Effectiveness of Electronic Cigarettes as a Tool for Smoking Cessation or Reduction

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Abstract

Objective: To examine the evidence concerning effectiveness of electronic cigarettes (e-cigarettes) in smoking cessation or reduction and reduction in desire to smoke and withdrawal symptoms. **Data Sources:** A PubMed literature search through May 2014 was performed using search terms *electronic cigarettes* or *e-cigarettes*; *smoking* or *tobacco*; and *efficacy* or *effectiveness* limited to clinical trials in humans. Cochrane Library and International Pharmaceutical Abstracts were searched using the term *electronic cigarettes*. Relevant citations from identified articles were reviewed. **Study Selection and Data Extraction:** All English-language clinical trials assessing cessation, reduction in cigarette use, desire to smoke, and/or reduction in withdrawal symptoms with e-cigarettes were included. **Data Synthesis:** Of 7 trials, one showed similar 6-month abstinence rates between e-cigarettes and nicotine patches. Another trial reported 12.5% of participants achieving abstinence at 24 months with e-cigarettes. Three studies demonstrated significant percentages of patients maintaining $\geq 50\%$ reduction in cigarettes/day from baseline to 24 or 52 weeks. Another trial showed significant reductions in cigarette use from baseline through 52 weeks with e-cigarettes; no difference in abstinence rates beyond 12 weeks was found between nicotine and placebo e-cigarettes. Only 2 trials assessed reduction in desire to smoke or withdrawal symptoms, and results varied. **Conclusions:** The limited evidence available supports that e-cigarettes may be effective as monotherapy for smoking cessation and reduction. However, superiority to nicotine replacement therapy was not proven. Limited conclusions can be drawn regarding reduction in desire to smoke and withdrawal symptoms. The unknown long-term safety risk should also be considered.

Keywords

smoking cessation, literature evaluation, delivery systems, disease management, ambulatory care

Background

In 2012, 18.1% (42.1 million) of US adults reported being a current smoker.¹ Of those people and those who reported quitting during 2012, 52.9% had attempted to quit for at least 1 day in the preceding year.¹ This statistic highlights the need for effective tobacco cessation aids.

Smoking is considered the leading cause of preventable death in the United States, with approximately 20 million smoking-related deaths since 1964.² The 2014 Surgeon General's report detailing smoking-related health risks (including cancer, significant cardiovascular and respiratory disease, detrimental reproductive effects, and diabetes) had sufficient data to support a potential causal relationship between smoking and disease. Additionally, from 2009 to 2012 smoking was associated with \$289 to \$332.5 billion in economic loss, of which \$132.5 to \$175.9 billion went to direct medical care.² Decreasing the rate of smoking could improve health and productivity while decreasing health care costs.

The US Department of Health and Human Services (HHS) identified 7 first-line medications effective for the treatment of tobacco use and dependence. Five of these are nicotine replacement therapies (NRTs) that are available in multiple formulations including a gum, inhaler, lozenge, nasal spray, and patch. Bupropion SR and varenicline are 2 non-nicotine products recommended by the HHS.³

Selection of smoking cessation agents is based on patient specific contraindications, cost, and patient preference. Although not Food and Drug Administration (FDA) approved, the electronic cigarette (e-cigarette) has been studied in recent years as a tool to help reduce or quit smoking. E-cigarettes are battery-powered devices that vaporize a

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liquid solution that may or may not include nicotine.⁴ Although there is no tobacco in the e-cigarette, there are concerns about other potential risks including potential toxins in the vapor.⁵ A recent review indicates that most surveys have reported mild side effects such as dry mouth, throat irritation, dry cough, vertigo, headache, and nausea.⁶ Long-term safety was not addressed in this review; however, studies that focus on effectiveness were analyzed.

