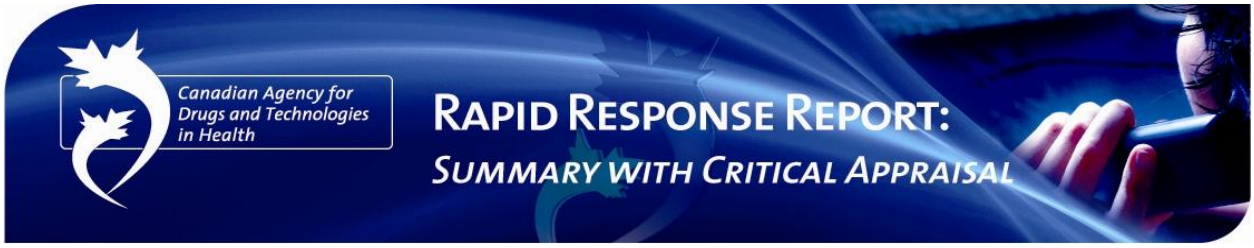

TITLE: Electronic Cigarettes: A Review of the Clinical Evidence and Safety

DATE: 13 August 2012

CONTEXT AND POLICY ISSUES

Electronic-cigarettes (e-cigarettes) are an electronic nicotine delivery device powered by a battery, often resembling a cigarette.[1,2] E-cigarettes consist of a plastic tube, an electronic heating element, a liquid nicotine cartridge, and a lithium battery and atomization chamber with a membrane to suspend ingredients.[3] Their main function is to deliver nicotine to the respiratory system without tobacco combustion, and hence they are marketed as a safer alternative to smoking, as they eliminate the harmful tars and carbon monoxide.[4] Propylene glycol, a chemical used to generate artificial "smoke" is added to the liquid vehicle to simulate the appearance of using a real cigarette.[5] Artificial aromas and flavors are also added to the liquid vehicle.[5] Because most e-cigarettes are designed to look like traditional cigarettes, they can simulate the visual, sensory and behavioral aspects of smoking.[4]

Information on the pharmacology, toxicology, and safety of e-cigarettes is limited.[4] Some tobacco-specific impurities and potential harmful chemical products are found in the commonly available brands of e-cigarettes.[6-8] Most e-cigarettes and mixtures are manufactured in China.[9] Both US Food and Drug Administration[10,11] and Health Canada[12] have issued warnings of health risks posed by e-cigarettes. Because of the lack of data about their safety and efficacy, e-cigarettes have been banned in Australia, Canada, Singapore and Brazil.[1,2] However, consumer interest in e-cigarettes is growing rapidly and concerns about their unregulated use are increasing.[13]

The purpose of this report is to review the clinical evidence regarding the utility, safety and harms associated with electronic cigarettes for smoking cessation in adults.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the utility of electronic cigarettes for smoking cessation?
2. What is the clinical evidence regarding the safety and harms associated with electronic cigarettes and the associated cartridges?

KEY MESSAGE

Low-quality evidence showed that e-cigarette use can reduce the desire to smoke. Awareness of the product has increased among smokers, who use e-cigarettes for smoking reduction. Side effects of e-cigarette use in the included studies were minor, with the exception of one case of exogenous lipoid pneumonia associated with e-cigarette use.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including Ovid MEDLINE, Ovid PsycINFO, PubMed, The Cochrane Library (2012, Issue 6), University of York Centre for Reviews and Dissemination (CRD), ECRI (Health Devices Gold) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and July 13, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients who smoke
Intervention	Electronic cigarettes Electronic nicotine delivery systems
Comparator	Any
Outcomes	Safety Efficacy/utility Harms
Study Designs	Heath technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized controlled trials, case series and case studies

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were duplicate publications of the same study, or included in a selected health technology assessment or systematic review.

Critical Appraisal of Individual Studies

The quality of the included studies was assessed using the Downs and Black checklist.[14] Formal critical appraisal of case studies and case series was not performed, as these are considered to be inferior quality. The quality of these studies will be discussed with other limitations.

For the critical appraisal of studies, a numeric score was not calculated. Instead, the strength and limitations of the study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 41 citations. Upon screening titles and abstracts, 15 potential relevant articles were retrieved for full-text review. Two additional relevant reports were retrieved from previous CADTH report.[15] Of the 17 potentially relevant articles, 10 met the inclusion criteria. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

Two RCTs, one before-after study, five surveys and two case reports were retrieved. The study characteristics are summarized in Appendix 2.

<u>Randomized controlled trials</u>

The trial by Dawkins et al. 2012[5] examined whether the e-cigarette can reduce desire to smoke and abstinence-related withdrawal symptoms over a 20 minute period. A total of 86 smokers were randomly allocated to either 18 mg nicotine e-cigarette (nicotine), 0 mg e-cigarette (placebo), or just hold the e-cigarette (just hold) groups. The three groups did not significantly differ in age, gender, ethnicity or nicotine dependence ($P > 0.15$ in all cases). Participants rated their desire to smoke and withdrawal symptoms at baseline (T1), five minutes (T2), and 20 minutes (T3) after using the e-cigarette for 5 minutes. The six nicotine withdrawal symptoms examined were depression, irritability, anxiety, restlessness, hunger, and poor concentration. A subset of participants (N=60, 29 females) also completed the Letter Cancellation Task and the Brown-Peterson Working Memory Task between T2 and T3. The first author of this trial had a collaborative relationship with Electronic Cigarette Company (TECC) who supplied the e-cigarettes and cartridges for this study.

