000 and 2004, an estimated 442 100 deaths were attributable to smoking in the United States. Products exist that can increase cessation rates and reduce this risk. E-cigarettes have gained popularity for smoking cessation/reduction and mitigation of withdrawal effects while still continuing to have a “smoking experience”. Research investigating the efficacy and safety of electronic cigarettes is limited. This systematic review is a summary of applicable studies regarding the efficacy and safety of electronic cigarettes as a tobacco cessation product.

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**Conclusion:** E-cigarettes have been shown to increase cessation rates without significant adverse effects. However, quality of the e-cigarette was inconsistent. There is no regulatory oversight to guarantee safety in the U.S. Evidence is insufficient to properly assess the benefits and harms of e-cigarettes. There is a lack of evidence to support routinely recommending the use of electronic cigarettes for smoking cessation at this time. Further randomized controlled studies are in progress.

**Keywords:** Electronic Cigarette, e cigarette, e-cigarette, tobacco, cessation, efficacy
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Table I: Characteristics of Reviewed Studies

List of Abbreviations

nAChRs ............................................................nicotinic cholinergic receptors
NRT ........................................................................................nicotine replacement therapy
ENDD ..................................................................electronic nicotine delivery device
CO .....................................................................................carbon monoxide
eCO ..........................................................exhaled carbon monoxide
CI ...........................................................................Confidence Interval
ppm ..........................................................parts per million
FDA ..........................................................U.S. Food and Drug Administration
WHO ..........................................................World Health Organization
E-Cigarettes ..................................................Electronic Cigarettes
GNSBQ ..................................................Glover Nilsson Smoking Behavioral Questionnaire
NNT ..................................................Number Needed to Treat
The Efficacy and Safety of Electronic Cigarettes as a Tobacco Cessation Product

BACKGROUND

In the United States, tobacco smoking or secondhand smoke exposure is the leading cause of preventable death. There is an estimated 8.6 million who are seriously ill as a result of this exposure.\(^1\) Between 2000 and 2004, an estimated 442,100 deaths were attributable to smoking in the United States.\(^2\)

Tobacco contains (s)-nicotine which binds to nicotinic cholinergic receptors (nAChRs). When tobacco is smoked, (s)-nicotine is carried into the lungs and ultimately absorbed into the pulmonary venous circulatory system. The nicotine travels from the pulmonary venous circulation to the arterial circulation and into the brain where it binds nAChRs. These receptors are found in both the peripheral and central nervous systems. It is believed that the cardiovascular effects of nicotine are a result of the binding of one subunit of the nAChRs.\(^3\) Once the receptor is bound by (s)-nicotine, the neurotransmitters dopamine, norepinephrine, acetylcholine, serotonin, gamma aminobutyric acid (GABA), glutamate, and endorphins are released.\(^3\) Dopamine causes stimulation and pleasure as well as decreases anxiety. These psychoactive effects on the body lead to the addictive nature of nicotine.\(^3\) Catecholamines released are responsible for increasing heart rate and contractility and constricting coronary blood vessels leading to increased blood pressure. These catecholamines also constrict blood vessels in the
skin resulting in restricted blood flow and increased vascular resistance. Nicotine also contributes to insulin insensitivity.

Some of the potential harmful effects of nicotine include nicotine intoxication, increased rates of atherosclerosis formation, hypertension, myocardial infarction, stroke, sudden death, peptic ulcer disease, esophageal reflux, delayed wound healing, fetal neurotoxicity, spontaneous abortion, premature labor, and low birth weight neonates. Tobacco smoke contains many toxic and carcinogenic chemicals that contribute to the development of disease and ultimately death.

Smoking cessation can reduce the risk of developing these diseases and slow their progression. Smoking cessation leads to withdrawal symptoms that include irritability, restlessness, depressed mood, anxiety, impaired concentration, increased appetite, and difficulty sleeping. Tobacco dependence is behavioral, cognitive, and physiological.