Literature Review

A systematic review was performed from time of database inception through May 2014 using PubMed with the search terms *electronic cigarettes* or *e-cigarettes*; *smoking* or *tobacco*; *efficacy* or *effectiveness*, with results limited to clinical trials in humans. Cochrane Database of Systematic Reviews and International Pharmaceutical Abstracts were searched from time of inception through May 2014 using the search term *electronic cigarettes*. Relevant citations from identified articles were also reviewed. Abstracts, case series, and surveys were excluded. The overall search strategy was to identify trials evaluating the effectiveness of e-cigarettes. For purposes of this article, effectiveness was defined as cessation or reduction of smoking, reduction in desire to smoke, or reduction in withdrawal symptoms. A summary of the 7 trials included in this review is shown in Table 1.^{5,7-12}

Dawkins et al performed a randomized controlled trial in the United Kingdom that assessed the reduction in desire to smoke and abstinence-related withdrawal symptoms over a 20-minute period with e-cigarettes.⁷ Eighty-six e-cigarette naive smokers were randomized to the White Super 18 mg nicotine e-cigarette group, the placebo e-cigarette group, or to the “just hold” group, which held the e-cigarette but did not puff. The participants’ intention to quit was not stated. The primary outcomes were change in desire to smoke over time, as evidenced by the mean change in the Fagerstrom Test of Nicotine Dependence (FTND) score, and the mean change in the Mood and Physical Symptoms Scale (MPSS) score, which assessed 6 nicotine withdrawal symptoms of anxiety, poor concentration, depression, hunger, irritability, and restlessness. These were assessed after e-cigarettes were used ad libitum for 5 minutes. From baseline (T1) to 5 minutes (T2) there was no statistically significant difference in the FTND score for any group. Among males, the FTND score from T1 to 20 minutes (T3) was significantly reduced with nicotine compared to placebo e-cigarette ($P < .05$), with placebo compared to “just hold” ($P < .05$), and with nicotine compared to “just hold” ($P < .001$). Among females, the FTND score from T1 to T3 was not significantly reduced with nicotine compared to placebo ($P > .05$); however, it was significantly reduced with placebo compared to “just hold” ($P < .01$) and with nicotine compared to “just hold” ($P < .05$). These results demonstrate that e-cigarettes, with or without nicotine, may be beneficial in reducing the hand-to-mouth sensorimotor aspect of

smoking. Based on MPSS scores, men in the nicotine group experienced significantly less withdrawal symptoms of anxiety, poor concentration, irritability, and restlessness from T1 to T3 as compared to both the “just hold” and placebo groups (all $P < .05$). For women in the nicotine group there was significantly less depression from T1 to T3 as compared to the “just hold” group ($P < .05$). This study was limited by the relatively short duration of abstinence (1-2 hours) prior to the participants completing the FTND and MPSS, which was reflected in the low MPSS scores. A longer duration of abstinence would have provided more clinically applicable results.

Bullen et al conducted a randomized controlled trial in New Zealand that assessed the effectiveness of 13 weeks of nicotine e-cigarettes as compared to nicotine patches or placebo e-cigarettes for smoking cessation.⁵ The study included 657 adult smokers wanting to quit after smoking ≥ 10 cigarettes per day for the past year. Participants were randomized to receive the Elusion 16 mg nicotine e-cigarette, 21 mg/24 hour nicotine patch, or a placebo e-cigarette. E-cigarettes were to be used as desired; no maximum limitation was reported in the study. All participants were referred to telephone-based behavioral support. The primary outcome was continuous abstinence at 6 months, as supported by exhaled breath carbon monoxide (eCO) measurement. Lower eCO levels, typically < 10 ppm, reflect recent smoking abstinence.¹³ Although differences were not statistically significant, abstinence at 6 months was highest in the nicotine e-cigarette group (7.3%) as compared to the nicotine patch group (5.8%; $P = .46$) and the placebo e-cigarette group (4.1%; $P = .44$). Quit rates were lower than predicted, likely due to low utilization of behavioral support compared to studies in HHS guidelines.³ This resulted in the study not meeting power and the inability to conclude superiority of nicotine e-cigarettes to nicotine patches or placebo e-cigarettes. However, the study’s abstinence rates were similar to rates seen in NRT studies without behavioral support. Additionally, a post hoc analysis suggested that nicotine e-cigarettes were at least as effective as patches in achieving abstinence. These study results suggest that nicotine e-cigarettes may be an effective alternative to NRT currently recommended.