The trial by Bullen et al. 2010[16] measured the short-term effects of e-cigarettes on desire to smoke, withdrawal symptoms, acceptability, pharmacokinetic properties and adverse effects in a cross-over trial design. A total of 40 adult (47.6 ± 12.4 years) dependent smokers (20.2 ± 7.3 cigarettes smoked per day) were randomly assigned to use one of four different products: e-cigarette containing nicotine (16 mg), placebo (0 mg), Nicorette nicotine inhaler or their usual cigarette on each of four study days three days apart, with overnight smoking abstinence before use of each product. The primary outcome was change in desire to smoke measured by an 11-point visual analog scale before and at various intervals within one hour of use. Secondary outcomes were withdrawal symptoms, acceptability and adverse events. This trial was sponsored by industry, Ruyan Group (Holdings) Limited.

Uncontrolled before-after study

The before-after study by Polosa et al. 2011[17] examined the efficacy and safety of the e-cigarettes in long-term smoking cessation and smoking reduction in regular smokers who were experimenting with e-cigarettes. A total of 40 regular and relatively healthy smokers (26 males, 14 females, mean age 42.9 ± 8.8 years) were recruited from a local hospital in Italy. Participants were invited to attend a total of five study visits: at baseline, week-4, week-8, week-12 and week-24. Outcome measures were product use, number of cigarettes smoked, exhaled carbon monoxide level, smoking reduction and abstinence rates, adverse events and product preferences. The study was supported by e-cigarette company (Arbi Group SrI, Italy).

Surveys

The internet survey by Etter and Bullen 2011[18] assessed the profile, utilization pattern, satisfaction and perceived effects among users of e-cigarettes. There were a total of 3,587 participants who had median age of 41 years, were 61% men and 70% were former smokers. The participants were from the US (62%), France (14%), UK (6%), Switzerland (4%), Canada (3%) and other countries (11%). The questionnaire covered utilization, satisfaction, reasons for use, reasons for stopping use, withdrawal symptoms, and adverse events of using e-cigarettes. One of the authors had previously received research funding from e-cigarette company (Ruyan, Hong Kong).

The face-to-face survey by Foulds et al. 2011[19] aimed to identify the e-cigarette used by experienced e-cigarette users, their pattern of e-cigarette use and the impact on tobacco use. The survey took place during a 3-hour session of a meeting of e-cigarette enthusiasts in Philadelphia, USA. Of the 105 questionnaires returned from 110 handed out, 104 were included in data analysis. The authors declared that they had no financial connections with the tobacco or electronic cigarette industries.

McQueen et al. 2011[20] conducted an interview (survey) with 15 e-cigarette users from an e-cigarette convention (MidWest Vapefest in St. Louis, MO, USA, in August 2010) to better understand e-cigarettes as well as the personal experiences and motivations of e-cigarette users. Interview length ranged from 39 to 79 minutes. The study was not sponsored by industry.

The customer-based mail-in survey by Regan et al. 2011[21] assessed the awareness, mode of use of e-cigarettes, demographic characteristics and tobacco use of e-cigarette users. The survey was completed by 10,587 adults in 2009 (response rate=49.8%) and 10,328 adults in 2010 (response rate=51.6%). Source of funding for this study was not reported.

The study by Seigel et al. 2011[22] examined the effectiveness of e-cigarettes for smoking cessation using an online (email) survey of smokers who purchased a particular brand (Blu) of e-cigarettes during a 2-week period. The email invitation was sent to potential subjects seven months after their initial e-cigarette purchase. Of 222 respondents (response rate 4.5%), data of 216 were included in the analyses. Participant characteristics, e-cigarette use patterns and 6-month smoking status were examined. Source of funding for this study was not reported.

Case reports

The case study by McCauley et al. 2012[23] reported a case of a 42-year-old woman who had been using e-cigarettes for 7 months prior, and was admitted to the hospital with a 7-month

history of dyspnea, productive cough, and subjective fevers. In the hospital, the patient was under physical examination, and multiple laboratory tests. The authors reported that they had no conflict of interest with any companies/organizations.

The case study by Caponnetto et al. 2011[24] reported three cases of heavy smokers who had experience with the e-cigarettes. Those were Caucasian smokers (two men aged 47 and 65 years and one woman aged 38 years) with history of recurrent relapses after multiple attempts to quit smoking using FDA-approved medications and counseling. Source of funding was not reported.

Summary of Critical Appraisal

Strengths and limitations of the individual studies are provided in Appendix 3.

Both RCTs[5,16] were single-blinded. Random assignment was not concealed from staff and there was no attempt to blind those measuring the main outcomes. Neither RCT provided a list of principle confounders, nor an adequate adjustment for confounding in the analyses. It was unclear whether the trials had sufficient power to detect a clinically important effect, although one trial[16] mentioned a power calculation. Adverse events were reported in one trial.[16] However, the objectives, main outcomes to be measured and interventions of interest were explicit in both trials. Statistical tests used to assess the main outcomes were appropriate, as both trials provided estimates of the random variability in the data and reported the actual P-values. The outcome measures were clearly described, and participants in the intervention groups were recruited from the same population, over the same period of time, and were randomly assigned to each group.

Of the eight included observational studies, two were case studies reporting one patient[23] and three participants,[24] one before-after study,[17] and five surveys.[18-22] One of the main limitations of the before-after study was the threat of selection bias due to its non-randomized nature. In addition, there was no attempt to blind those measuring the main outcomes, and it was unclear whether the study had sufficient power to detect a clinically important effect, although the study did report a power calculation. The main limitations of the surveys were that the inclusion or exclusion criteria of the participants were not explicit, power calculation for primary outcomes were not reported, and sufficient power to detect a clinically important effect was not determined. However, objectives and main outcomes to be measured were explicit, and participants were recruited from the same population and over the same period of time in all surveys. Actual probability values were reported in all except one survey.[20]

Summary of Findings

The overall findings are summarized below, and findings from the individual studies and authors' conclusions are provided in Appendix 4.

<u>Randomized controlled trials:</u>

In the trial by Dawkins et al., 2012[5] the desire to smoke after using the e-cigarettes declined over time for both 18 mg nicotine e-cigarette (nicotine) and placebo groups compared to just holding the e-cigarette (just hold) group. The difference was statistically significant for males and females from 5 to 20 minutes (Males: Just hold vs. nicotine: $P < 0.001$; Just hold vs. placebo: $P < 0.05$; Females: Just hold vs. nicotine: $P < 0.05$; Just hold vs. placebo: $P < 0.01$).