Smoking cessation often requires multiple attempts before a person is successful. Most smokers attempt to quit on their own, which is the least successful method of quitting. It has been reported that approximately 80% of smokers who try to quit on their own relapse within one month. Only 3% of smokers achieve sustained abstinence. Treatments exist that can improve the long-term success for those wishing to quit. These treatments include counseling, nicotine replacement therapy (NRT), and non-nicotine medications. In a 2002 meta-analysis, the investigators reported a 7% long term successful abstinence using over-the-counter NRT. Their use is very low among smokers during attempts at quitting. This highlights the need for unique products that will increase the use and success of smoking cessation treatment.
Electronic nicotine delivery devices (ENDD), in the form of electronic cigarettes, arrived on the market in 2004. The first electronic cigarette was marketed by a Chinese company, Ruyan®. Electronic cigarettes resemble a cigarette and are powered by a battery. They are activated by the act of drawing on the mouthpiece. Each time a person draws on the mouthpiece, the nicotine-propylene glycol solution held in a cartridge at the end of the device is vaporized. The appearance of the vapor resembles smoke. However, the vapor does not contain combustion products. The electronic cigarette is increasing in popularity worldwide as a cessation/reduction product. Users report using the product to quit/reduce smoking and mitigate the withdrawal effects of smoking cessation while still continuing to have a “smoking experience.”

Research of the efficacy and safety of electronic cigarettes as a short or long-term smoking cessation tool is limited. In December 2009, Bullen et al reported the Ruyan® 16 mg electronic cigarette reduced desire to smoke with minimal adverse effects during participants 9-hour exposure. Serum cotinine can be used as a way to quantify the intake of nicotine. In the 2010 study, A Clinical Laboratory Model for Evaluating the Acute Effects of Electronic “Cigarettes”: Nicotine Delivery Profile and Cardiovascular and Subjective Effects, the authors concluded that ten puffs using an electronic cigarette exposed participants to no measurable nicotine or CO and did not result in increased heart rate. In contrast, Flouris et al reported that serum cotinine levels after electronic cigarette use was similar to those seen in cigarette smoking with no significant interference in lung function in January 2013. Also in January 2013, Goniewics et al reported the vapor produced with electronic cigarette use contained potentially toxic elements. However, the levels detected were 9-450 times less than those found in usual
cigarettes. The authors supported the use of electronic cigarettes as a tool to reduce harm.¹³

The aim of this systematic literature review was to summarize what is known and what contribution further research can offer regarding the efficacy and safety of electronic cigarettes as a smoking cessation product.

METHODS
An exhaustive medical literature search was performed using Medline-OVID, CINAHL, and Health Reference Center-Academic using the keywords: electronic cigarette, e-cigarette, and e cigarette. The search was refined to include only those articles that were English language and included human research participants. The references of these articles were reviewed for relevant articles. Articles with first-hand research data evaluating the efficacy and safety of electronic cigarettes were included. The included articles were assessed for quality utilizing the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).¹⁴ Lastly, a search of the National Institute of Health (NIH) clinical trials website revealed currently registered trials examining the efficacy and safety of electronic cigarettes in smoking cessation. This search revealed eleven trials currently registered, eight currently recruiting, one not yet recruiting and two active but not recruiting.

RESULTS
The search of Medline-OVID, CINAHL, and Health Reference Center-Academic produced a total of 293 articles to be reviewed. After reviewing these articles for relevance to smoking cessation and efficacy, three articles met the inclusion criteria. There were two randomized controlled trials and one observational study.
This randomized controlled trial investigated the effect of 16 mg electronic cigarettes, nicotine-free electronic cigarettes, and nicotine patches on smoking cessation as well as adverse effects (serious and non-serious) during the 6-month study period. Analysis of the electronic cigarette confirmed that the vapor liquid did not contain diethylene glycol, which is a toxin. Analysis also determined that the cartridges labeled 16 mg contained anywhere from 10-16 mg/mL of nicotine and those labeled nicotine-free did not contain nicotine. The primary outcome of the study was continuous smoking abstinence defined as $\leq 5$ cigarettes during the 6 months after their quit date. Study participants self-reported abstinence. Exhaled carbon monoxide (eCO) levels were measured as a confirmation of non-smoking status ($<10$ ppm). The secondary outcomes were continuous abstinence, 7-day point prevalence abstinence, number of cigarettes/day, time to relapse, number of patches or cartridges used, other cessation treatments used, withdrawal symptoms, stage of addiction, smoking latency, and adverse events. It was not reported how the data on the number of cigarettes/day, time to relapse, number of patches or cartridges used, other cessation treatments used, withdrawal symptoms, stage of addiction, smoking latency, and adverse events were compiled. It appears that they were reported by participants to Quitline, a behavioral support organization. Secondary outcomes were assessed at 1, 3, and 6 months following quit dates.  