Caponnetto et al reported a double-blind, randomized, controlled, proof-of-concept trial including 300 Italians who smoked ≥ 10 cigarettes/day for ≥ 5 years and were not intending to quit.⁸ Participants were randomized into 3 study groups: group A received Categoria 7.2 mg nicotine e-cigarette for 12 weeks; group B received Categoria 7.2 mg nicotine e-cigarette for 6 weeks followed by 5.4 mg nicotine e-cigarette for 6 weeks; group C received the placebo e-cigarette for 12 weeks. E-cigarettes could be used ad libitum up to 4 cartridges per day. All groups demonstrated a significant reduction of median value in tobacco cigarettes used per day from baseline to each study visit through week 52 (all $P < .001$). Between-group differences in cigarettes used per day were significant only at weeks 2, 6, and 8 ($P = .04, .01$, and

Table 1. Study Characteristics and Results.

Reference	Participants (n), Intention to Quit Smoking	Design	Regimen	Primary Outcome	Primary Outcome Results
Dawkins et al (2012) ⁷	86, Unspecified intention to quit	Randomized controlled trial	White Super nicotine 18 mg e-cigarette, placebo e-cigarette, or "just hold" each used ad libitum for 5 minutes	Change in desire to smoke (FTND score) and withdrawal symptoms (MPSS score) at baseline (T1), 5 minutes (T2), and 20 (T3) minutes after use	<i>Males:</i> FTND score (T1 to T3) significantly reduced with nicotine compared to placebo and "just hold," and placebo compared to "just hold." Significantly less anxiety, poor concentration, irritability, and restlessness (T1 to T3) as compared to "just hold" and placebo groups. <i>Females:</i> FTND score (T1 to T3) significantly reduced with placebo compared to "just hold" and nicotine compared to "just hold." Significantly less depression (T1 to T3) as compared to the "just hold" group.
Bullen et al (2013) ⁵	657, Intending to quit	Randomized controlled trial	Elusion nicotine 16 mg e-cigarette, nicotine 21 mg patch, or placebo e-cigarette for 13 weeks	Continuous smoking abstinence, 6 months after quit day	Verified continuous abstinence at 6 months after quit day: 7.3% (nicotine e-cigarette), 5.8% (nicotine patch), and 4.1% (placebo e-cigarette) of participants
Caponnetto et al (2013) ⁸	300, Not intending to quit	Prospective, randomized, controlled trial	Categoria nicotine 7.2 mg e-cigarette for 12 weeks, nicotine 7.2 mg e-cigarette for 6 weeks followed by nicotine 5.4 mg e-cigarette for 6 weeks, or placebo e-cigarette for 12 weeks	≥50% reduction in number of cigarettes/day and abstinence from baseline to weeks 12, 24, and 52	When comparing both nicotine e-cigarettes to placebo e-cigarettes: No significant difference in ≥50% reduction at week 12 or beyond; Significant reduction in abstinence with nicotine e-cigarettes at week 12 but not beyond
Bullen et al (2010) ⁹	40, Not intending to quit	Randomized crossover trial	Ruyan V8 nicotine 16 mg e-cigarette, placebo e-cigarette, Nicorette nicotine inhaler, or tobacco cigarettes for 1 day	Change in desire to smoke, measured as "area under the curve" over 60 minutes	Significantly greater reductions in desire to smoke with nicotine 16 mg e-cigarette as compared to placebo e-cigarette
Polosa et al (2011) ¹⁰	40, Not intending to quit	Prospective proof-of- concept study	Categoria nicotine 7.4 mg e-cigarette ad libitum for 6 months	50% reduction in cigarettes/day at week 24	32.5% of participants achieved a 50% reduction in cigarettes/ day
Polosa et al (2013) ¹¹	40, Not intending to quit	Prospective observational study	Categoria nicotine 7.4 mg e-cigarette ad libitum for 24 weeks	≥50% reduction in cigarettes/day; 80% reduction in cigarettes/day and abstinence at 24 months	27.5% of participants achieved a 50% reduction in cigarettes/ day; 15% achieved an 80% reduction and 12.5% achieved abstinence
Caponnetto et al (2013) ¹²	14, Not intending to quit	Prospective pilot study	Categoria nicotine 7.2 mg e-cigarette ad libitum for 52 weeks	Sustained, self- reported 50% reduction in the number of cigarettes/day	50% of participants sustained a 50% reduction; median of 30 tobacco cigarettes/day decreased to 15 cigarettes/ day

Abbreviations: FTND, Fagerstrom Test of Nicotine Dependence; MPSS, Mood and Physical Symptoms.