Comparing the nicotine and placebo groups, the desire to smoke was significantly reduced for males ($P < 0.05$), but not for females ($P > 0.05$).

Males in the nicotine group experienced a statistically significant decline in symptoms such as anxiety, poor concentration, irritability and restlessness compared to just hold ($P < 0.01$) and placebo ($P < 0.05$) groups, while females in the nicotine and just hold groups were associated with a statistically significant decline in depression and poor concentration compared with the placebo ($P < 0.05$).

For the letter cancelation task, there was no significant difference between groups in the speed to complete task, but the number of errors made was significantly worse in the just hold group versus placebo ($P < 0.05$).

For memory test, the nicotine group performed consistently better with significant group differences at all times tested. More individuals in the nicotine group achieved correct recall compared to placebo ($P < 0.004$) or to just hold group ($P < 0.004$).

This trial did not report safety outcomes of e-cigarettes.

It was concluded that the e-cigarettes can reduce the desire to smoke and withdrawal symptoms 20 minutes after use, particularly for males, and can improve working memory performance.

In the 2010 trial by Bullen et al.,[16] participants using the 16 mg nicotine e-cigarette had a greater decrease in the desire to smoke over a 60 minute period compared to placebo (-2.6 units vs. -1.8 units; mean difference 0.82, 95% confidence interval [CI] 0.25 to 1.38, $P = 0.006$).

The use of 16 mg nicotine e-cigarettes was associated with a reduction of irritability, restlessness and poor concentration compared with placebo, but the differences were not statistically significant.

When adjusted for multiple comparisons, the reduction in desire to smoke observed with the 16 mg nicotine e-cigarette compared to placebo was no longer significant ($P = 0.21$). The use of usual cigarettes significantly reduced the desire to smoke compared to 16 mg nicotine e-cigarette ($P = 0.003$), placebo ($P < 0.0001$) or Nicorette inhaler ($P = 0.001$). No significant difference in desire to smoke was found between 16 mg nicotine e-cigarette and Nicorette inhaler ($P = 0.99$), or between placebo and Nicorette inhaler ($P = 0.33$).

Compared to the Nicorette inhaler, the 16 mg nicotine e-cigarette was rated higher for pleasantness by 1.49 units (95% CI 9.23 to 2.74, $P = 0.016$). Among participants, 58% said they preferred the e-cigarettes, 25% preferred the inhalator and 13% liked neither.

Pharmacokinetics showed that the usual cigarettes achieved the fastest time to peak nicotine concentration followed by the 16 mg nicotine e-cigarettes and the Nicorette inhaler. Usual cigarettes also attained highest Cmax for nicotine than other products.

The most frequently reported adverse events were mouth and throat irritation, which were most common with the Nicorette inhaler (88%) and less with 16 mg nicotine e-cigarette (38%). Nausea was more common in the 16 mg nicotine e-cigarette (29%) than the Nicorette inhaler (18%). No serious adverse events such as death or hospitalization occurred during the study.

It was concluded that the use of 16 mg e-cigarettes could reduce the desire to smoke after overnight abstinence, was well tolerated and had a pharmacokinetic profile similar to Nicorette inhaler.

Uncontrolled before-after study

In the before-after study by Polosa et al. 2011,[17] at week-24, 32.5% of the regular smokers using e-cigarettes were able to reduce the number of cigarettes/day by 50%, 12.5% sustained reduction in number of cigarette/day by 80%, and 22.5% sustained smoking abstinence. The adverse events associated with e-cigarettes were mouth irritation (20.6%), throat irritation (32.4%) and dry cough (32.4%), which were diminished over by week-24. It was concluded that e-cigarettes can help smokers to reduce cigarette consumption without major adverse events.

Surveys

Of the 3,587 adult participants in the internet survey by Etter and Bullen 2011,[18] 83.5% were e-cigarette users, 15.2% never users, and 1.3% past users. The brands of e-cigarette used varied by countries. Among daily users, the median duration was 3 months, with 15% using for one or more years. Daily users drew an average of 120 puffs per day, refilled their e-cigarettes an average 5 times a day, and spent US$33 per month for their e-cigarettes. Most (96%) bought their e-cigarettes on the internet and mainly used at home (98%) or in their car (90%). Over 90% of current smokers and former smokers reported that e-cigarettes helped them to reduce or to quit smoking, respectively. Only 10% still experienced the urge to smoke while using the e-cigarettes. Common adverse events were burned throat (22%) and dry mouth/throat (26%). There were some concerns that e-cigarettes might be toxic (6%), or could lead to dependence (8%). Reasons for use of the e-cigarettes included avoiding toxic effects of tobacco (84%), quitting smoking or avoiding relapse (77%), dealing with craving for tobacco (79%), dealing with tobacco withdrawal symptoms (67%) and economic reasons (57%). Forty-seven individuals stopped using e-cigarettes. Reasons for discontinuing were: because they did not need them anymore, thought they would not relapse to smoking if they stopped, product quality, did not reduce craving, relapse to smoking, did not help them to quit smoking, feared its side effects, or replaced with a smoking cessation medication. Of the e-cigarette users, 90% felt that e-cigarettes helped to relieve craving to smoke, and 0.9% reported having used e-cigarettes to inhale other substances. Compared to current smokers, those who stopped smoking were more likely to use e-cigarettes and to ever use smoking cessation medications, used e-cigarettes over a longer period of time, took more puffs per day, and more likely to report that e-cigarettes helped them to quit or reduce smoking. It was concluded that e-cigarettes were used by former smokers to avoid relapse and as an aid to reduce or to quit smoking.