The study included 657 adult smokers recruited from community newspapers in Auckland, New Zealand. The eligibility criteria for the study were smokers 18 years and older who had smoked 10 or more cigarettes/day for the past year, and interested in smoking cessation. Interested parties were excluded from the study if they were pregnant.
or breastfeeding, were using cessation drugs or in an existing cessation program, reported myocardial infarction, stroke, or severe angina in the past 2 weeks, and were those with poorly controlled medical disorders, allergies, or chemical dependence. Those who met the inclusion criteria were randomized to the 16 mg nicotine electronic cigarette, nicotine-free nicotine electronic cigarette, or nicotine patch groups by the study statistician in a 4:4:1 ratio via a computerized block randomization, block size nine, stratified by ethnicity, sex, and level of nicotine dependence. Withdrawal symptoms and stage of addiction at baseline were assessed using the Autonomy over Tobacco Scale (AUTOS).\textsuperscript{15} AUTOS is a tool used to determine psychological dependence, withdrawal, and cue-induced urges as they relate to tobacco addiction.\textsuperscript{16}

All participants’ were administered the Glover Nilsson Smoking Behavioral Questionnaire (GN-SBQ) to determine their behavioral dependence.\textsuperscript{17}

The group allocations were 289 to the 16 mg electronic cigarettes group, 73 to the nicotine-free nicotine electronic cigarettes group, and 295 to the nicotine patches group. Those allocated to the 16 mg electronic cigarettes and nicotine-free electronic cigarettes were provided an e-cigarette, spare battery and charger, and cartridges (with labels masked to nicotine content) accompanied by instructions to use them as desired for 1 week before and up to 12 weeks after their chosen quit date. Those allocated to the nicotine patch were provided exchange cards that could be taken to a community pharmacy and instructions to use them daily for 1 week before and up to 12 weeks after their chosen quit date. Allocation blinding of the participants to the electronic cigarettes and patches was not possible. Participants allocated to the electronic cigarette groups were blinded as far as their allocation between 16 mg electronic cigarettes and nicotine-
free electronic cigarettes. Participants were blinded within the electronic cigarette groups through masking of the nicotine content on the labels of the products. However, the research assistants responsible for performing the outcome assessments were blinded to group allocation.\textsuperscript{15}

All participants were referred to Quitline, who provided telephone-based behavioral support. Participation in Quitline was not required by the study. Quitline provided the researchers with usage reports.\textsuperscript{15}

The study groups were similar with respect to known prognostic variables at the beginning of the study. Loss to follow-up was 48/289 (22\%) in the 16 mg electronic cigarette group, 80/295 (27\%) in the nicotine patch group and 16/73 (22\%) in the nicotine-free electronic cigarette group. All patients were analyzed in the group to which they were first allocated with an intention to treat philosophy.\textsuperscript{15}

The cessation rate 6 months after quit date was highest in the 16 mg nicotine electronic cigarette group at 21/289 (17\%). The cessation rate 6 months after quit date in the nicotine patch group was 17/295 (5.8\%). In comparing these two groups, there was a relative risk of 2.9 and a number needed to treat (NNT) of 9. The cessation rate 6 months after quit date in the 0mg nicotine electronic cigarette groups was 3/73 (4.1\%). When comparing this group with the 16 mg e-cigarette group, there was a relative risk was 4.1 and a NNT of 8 results. The abstinence rate was much lower than anticipated and the authors stated that there was “insufficient statistical power to conclude superiority of the nicotine e-cigarettes to patches or to placebo e-cigarettes.”\textsuperscript{15} The 7-day point prevalence cessation rate 6 months after the quit date was highest in the nicotine-free electronic cigarette group at 16/73 (21.9\%). The 7-day point prevalence cessation rate 6 months
after quit date in the 16 mg nicotine electronic cigarette group at 61/289 (21.1%). The 7-day point prevalence cessation rate 6 months after quit date in the nicotine patch groups was 46/295 (15.6%).