.04, respectively). At these weeks, the placebo e-cigarette had the greatest usage. The decreased use was supported by significant reductions in eCO levels from baseline to each study visit ($P < .0001$). When comparing groups A and B (combined for statistical purposes) to group C, there was no significant difference in the percentage of patients achieving $\geq 50\%$ reduction in smoking at week 12 or beyond ($P = .70$). There was no difference between groups A and B versus group C in patients achieving abstinence from tobacco cigarettes at any study visit beyond week 12. At week 12, groups A and B had greater reductions ($P = .008$). Although participants were unwilling to quit and not encouraged to quit, visits took place at a smoking cessation clinic where written or other materials could have influenced participants to consider cessation. In contrast, quit rates may have been decreased due to the use of the Categoria brand e-cigarette, which was later removed from the market due to underperformance compared to other e-cigarettes.

Bullen et al conducted a single blind, randomized crossover trial including 40 New Zealand adults not intending to quit who smoked ≥ 10 tobacco cigarettes/day for at least the past year.⁹ The 4 interventions, each used for 1 day with a 3-day washout period in between, included Ruyan V8 16 mg e-cigarettes, placebo e-cigarette, Nicorette 10 mg nicotine inhaler, and the participants' usual tobacco cigarettes. The primary outcome was the change in desire to smoke, measured as "area under the curve" over a 60-minute period of use following ≥ 12 hours smoking abstinence. This curve was generated by assessing desire to smoke on an 11-point scale at prespecified intervals. During the 60-minute period, e-cigarettes and tobacco cigarettes were each used for 5 minutes; nicotine inhalers were used for 20 minutes. The study was powered to detect a difference between the placebo and 16 mg e-cigarette. The desire to smoke was significantly reduced with the 16 mg e-cigarette ($P = .006$); however, the difference was not significant after adjusting for multiple comparisons in secondary analyses ($P = .21$). Overall, both strengths of the e-cigarettes and Nicorette inhaler had similar reductions in the desire to smoke, but as expected, the use of tobacco cigarettes resulted in significantly greater reductions in desire to smoke compared to the 16 mg e-cigarettes, placebo e-cigarettes, and Nicorette inhalers ($P = .003$, $P < .0001$, and $P = .001$, respectively). Limited conclusions can be drawn due to the short treatment period.

Polosa et al reported a prospective proof-of-concept study including 40 Italians who smoked ≥ 15 cigarettes/day for ≥ 10 years and were unwilling to quit.¹⁰ Participants were provided Categoria brand 7.4 mg e-cigarettes to use ad libitum up to 4 cartridges per day over a 6-month period. The primary efficacy measure was a 50% reduction in the number of cigarettes/day at week 24 compared to baseline; 32.5% of participants attained this reduction ($P < .001$). Secondary measures were an 80% reduction in the number of cigarettes/day and sustained smoking abstinence (no cigarettes 30 days prior to the week 24 visit), both of which were

statistically significant ($P < .043$ and $.008$, respectively). For all measures, patient diary reports were supported by measured eCO levels. As a proof-of-concept study, the investigators intentionally selected patients unwilling to quit to make this a naturalistic observational study. This limits external validity but does provide data on the potential to reduce or quit smoking with e-cigarettes even without this intent. The study is limited by the high dropout rate; only 27 patients were included in the final analysis at week 24. Although participants were unwilling to quit and were not encouraged to quit, visits took place at a smoking cessation clinic where written or other materials could have influenced participants to consider cessation. Additionally, opportunistic sampling of hospital staff may have caused selection bias.