In the face-to-face survey by Foulds et al. 2011,[19] the participants (experienced e-cigarette users) were heavy smokers and two-thirds of those had tried to quit using smoking cessation medication. Seventy-three percent started the e-cigarettes with the intention to quit smoking, and 99% felt that the e-cigarettes had helped them to succeed in quitting smoking. Two-thirds used e-cigarette liquid with medium to high concentrations of nicotine (≥ 13 mg/cartridge), and the majority of experienced e-cigarette users did not use the most widely sold e-cigarettes ('NJOY' and 'Smoking Everywhere'), but used models that were larger in size, with higher voltage battery power. Safety outcomes were not reported in this study. It was concluded that smokers should be advised to use proven treatments (e.g. counseling and FDA-approved medicines) until more evidence on the safety and efficacy of e-cigarettes for smoking cessation is available.

In the interview survey of 81 e-cigarette users by McQueen et al. 2011,[20] most users were heavy smokers who used e-cigarettes to reduce health risk from tobacco smoking or to quit smoking, and who perceived that e-cigarette use was less expensive than tobacco smoking.

The reported benefits of the e-cigarettes included sense of taste and smell, ability to be physically active, and less coughing and breathlessness. Many e-cigarette users reported using lower nicotine concentrations over time and planned to use non-nicotine liquid in the future. E-cigarette users expressed concerns about potential bans in the future by the authorities, and demonstrated enthusiasm for research and advocacy. It was concluded that e-cigarette users report health benefits typical for smoking cessation despite continued using the e-cigarettes and was willing to participate in research.

The customer-based mail-in survey by Regan et al, 2011[21] showed that the awareness of e-cigarettes doubled from 16.4% in 2009 to 32.2% in 2010 ($P < 0.01$). The largest increase in awareness was among current smokers and adults between 35 and 40 years of age. Men had heard about e-cigarettes more often than women (odds ratio [OR] 1.34, 95% CI 1.17 to 1.53), but they were less likely to try e-cigarettes (OR 0.59, 95% CI 0.40 to 0.86). Those with less than high school education were less likely to heard about e-cigarettes (OR 0.67, 95% CI 0.47 to 0.96), but they were more likely to try e-cigarettes (OR 2.90, 95% CI 1.13 to 7.45), and more likely to have used e-cigarettes in the past month (OR 3.47, 95% CI 1.15 to 10.46) than those who earned a college degree or higher education. There was no difference in awareness between adults of different incomes, or between races. Current cigarette smokers were more likely to heard about e-cigarettes (OR 2.50, 95% CI 2.09 to 3.00), more likely to have tried (OR 5.71, 95% CI 3.72 to 8.76), and more likely to have used e-cigarettes in the past month (OR 3.06, 95% CI 1.72 to 5.42) than never-cigarettes. Tobacco users were more likely to try e-cigarettes (OR 5.55, 95% CI 3.80 to 8.11), and more likely to use e-cigarettes in the past month (OR 4.21, 95% CI 2.35 to 7.01) compared to non-tobacco users smokers. Among current cigarette smokers, the plans to quit smoking were similar between those who tried e-cigarettes and those who had never tried e-cigarettes. Thus, this study showed that there was a large increase in awareness and the use of e-cigarettes during the 1-year period survey.

The results of the online survey of first-time e-cigarette purchasers (N=216 respondents) by Seigel et al. 2011[22] showed that 66.8% respondents reported having reduced the number of cigarettes smoked per day after trying e-cigarettes, 49.3% reported reducing nicotine use, and 48.8% indicated that they quit smoking for a period of time after trying e-cigarettes. There were 31% of respondents reported not smoking in 6 months (95% CI 24.8% to 37.2%). Of those who stopped smoking, 56.7% were using e-cigarettes, 9.0% were using tobacco free nicotine products, and 34.3% were completely nicotine-free. Those respondents using e-cigarettes more than 20 times per day had quit rate of 70.0%. It was concluded that e-cigarettes are a promising smoking cessation aid.

Case reports

In the case study by McCauley et al., 2012[23] all physical examinations of the patient, except for bilateral rales, were normal. Results of laboratory tests showed blood counts were normal and microbiology for bacteria and viruses was negative. Chest radiography revealed new focal bilateral opacities, and CT images showed extensive bilateral upper- and lower-lobe patchy ground glass pulmonary opacities in a “crazy paving” pattern. Bronchoalveolar lavage cytological examination revealed abundant lipid-laden macrophages. The patient was diagnosed to have exogenous lipoid pneumonia due to e-cigarette use. The patient’s symptoms were improved after and chest radiograph was normal after she stopped using the e-cigarettes. According to the authors of the study, this is the first published case of exogenous lipoid pneumonia due to the use of glycerin-based e-cigarettes.

The case study by Caponnetto et al. 2011[24] reported successful smoking cessation with e-cigarettes in three heavy smokers who had a history of recurring relapses. They were prescribed smoking cessation medications and counseling, but relapse occurred after treatment. All three patients had used nicotine containing e-cigarettes two years prior. One stopped using e-cigarettes a few months later and had abstained from tobacco smoking for about 6 months, one was able to stop smoking after three months using e-cigarettes, and one was able to stop smoking after two months with e-cigarettes. The e-cigarette was well tolerated with no reported adverse events in all three patients, except for occasional dry cough reported in one patient. It was concluded that smokers who repeatedly failed to quit smoking with counseling and pharmacological therapies could achieved smoking cessation after using e-cigarettes.