The researchers compared the performance of 16 mg nicotine electronic cigarettes to nicotine patches. The continuous abstinence 6 months after quit date for this comparison was: relative risk of 1.26 with a 95% CI (0.68 to 2.34) and a risk difference of 1.51 with a 95% CI (-2.49 to 5.51), p - 0.46. The 7-day point prevalence abstinence 6 months after quit date for this comparison was: relative risk 1.35 with a 95% CI (0.96 to 1.91) and a risk difference of 5.52 with a 95% CI (-.075 to 11.79), p = 0.09. The performance of 16 mg electronic cigarettes were also compared to nicotine-free electronic cigarettes and yielded a continuous abstinence 6 months after quit date relative risk of 1.77 with a 95% CI (0.54 to 5.77) and a risk difference of 3.16 with a 95% CI (-2.29 to 8.61), p = 0.44. The 7-day point prevalence abstinence 6 months after quit date for this comparison was relative risk 0.96 with a 95% CI (0.59 to 1.57) and a risk difference of -0.81 with a 95% CI (-11.40 to 9.78),p = 0.88.

The authors report median time to relapse in the 16 mg nicotine electronic cigarette group as 35 days with a 95% CI (15 to 56). The median time to relapse in the nicotine patch group was reported as 14 days with a 95% CI (8 to 18), p < 0.0001. The median time to relapse in the nicotine-free electronic cigarette group was 12 days with a 95% CI (5 to 34), p = 0.09.

The reported difference in decrease in cigarettes/day when comparing the 16 mg nicotine electronic cigarette group with the nicotine patch group was 2 cigarettes/day, p = 0.002.
The authors report that AUTO scores in the combined electronic cigarette groups over the 6 month follow-up period decreased 50% from baseline. The nicotine patch groups’ AUTO scores decreased by 33%. The reduction in AUTO score from baseline to 6 months was 1.56, p = 0.02 when comparing the 16 mg nicotine electronic cigarette and the nicotine patch. The reduction in AUTO score from baseline to 6 months was 1.34, p = 0.19 when comparing the 16 mg nicotine electronic cigarette and the nicotine-free electronic cigarette.\textsuperscript{15}

The GNSBQ scores of the participants scoring “strong” or “very strong” at the beginning of the study were balanced. There was no evidence that there was an association between GNSBQ score and outcome. The data was not shown in the article.\textsuperscript{15}

Serious side effects (death, life threatening illness, admission to hospital or prolongation of hospital stay, persistent or significant disability or incapacity, congenital abnormality, medically important) were reported as 27 in the 16 mg nicotine electronic cigarette group, 14 in the nicotine patch group and 5 in the nicotine-free electronic cigarette group. Non-serious events were reported as 110 participants in the 16 mg nicotine electronic cigarette group, 105 in the nicotine patch group and 31 in the nicotine-free electronic cigarette group. There was a higher rate of adverse events in the 16 mg nicotine cigarette group overall. When comparing adverse events in the 16 mg nicotine cigarette group and the nicotine patch group, the event ratio was reported to be 1.50, 95% CI (0.82 to 1.34), p = 0.7. The authors believe that only one of these reported serious/non serious side effects in the nicotine patch group was definitely attributable to the study treatment and that a total of 3, (1 in each of the three study groups) was probably attributable to the study treatment. A total of 10, (5 from the 16 mg nicotine electronic
cigarette group, 4 from the nicotine patch group and 1 from the nicotine-free electronic cigarette group) were possibly attributable to the study treatment.\textsuperscript{15} Quitline’s services were accepted by 115/289 (40\%) in the 16 mg electronic cigarette group, 106/295 (36\%) in the nicotine patch group and 26/73 (36\%) in the nicotine-free electronic cigarette group.\textsuperscript{15}