Polosa et al reported a prospective observational study including 40 Italians who smoked ≥ 15 cigarettes/day for ≥ 10 years and were not intending to quit.¹¹ Participants were provided Categoria brand 7.4 mg e-cigarettes to use ad libitum up to 4 cartridges per day during a 24-week intervention phase with clinic visits at baseline and weeks 4, 8, and 12. After the intervention phase, e-cigarettes were not provided, but patients were advised to continue using any brand of e-cigarette if desired, and they were asked to return to clinic at 18 and 24 months. Efficacy measures included $\geq 50\%$ or $\geq 80\%$ self-reported reduction in the number of cigarettes/day or abstinence from baseline to each study visit. Patient reports were supported by eCO levels. At 24 months, 27.5% of subjects ($n = 23$) had $\geq 50\%$ reduction ($P < .003$), 15% of subjects had $\geq 80\%$ reduction ($P = .012$), and 12.5% quit ($P = .042$). Of those who quit, there was no continued use of e-cigarettes. Several factors may have influenced the results, including opportunistic sampling of hospital employees. Also, although participants were unwilling to quit and not encouraged to quit, visits took place at a smoking cessation clinic where written or other materials could have influenced participants to consider cessation. Although the statistical analysis was not robust, the authors state when comparing quit rates in this study to much lower cessation rates in the general Italian population, results imply the use of e-cigarettes increased quit rates in participants initially unwilling to quit. In fact, quit rates may have increased further if the study had used a higher performing e-cigarette than the Categoria brand removed from the market.

Caponnetto et al conducted a prospective 12-month pilot study in 14 patients with schizophrenia who were smoking ≥ 20 cigarettes/day for ≥ 10 years and not intending to quit smoking.¹² Participants were provided Categoria 7.4 mg nicotine e-cigarette to be used ad libitum up to 4 cartridges per day. The primary endpoint was a self-reported 50% reduction in the number of cigarettes/day, sustained for 30 days prior to week 52. Fifty percent of participants met the primary endpoint with median cigarette use decreasing significantly from 30 cigarettes/day to 15 cigarettes/day ($P = .018$). This reduction was supported by eCO levels. Although this study showed a significant reduction in cigarette smoking with the

use of e-cigarettes in patients with schizophrenia not intending to quit, the small sample size is a limitation.

Summary

Based on the reviewed literature, e-cigarettes may be effective as monotherapy for smoking cessation and reduction. Over 6 to 24 months, 3 small trials demonstrated a significant portion of participants achieving at least 50% reduction in the number of cigarettes smoked per day.¹⁰⁻¹² Notably, one of these studies demonstrated significant cessation rates without continued use of e-cigarettes as a substitution for tobacco cigarettes.¹¹ While there is some evidence for the effectiveness of e-cigarettes, there are limited data available to compare e-cigarettes to NRT. A post hoc analysis of one randomized controlled trial suggested that nicotine e-cigarettes were as effective as nicotine patches in achieving continuous abstinence at 6 months.⁵ Another smaller trial found similar reductions in the desire to smoke among users of nicotine e-cigarettes, placebo e-cigarettes, and the Nicorette inhaler, but this was not statistically proven.⁹ Overall, some results favor nicotine e-cigarettes compared to placebo e-cigarettes, while others show no difference.^{5,7-9} Only one identified trial aimed to assess superiority of nicotine e-cigarettes compared to nicotine patches, but this trial did not reach power.⁵ At this time, superiority has not been proven, but e-cigarettes may be an alternative to NRT, as they may satisfy the hand-to-mouth sensorimotor aspect of smoking.⁷

There are significant deficiencies in the current literature and further research is warranted. Though safety analysis is beyond the scope of this article, a primary concern is that long-term safety of e-cigarettes has not been established and e-cigarettes are pending regulation by the FDA. At this time, NRT has more safety data and the unknown long-term risks of e-cigarette use need to be considered with patients. Future studies should aim to identify the most effective strength of e-cigarettes, as the trials reviewed differed in e-cigarette brands and strengths. To determine this, it may be beneficial to assess baseline nicotine use in milligrams per day or number of cigarettes smoked per day and examine if these affect the ideal e-cigarette strength. Also, to increase external validity, future studies should target patients intending to quit. Additionally, none of the reviewed trials were completed in the United States. Since smoking cessation attitudes may differ by location, multinational studies would be beneficial. Overall, further multinational studies should focus on long-term safety, optimal dosing, patients' intending to quit, and comparisons to NRT.

Declaration of Conflicting Interests

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