Limitations

Evidence on the utility and safety of e-cigarettes was limited to two small RCTs (n = 86 and n = 40) of short study follow-up (20 to 60 minutes) and observational studies, which included two case studies, one before-after study and five surveys. The RCTs were designed to investigate the short term effects of e-cigarettes on the desire to smoke and withdraw symptoms, but did not assess the effect on quitting or smoking abstinence of the e-cigarette use. One RCT reported adverse events after brief e-cigarette use without providing any statistical analysis.[16] The population in the before-after study was small (n = 40), and 32.5% of the participants were lost to follow-up at their final visit. Hence the results observed may be due to a chance finding and not to a true effect. The assessments of withdrawal symptoms, cognition, awareness, utilization, satisfaction and other outcome measures such as adverse events in the surveys were not rigorous, and were likely affected by recall bias. Case studies are considered inferior quality evidence and while they are useful for capturing individual potentially rare events, they do not give an indication of the frequency of these events. Four studies had relationships with or were sponsored by the industry, and three did not report the source of funding. Therefore, the evidence should be considered with caution.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

No research has been conducted to test the safety and efficacy of e-cigarettes as smoking cessation aids. The findings of two small and short-term RCTs suggest that e-cigarettes can reduce the desire to smoke and reduce withdrawal symptoms. Evidence on the increased awareness, utility and safety of e-cigarettes was reported in one before-after and five survey studies, which found potential benefits of e-cigarettes in helping smokers to reduce cigarettes consumption, to prevent relapse, and to help smoking cessation without major side effects. Interpretation of those findings should be made with caution, as they derived from low-quality evidence and some studies were either sponsored by industry or did not report the source of funding. One study, however, reported a case where a woman was diagnosed to have exogenous lipoid pneumonia due to e-cigarettes use. Given the limitations of the current low-quality evidence, the safety, efficacy and utility of e-cigarettes remain to be determined.

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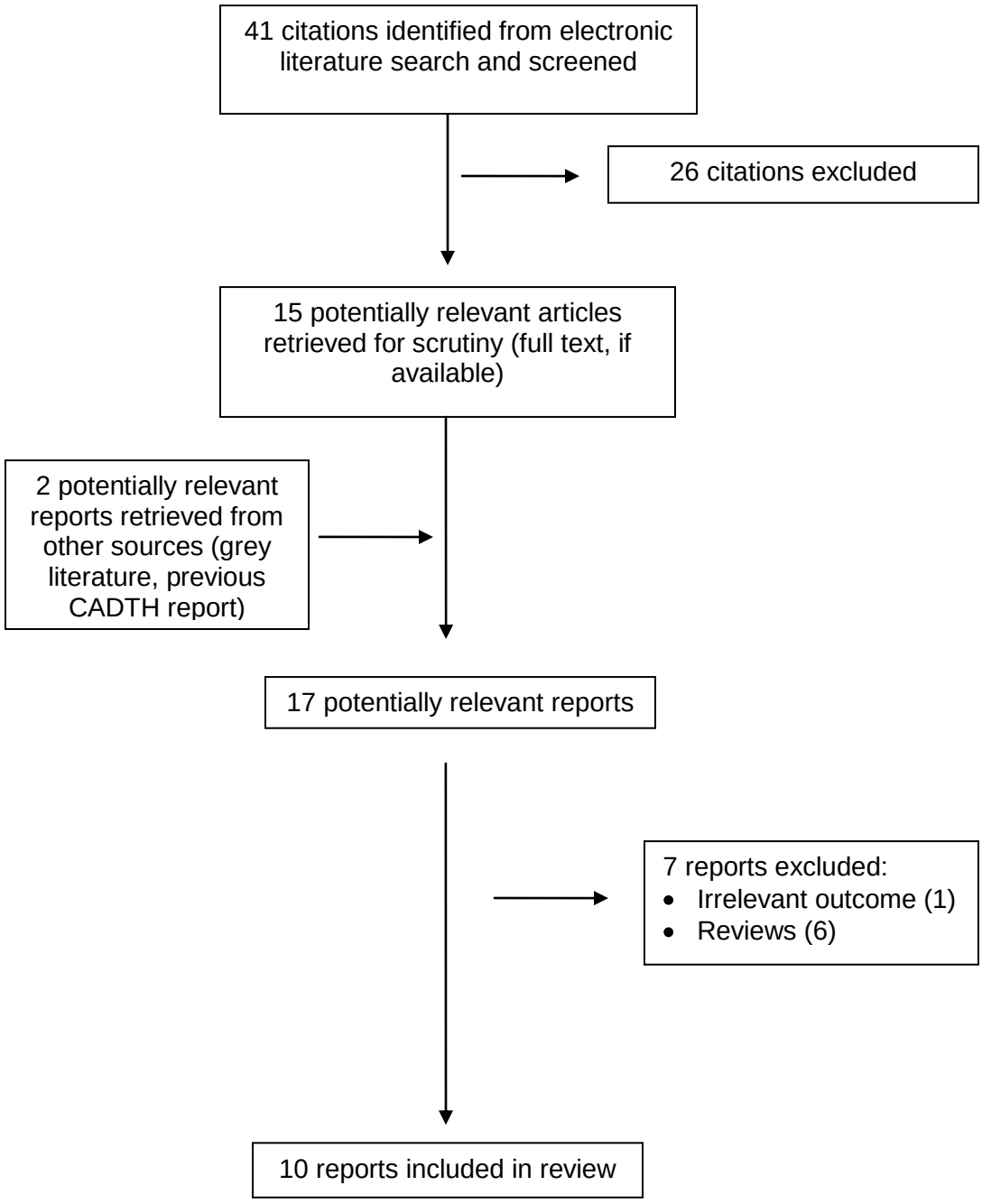
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Clinical Study