Participants in the 16 mg nicotine electronic cigarette group reported using 1 to 3 cartridges/day at 1 month after quit date, 1 cartridge/day at 3 months after the quit date, and 0.7 cartridges/day at 6 months after the quit date. Those in the nicotine patch group reported an average of 1 patch/day consistently from 1 month to 6 months after the quit date. Finally, participants in the nicotine-free electronic cigarette group reported 1.1 cartridges/day at 1 month after the quit date, 1.2 cartridges/day at 3 months after the quit date and 0.7 cartridges/day at 6 months after the quit date.\textsuperscript{15}

The authors reported that in the combined 16 mg nicotine electronic cigarette groups, 2 used bupropion and 1 used verenicline in the 30 days prior to the 6 month follow-up visit. In the nicotine-free electronic cigarette 3 used verenicline in the 30 days prior to 6 months from their quite dates.\textsuperscript{15}

The first limitation of this study as identified by the authors was “the effect size and estimates of abstinence on which the study sample size was calculated were optimistic; hence, statistical power to detect differences was reduced.” Second, the loss to follow-up and withdrawal rate was higher in the nicotine patch group. The authors believe that participants may have been interested in the study because they were curious about electronic cigarettes and once randomized to the nicotine patch group, they became disinterested in the study. Another possible explanation given by the authors was that
participants may had used nicotine patches without success in the past, and it is conceivable that they would have given up on the patch and withdrawn from the study. Third, the authors feel that the behavioral support in this study may not have been intensive enough and a more intensive behavioral support model may have improved abstinence rates.¹⁵

**Caponnetto et al**

This double blind, randomized controlled trial¹⁸ examined the effect of 7.2 mg nicotine electronic cigarettes, hereafter referred to as Group A; 7.2 mg for 6 weeks, then transition to 5.4 mg nicotine electronic cigarettes, hereafter referred to as Group B; and nicotine-free electronic cigarettes, hereafter referred to as Group C; on smoking reduction/cessation and adverse effects (dry cough, mouth irritation, shortness of breath, throat irritation, and headache). An analysis of the nicotine content of the cartridges used in this study was performed. However, the report is not available in English so determining the actual nicotine content of the cartridges was not possible for this review. The primary outcome of the study was > 50% reduction in cigarettes/day at the 52-week study visit from baseline. The secondary outcome was sustained smoking abstinence at the 52-week study visit. Study participants self-reported the number of cigarettes/day. Exhaled carbon monoxide (eCO) levels were measured as a confirmation of smoking status and reduction from baseline. Participants kept a diary detailing product use (number of cartridges used), tobacco cigarettes smoked (cigs/day), withdrawal symptoms and adverse events.¹⁸

The study included 300 participants recruited from advertisements in a local newspaper in Catania, Italy. The eligibility for study inclusion was adult smokers in
good health, age 18-70 yrs., using ≥ 10 factory made cigarettes/day for at least the past five years, not attempting /wishing to quit in the next 30 days. Exclusion criteria for the study were symptomatic cardiovascular disease, symptomatic respiratory disease, regular psychotropic medication use, current or past history of alcohol abuse, use of smokeless tobacco or nicotine replacement therapy, pregnancy or breastfeeding.  

Participants were randomized by a computer generated randomization sequence with a block size of 15 and an allocation ratio of 5:5:5. Each group contained 100 participants. External packaging was identical for all three strengths of cartridges in order to blind group allocation. The authors do not explicitly explain the blinding of the investigators to group allocation. A local distributor provided the study supplies (two rechargeable batteries, a charger, two atomizers along with instructions on how to charge, activate and correctly use the electronic cigarette) free of charge to the participants. The groups were provided with an electronic cigarette kit and enough cartridges to last until each follow-up visit. Participants were not encouraged or given any motivation to cease smoking.  