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Intervention	Comparators	Clinical Outcomes
Dawkins et al., 2012[5] UK	RCT; single-blind 20 minutes Baseline (T1) 5 min (T2) 20 min (T3) after using (or just hold) the electronic cigarette	86 e-cigarette naïve smokers (43 female, 43 male; age range: 18-52 [mean: 28.8])	Nicotine (18 mg nicotine electronic-cigarette)	• Placebo (0 mg nicotine electronic-cigarette) • Just hold e-cigarette	• Desire to smoke • Mood and physical symptoms • Letter cancelation task • Brown-Peterson Memory Test
Bullen et al. 2010[16] Australia	RCT; single-blind Four study days, 3 days apart	40 adult dependent smokers Age (mean ± SD): 47.6 ± 12.4 years 53% women Average 20.2 ± 7.3 cigarettes per day	Electronic-cigarettes (16 mg nicotine)	Placebo (0 mg nicotine electronic-cigarette)	• Desire to smoke and withdrawal symptoms • Product preferences • Pharmacokinetics • Adverse events
Polosa et al. 2011[17] Italy	Uncontrolled before-after study 24 weeks (5 visits)	40 regular smokers (unwilling to quit). invited to use the 'Catagoria' e-cigarette with a focus on smoking reduction and smoking abstinence 26 males, 14 females; mean ± SD age of 42.9 ± 8.8 years Regular smokers (mean ± SD): 34.9 ± 14.7 pack/years	Electronic-cigarettes	NA	• 50% reduction in the number of cigarettes/day at week-24 • 80% reduction in the number of cigarettes/day at week-24 • Sustained smoking abstinence at week-24 (quitters)
Etter and Bullen 2011[18] New Zealand	Internet survey	3587 participants (70% former tobacco smokers, 61% men, mean age 41 years)	Electronic-cigarettes	NA	Internet questionnaire • Participant characteristic • Daily users versus never users of e-cigarettes • Utilization • Satisfaction • Reasons for use • Reasons for stopping use • Withdrawal symptoms

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Intervention	Comparators	Clinical Outcomes
					• Use to inhale other substances • Comparing current and former tobacco smokers
Foulds et al. 2011[19] USA	Survey 3-hour interview	104 experienced e-cigarette users	Electronic-cigarettes	NA	• Demographics • Electronic-cigarette use history • Tobacco use history • Beliefs about electronic-cigarette
McQueen et al. 2011[20] USA	Survey Interview length: 39 – 79 min	15 electronic-cigarette users from a convention	Electronic-cigarettes	NA	• Personal experience • Motivation of using electronic-cigarettes
Regan et al. 2011[21] USA	Survey Consumer-based mail-in survey in 2009 and 2010	10, 587 adults in 2009 and 10,328 adults in 2010	Electronic-cigarettes	NA	• Awareness • ever use and past month use of e-cigarettes from 2009 to 2010 • demographic characteristics and tobacco use of e-cigarette users
Siegel et al. 2011[22] USA	Survey Online survey (7 months after initial e-cigarette purchase)	216 adult respondents who had tried e-cigarettes 71.5% male, 28.5% female 81.1% had smoked for ≥ 6 years 64.7% reported having made ≥ 3 quit attempts	Electronic-cigarettes	NA	• Cessation or reduction of tobacco after e-cigarette use • E-cigarette use pattern and 6-month smoking status
McCauley et al., 2012[23] USA	Case study	A 42-year-old women admitted to hospital with a 7-month history of dyspnea, productive cough and subjective fevers <u>Medical history</u>: asthma, rheumatoid arthritis, fibromyalgia,	Used electronic-cigarette about 7 months prior	NA	• Physical examination • Laboratory tests and imaging findings • Diagnosis

First Author, Publication Year, Country	Study Design, Length of Follow-up	Patient characteristics, sample Size (n)	Intervention	Comparators	Clinical Outcomes
		schizoaffective disorder, and hypertension Medications: amlodipine, albuterol metered dose inhaler, lovastatin, lisonopril, multiple vitamins, cyclobenzaprine, citalopram, and multiple psychiatric medications			
Caponnetto et al. 2011[24] Italy	Case study	Three heavy smokers, Caucasians (2 men aged 47 and 65 years, and one woman aged 38 years), with history of recurrent relapses	Electronic-cigarettes	NA	• Smoking abstinence for at least 6 months
NA=not applicable; **RCT**=randomized controlled trial					

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
Dawkins et al., 2012[5] UK	• Hypothesis/objective, main outcomes to be measured, and interventions of interest were explicit • The study provided estimates of the random variability in the data and actual p-values were reported • Attempt was made to blind study subjects • Statistical tests used to assess the main outcomes were appropriate • The outcome measures were clearly described • Participants in intervention groups were recruited from the same population, over the same period of time, and were randomized to the interventions groups • Study subjects were randomized to the intervention groups	• The inclusion/exclusion criteria of included patients and the main findings of the study were not clearly described • All important adverse events were not reported • The study did not identify the source of population recruited • No attempt was made to blind those measuring the main outcomes • A list of principal confounders was not provided • Unable to determine compliance with the interventions • Random assignment was not concealed from staff • Unable to determine if there was adequate adjustment for confounding in the analyses • The trial did not report power calculation, or did not have sufficient power to detect a clinically important effect
Bullen et al. 2010[16] Australia	• Hypothesis/objective, main outcomes to be measured, patient characteristics and interventions of interest were explicit • The study provided estimates of the random variability in the data and actual p-values were reported • All important adverse events were reported • Attempt was made to blind study subjects • Statistical tests used to assess the main outcomes were appropriate • The outcome measures were clearly described • Participants in intervention groups were recruited from the same population, over the same period of time, and were randomized to the interventions groups • Study subjects were randomized to the intervention groups • Loss of patients to follow-up were taken into account (intention-to-treat analysis) • The trial did report power calculation	• The main findings of the study were not clearly described • A list of principal confounders was not provided • The characteristics of patients lost to follow-up were not described • Unable to determine if the subjects asked or prepared to participate in the study representative of the entire population from which they were recruited • No attempt was made to blind those measuring the main outcomes • Unable to determine compliance with the interventions • Random assignment was not concealed from staff • Unable to determine if there was adequate adjustment for confounding in the analyses • Unable to determine if the trial had sufficient power to detect a clinically important effect
Polosa et al. 2011[17] Italy	• Hypothesis/objective, main outcomes to be measured and characteristics of participants were explicit • All important adverse events were reported • The characteristics of participants lost to follow-up were described • Probability (actual p value) was reported for main outcome • Participants represented the entire population	• No attempt was made to blind those measuring the main outcomes • Non-RCT (uncontrolled before-after) • Unable to determine if the study had sufficient power to detect a clinically important effect