Study participants were instructed to use the product ad libitum throughout the day, not to exceed a 4 cartridge/day maximum as recommended by the manufacturer of the product. Participants attended follow-up visits at 2, 4, 6, 8, 10, 12, 24, and 52 weeks. At each of these visits, participant eCO levels were recorded, study diaries were given to study personnel and unused study products were turned in. After 12 weeks, no additional cartridges were provided to the participants. However, participants were told they could continue to use the electronic cigarettes. Saliva cotinine levels were measured at 6 and 12 weeks in participants who reported no smoking and had an eCO ≤ 7 ppm. Study
groups were similar with respect to prognostic variables. Loss to follow-up was 35/100 (35%) in Group A, 37/100 (37%) in Group B, 45/100 (45%) in Group C. All patients were analyzed in the group to which they were first allocated with an intention to treat philosophy.\textsuperscript{18}

At week 52, 10/100 (10%) of those allocated to Group A, 9/100 (9%) of those allocated to Group B 12/100 (12%) of those allocated to Group C had reduced their cigarettes/day by $\geq 50\%$, $p = 0.24$.\textsuperscript{18}

At week 52, 13/100 (13%) of those allocated to Group A, 9/100 (9%) of those allocated to Group B and 4/100 (4%) of those allocated to Group C had achieved smoking abstinence and had eCO concentrations of $\leq 7$ ppm, $p = 0.24$.\textsuperscript{18}

Self-reported adverse effects by the remaining 183 participants of the study at 52-weeks are as follows: throat irritation 37/183 (20.2%), mouth irritation 34/183 (18.6), dry cough 37/183 (20.2%), headache 5/183 (2.7%), shortness of breath 15/183 (8.1%). No serious adverse effects were reported during the study.\textsuperscript{19} These figures were extracted from graphs contained in the article. They were not reported in written form.\textsuperscript{18}

The authors identified several limitations of this study. First, the study design was such that the investigators recruited smokers not interested in smoking cessation. As a result, direct comparison with other smoking cessation products is not feasible. Secondly, the study was designed with the concept that nicotine is the main culprit leading to smoking addiction. The study did not include a “control group specifically for e-cigarette use.” Third, approximately 40% of the study participants were lost to follow-up. Fourth, there were frequent technical difficulties with the e-cigarettes used in the study. Fifth, the model of e-cigarette used in the study is no longer available. The e-
cigarettes currently available perform at a much high level than those used in the study. Sixth, the population from which the study participants were recruited adhered to a so-called “coffee puff-break,” whereby work or leisure activities were halted and everyone drank coffee and smoked tobacco products. Finally, withdrawal symptoms could have been subject to recall bias.

Polosa et al

This observational study examined the effect of electronic cigarettes with 7.4 mg nicotine liquid on reduction/cessation of smoking as well as adverse events (ie., throat irritation, mouth irritation, sore throat, dry cough, dry mouth, mouth ulcers, dizziness, headache, and nausea) over a 24-week period. Following random analysis, it was confirmed that the nicotine content per cartridge used in the electronic cigarettes was 7.25 mg. The primary outcome of the study was > 50% reduction in cigarettes/day for a 30-day period prior to the 24-week study visit from baseline. The secondary outcomes were > 80% reduction in cigarettes/day for a 30-day period prior to the 24-week study visit from baseline and sustained smoking abstinence for a 30-day period prior to the 24-week study visit. Study participants self-reported the number of cigarettes/day. Exhaled carbon monoxide (eCO) levels were measured as a confirmation of smoking status and reduction from baseline. Participants kept a diary detailing product use (number of cartridges used), tobacco cigarettes smoked (cigs/day) and adverse events.

The study included 40 adult smokers recruited by local hospital staff in Catania, Italy. The eligibility criteria for the study was healthy smokers 18-60 years, smoking ≥ 15 factory made cigarettes/day for at least ten years and not currently wanting or attempting to quit smoking in the following 30 days. Interested parties were excluded.
from the study if they reported a history of alcohol or illicit drug use, major depression or other psychiatric condition, recent myocardial infarction, angina pectoris, high blood pressure (BP >140/90), diabetes mellitus, severe allergies, poorly controlled asthma or other airway diseases. Given that this was an observational study, the participants were not randomized. All participants were provided with the 7.4 mg electronic cigarettes, instructed on proper operation of the product and instructed to use the product ad libitum throughout the day, not to exceed a 4 cartridge/day maximum as recommended by the manufacturer of the product.\textsuperscript{19}

Those included in the study were scheduled to return for study visits at 4, 8, 12 and 24 weeks. At each of these visits, participant eCO levels were recorded, study diaries were given to study personnel, and unused study products were turned in. Participants were not encouraged or given any motivation to cease smoking. However, smoking cessation assistance was provided to those who asked for assistance. If this occurred, the participant was removed from the study. The number of participants removed under these circumstances was not reported.\textsuperscript{19}