First Author, Publication Year	Strengths	Limitations
	• No retrospective unplanned subgroup analyses were reported • Follow-up was the same for all participants • Participants in intervention groups were recruited from the same population and over the same period of time • The study did report power calculation	
Etter and Bullen 2011[18] New Zealand	• Hypothesis/objective and main outcomes to be measured were explicit • Adverse events were reported • Probability (actual p value) was reported • Participants represented the entire population • Participants in intervention groups were recruited from the same population and over the same period of time	• Inclusion/exclusion criteria of the participants were not explicit • No attempt was made to blind those measuring the main outcomes • Non-RCT (survey) • No power calculation for primary outcome was reported • Unable to determine if the study had sufficient power to detect a clinically important effect
Foulds et al. 2011[19] USA	• Hypothesis/objective and main outcomes to be measured were explicit • Probability (actual p value) was reported • Participants represented the entire population • Participants in intervention groups were recruited from the same population and over the same period of time	• Inclusion/exclusion criteria of the participants were not explicit • Adverse events were not reported • No attempt was made to blind those measuring the main outcomes • Non-RCT (survey) • No power calculation for primary outcome was reported • Unable to determine if the study had sufficient power to detect a clinically important effect
McQueen et al. 2011[20] USA	• Hypothesis/objective and main outcomes to be measured were explicit • No retrospective unplanned subgroup analyses were reported • Participants in intervention groups were recruited from the same population and over the same period of time	• Inclusion/exclusion criteria of the participants were not explicit • Adverse events were not reported • Actual probability values were not reported • Unable to determine if participants represented the entire population • No attempt was made to blind those measuring the main outcomes • Non-RCT (survey) • No power calculation for primary outcome was reported • Unable to determine if the study had sufficient power to detect a clinically important effect
Regan et al. 2011[21] USA	• Hypothesis/objective and main outcomes to be measured were explicit • Probability (actual p value) was reported • Participants represented the entire population • Participants in intervention groups were recruited from the same population and over the same period of time	• Inclusion/exclusion criteria of the participants were not explicit • Adverse events were not reported • No attempt was made to blind those measuring the main outcomes • Non-RCT (survey) • No power calculation for primary outcome was reported • Unable to determine if the study had sufficient power to detect a clinically important effect

First Author, Publication Year	Strengths	Limitations
Siegel et al. 2011[22] USA	• Hypothesis/objective and main outcomes to be measured were explicit • Probability (actual p value) was reported • Participants represented the entire population • Participants in intervention groups were recruited from the same population and over the same period of time	• Inclusion/exclusion criteria of the participants were not explicit • Adverse events were not reported • No attempt was made to blind those measuring the main outcomes • Non-RCT (survey) • No power calculation for primary outcome was reported • Unable to determine if the study had sufficient power to detect a clinically important effect
McCauley et al., 2012[23] USA	•	• Case study of one patients
Caponnetto et al. 2011[24] Italy	•	• Case study of three participants

APPENDIX 4: Main Study Findings and Authors' Conclusions

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings</th></tr>
<tr><td>Dawkins et al., 2012[5]

UK</td><td><u>Q1: Efficacy / utility</u>
<u>Desire to smoke</u>
• Desire to smoke declined overtime for both Nicotine and Placebo groups compared to Just hold
  • Males: Just hold vs. nicotine: P < 0.001; Just hold vs. placebo: P < 0.05
  • Females: Just hold vs. nicotine: P < 0.05; Just hold vs. placebo: P < 0.01
• Desire to smoke significantly declined for the Nicotine vs. Placebo for males (P < 0.05), but not females (P > 0.05)

<u>Mood and Physical Symptoms Scale (MPSS)</u>
• Males: after 20 min, decline in symptoms (anxiety, poor concentration, irritability, and restlessness) in the nicotine group was significantly lower than the Just hold (P < 0.01) and Placebo (P < 0.05) groups.
• Females: after 20 min, decline in symptoms (depression, poor concentration) in the nicotine and just hold groups was significantly lower than Placebo (P < 0.05) group.

<u>Letter cancelation task</u>
• No significant difference between groups in the speed to complete task
• Number of errors made: worse in Just hold vs. Placebo (P < 0.05)

<u>Brown-Peterson Memory Test</u>
• Nicotine group performed consistently better with significant group differences at 6 s (P < 0.05), 12 s (P < 0.05), 15 s (P < 0.01) and 18 s (P < 0.01)
• More individuals in the Nicotine group achieved correct recall vs. Placebo at 15 s and 18 s interval (P < 0.004), and vs. Just hold group at 18 s interval (P < 0.004)
<u>Q2: Safety / harms</u>
Not reported</td></tr>
<tr><td colspan="2">Authors' Conclusions: "Our findings suggest that the electronic cigarette can reduce desire to smoke and nicotine withdrawal symptoms 20 min after use and that the nicotine content may be more important for males. This also the first study to demonstrate that the nicotine e-cigarette can improve working memory performance. Taken together these findings suggest that the electronic cigarette may aid smoking cessation and highlights the need for further research regarding the importance of the nicotine content and effects on a wider repertoire of cognitive functioning." p972-973</td></tr>
<tr><td>Bullen et al. 2010[16]

Australia</td><td><u>Q1: Efficacy / utility</u>

Primary comparison of change in desire to smoke and other withdrawal symptoms from baseline between 0 to 16 mg nicotine e-cigarette
<table>
<tr><th>Withdrawal symptom*</th><th>Mean change (95% CI)</th><th>P value</th></tr>
<tr><td>Desire to smoke</td><td>0.82 (0.25 to 1.38)</td><td>0.006</td></tr>
<tr><td>Irritability</td><td>0.26 (-0.48 to 0.99)</td><td>0.48</td></tr>
<tr><td>Restlessness</td><td>0.53 (-0.11 to 1.18)</td><td>0.10</td></tr>
<tr><td>Poor concentration</td><td>0.39 (-0.30 to 1.07)</td><td>0.26</td></tr>
</table>
*Visual analogue scale 0 to 10