Twenty-seven participants attended all study visits. Thirteen participants were lost to follow-up. Those lost to follow-up were included in the 24 week analysis as part of the study’s intention to treat analysis. It is of note that there were a larger number of males lost to follow-up than females. The authors report an overall 80% reduction in median cigarette/day use (25 to 5), p < 0.001. Of the 40 participants, 13 (32.5%) exhibited a sustained > 50% reduction in cigarettes/day, p < 0.001, 5 (12.5%) exhibited a sustained > 80% reduction in cigarettes/day, p= 0.043, and 9 (22.5%) exhibited sustained abstinence, p = 0.008. Self-reported adverse effects by the remaining 27 participants of
the study at 24 weeks are as follows: throat irritation 4/27 (14.8%), mouth irritation 2/27 (7.4%), dry cough 3/27 (11.1%), dry mouth, 1/27 (3.7%), dizziness 1/27 (3.7%), headache 1/27 (3.7%), nausea 1/27 (3.7%). No serious adverse effects were reported during the study.¹⁹

There were several limitations identified by the authors. First, there was a limitation due to the small size of the study as well as the result of chance and no true outcome due to the uncontrolled nature of the design. Due to this, the authors believe the results should be viewed with caution. Second, there was 13/27 (32.5%) loss to follow-up. Third, because the participants were unwilling to quit and the electronic cigarette was used throughout the study; a comparison with other smoking cessation products cannot be made. Fourth, there were technical defects with the electronic cigarettes, which could have contributed to the number loss to follow-up as well as participants failure to cease smoking. Lastly, typical withdrawal symptoms usually seen in smoking cessation studies were not reported by the participants. This could be the result of the fact that identifying these symptoms was not rigorous in the study, which could have resulted in recall bias.¹⁹

**DISCUSSION**

Electronic cigarettes represent another potential smoking cessation product that is not currently being offered in the healthcare setting in the United States. Some consumers are already using electronic cigarettes as a smoking cessation product while others are using them to mitigate withdrawal symptoms due to increasing smoking restrictions in the United States. Still, other consumers see them as a way to continue having a smoking experience without the harmful effects and smell of tobacco cigarettes.
In 2008, WHO agreed that the electronic cigarette might prove a useful tool in smoking cessation and that studies were needed to confirm their efficacy and safety.\textsuperscript{20} WHO confirmed that the actual content of the cartridges used in electronic cigarettes varies according to testing that has been done. As a result, there is no way for the consumer to be sure what level of nicotine and other chemicals are in various electronic cigarette cartridges. As a result, in July of 2013, consumers were advised not to use electronic cigarettes until specific products have been evaluated for their efficacy and safety.\textsuperscript{21} The US Department of Health and Human Services stated that electronic cigarettes contain ingredients known to cause toxicity in humans and that no studies addressing the safety of electronic cigarettes have been submitted to the FDA. Due to this, consumers don’t know what chemicals are in the cartridges, how much nicotine is in each cartridge, or if they are safe for use. The FDA has not approved any electronic cigarettes for therapeutic use as of January 17, 2014. There are countless brands of electronic cigarettes available in the United States. Currently there isn’t any regulatory body in the United States that is overseeing consistency in these products. In Fall 2013, the FDA issued a proposed rule which will allow the FDA to oversee the use and safety of electronic cigarettes.\textsuperscript{22}

The studies\textsuperscript{15,18,19} all illustrated favorable smoking cessation rates with limited adverse effects. However, there are several concerns that still limit their use as a routine smoking cessation product. Inconsistent manufacturing practices do not guarantee the consumer that the package labeling accurately reflects the true nicotine content and toxins contained in the e-cigarette. Also, to date, no studies have published results of studies lasting more than one year; therefore, the effects of long-term use are not known.
Bullen et al\textsuperscript{15} recognized several limitations to their study. The first limitation of this study as identified by the authors was “the effect size and estimates of abstinence on which the study sample size was calculated were optimistic; hence, statistical power to detect differences was reduced.” Second, the loss to follow-up, and withdrawal rates were higher in the nicotine patch group. This may have been due to curiosity about electronic cigarettes and when allocated to the nicotine patch group, participants became disinterested. The loss also could have been a result of past unsuccessful usage of nicotine patches. Finally, the Quitline behavioral support offered in the study may not have been intensive enough and the researchers believe that more intensive behavioral support may have improved abstinence rates.

Caponnetto et al\textsuperscript{18} reported that inclusion criteria required that respondents not be attempting or interested in smoking cessation. This may have caused the findings of the study to be undervalued due to the participants’ lack of desire to quit smoking. The study was designed with the concept that nicotine is the main culprit leading to smoking addiction. The study did not include a “control group specifically for e-cigarette use.” There was a significant loss to follow-up, approximately 40%. However, the analysis was performed with intention to treat analysis philosophy. There were frequent technical difficulties with the electronic cigarettes used in this study. As a result, the findings of the study could be undervalued due to participants ceasing to use the electronic cigarettes. Furthermore, the electronic cigarette used in the study is inferior to those being marketed today and as a result, may not have performed as well as todays’ electronic cigarettes. The study took place in Italy where it is a social norm to take a “coffee puff-break.” Electronic cigarettes might have performed better in locations where this was not the
social norm. Finally, the withdrawals symptoms experienced by the participants may have been undervalued as a result of the symptoms being self-reported during follow-up visits and would be subject to potential recall bias.

In Polosa et al\textsuperscript{19}, the authors noted several study limitations. The study was a small uncontrolled study and as a result, the findings may be due to chance rather than the electronic cigarette. Also, there was a 32.5\% loss to follow-up which is very significant given the small number of participants in the study. However, the analysis was performed with intention to treat analysis. Again, there were technical defects with the electronic cigarettes which could have contributed to the number loss to follow-up. As a result, the findings of the study could be undervalued due to participants ceasing to use the electronic cigarettes. One of the inclusion requirements of the study was that the respondents had to not be attempting or desiring to stop smoking. As a result, the readiness to quit of those included in the study was not assessed. The findings of the study may be undervalued as a result of the participants’ lack of desire to quit smoking. Finally, the withdrawals symptoms experienced by the participants may have been undervalued as a result of the symptoms being self-reported during follow-up visits and would be subject to potential recall bias.

**CONCLUSION**

The studies reviewed demonstrate that the specific electronic cigarettes studied are effective and do not exhibit any significant adverse effects as a smoking cessation product. However, the studies also demonstrated that the labeling found on the cartridges used in the studies did not correctly reflect the nicotine content. The combined quality of
the three studies reviewed after assessment using GRADE criteria is moderate. There is insufficient evidence to properly assess the benefits and harms of electronic cigarettes due to inconsistencies in the manufacturing process. There is a lack of evidence to support routinely recommending the use of electronic cigarettes for smoking cessation at this time. Further randomized controlled studies examining the efficacy and safety are currently in process. These studies are expected to further clarify the efficacy and safety of electronic cigarettes as a smoking cessation product.
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Table I. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Factors Increasing Quality</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullen et al. 15</td>
<td>Randomized Controlled Trial</td>
<td>Very Serious a,b</td>
<td>No Serious</td>
<td>No Serious</td>
<td>No Serious</td>
<td>Upgrade 1 Level c</td>
<td>Moderate</td>
</tr>
<tr>
<td>Caponnetto et al. 18</td>
<td>Randomized Controlled Trial</td>
<td>Serious a</td>
<td>No Serious</td>
<td>No Serious</td>
<td>No Serious</td>
<td>Upgrade 1 Level c</td>
<td>High</td>
</tr>
<tr>
<td>Polosa et al. 19</td>
<td>Observational</td>
<td>Serious a</td>
<td>No Serious</td>
<td>Serious d</td>
<td>Serious e</td>
<td>None</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

a High attrition rate.
b Group allocation of patients to the e-cigarette and nicotine patches could not be concealed from the participants. However, they were concealed from the research assistants performing the outcome assessments.
c All plausible confounders would underestimate the treatment effect.
d Smoking cessation is not the primary outcome of the study.
e Small sample size