Secondary analyses using multivariate* comparison of change in desire to smoke from baseline between all products
<table>
<tr><th>Product comparison</th><th>Mean difference (95% CI)</th><th>Adjusted p value</th></tr>
<tr><td>0 mg vs. 16 mg nicotine e-cigarette</td><td>0.80 (-0.27 to 1.86)</td><td>0.21</td></tr>
<tr><td>0 mg vs. Nicorette inhaler</td><td>0.69 (-0.38 to 1.77)</td><td>0.33</td></tr>
<tr><td>0 mg vs. usual cigarette</td><td>2.23 (1.17 to 3.30)</td><td><0.0001</td></tr>
<tr><td>16 mg vs. Nicorette inhaler</td><td>-0.10 (-1.16 to 0.95)</td><td>0.99</td></tr>
<tr><td>16 mg vs. usual cigarette</td><td>1.44 (0.39 to 2.48)</td><td>0.003</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>First Author, Publication Year, Country</th><th>Main Findings</th></tr>
<tr><td></td><td>
<table>
<tr><td>Nicorette inhaler vs. usual cigarette</td><td>1.54 (0.48 to 2.59)</td><td>0.001</td></tr>
</table>
*Multivariate analysis was used to adjust for treatment period, baseline craving, within-participant correlation as a random effect and multiple comparison using Tukey-Kramer method

<table>
<tr><th>Product</th><th>Mean tmax (min) (95% CI)</th><th>Mean Cmax (ng/ml) (95% CI)*</th></tr>
<tr><td>Usual cigarette (n=9)</td><td>14.3 (8.8 to 19.9)</td><td>13.4 (6.5 to 20.3)</td></tr>
<tr><td>16 mg nicotine e-cigarette (n=8)</td><td>19.6 (4.9 to 34.2)</td><td>1.3 (0.0 to 2.6)</td></tr>
<tr><td>Nicorette inhalator (n=10)</td><td>32.0 (18.7 to 45.3)</td><td>2.1 (1.0 to 3.1)</td></tr>
</table>
*Corrected for baseline nicotine levels

<table>
<tr><th rowspan="2">Adverse event</th><th colspan="2">0 mg e-cigarette</th><th colspan="2">16 mg e-cigarette</th><th colspan="2">Nicorette inhalator</th></tr>
<tr><th>n/N*</th><th>%</th><th>n/N</th><th>%</th><th>n/N</th><th>%</th></tr>
<tr><td>Mouth/throat irritation†</td><td>14/64</td><td>22</td><td>22/58</td><td>38</td><td>36/41</td><td>88</td></tr>
<tr><td>Aching jaws</td><td>4/35</td><td>11</td><td>3/37</td><td>8</td><td>2/37</td><td>5</td></tr>
<tr><td>Nausea</td><td>6/33</td><td>18</td><td>9/31</td><td>29</td><td>6/36</td><td>18</td></tr>
<tr><td>Flatulence/belching/hiccups/heartburn</td><td>6/111</td><td>5</td><td>6/113</td><td>5</td><td>11/147</td><td>23</td></tr>
<tr><td>Vertigo/feeling high</td><td>9/69</td><td>9</td><td>14/66</td><td>21</td><td>12/66</td><td>18</td></tr>
<tr><td>Headache</td><td>7/32</td><td>22</td><td>6/34</td><td>18</td><td>6/33</td><td>18</td></tr>
<tr><td>Sweatiness/clammy skin</td><td>3/75</td><td>4</td><td>3/77</td><td>4</td><td>2/76</td><td>3</td></tr>
<tr><td>Palpitations</td><td>0/38</td><td>0</td><td>2/38</td><td>5</td><td>0/39</td><td>0</td></tr>
</table>
*n=number of events, N=number of participants in each group. In some cases, groups were pooled because of similarity of symptoms, hence the large numbers

† 0 mg vs. inhalator P < 0.001; 16 mg vs. inhalator P < 0.001
</td></tr>
<tr><td colspan="2">Authors' Conclusions: "The 16 mg Ruyan V8 electronic nicotine delivery device (ENDD) alleviated desire to smoke after overnight abstinence was well tolerated and had a pharmacokinetic profile more like the Nicorette inhalator than a tobacco cigarette. Evaluation of the ENDD for longer-term safety, potential for long-term use and efficacy as a cessation aid is needed." p.98</td></tr>
<tr><td>Polosa et al. 2011[17]

Italy</td><td><u>Q1: Efficacy / utility</u>
• 27 out of 40 participants completed the study at week-24
• Characteristics of those lost to follow-up were not different from participants who completed the study
• With intention-to-treat (ITT) analysis, 32.5% (13/40) sustained 50% reduction in the number of cigarette/day at week-24; median of 25 cigarettes/day decreasing to 6 cigarettes/day (P < 0.001)
• 12.5% (5/40) sustained 80% reduction at week-24; median of 30 cigarettes/day decreasing to 6 cigarettes/day (P = 0.043)
• 22.5% (9/40) sustained smoking abstinence at week-24; 6/9 still using e-cigarettes by the end of the study
• 2 to 3 cartridges/day were used throughout the study

<u>Q2: Safety / harms</u>
• Mouth (20.6%) and throat (32.4%) irritation
• Dry cough (32.4%)
• These adverse effects diminished substantially by week-24</td></tr>
<tr><td colspan="2">Authors' Conclusions: "The use of e-Cigarette substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit." p.1</td></tr>
<tr><td>Etter and Bullen 2011[18]

New Zealand</td><td><u>Q1: Efficacy / utility and Q2: Safety</u>
<u>Participant characteristics</u>
• 3587 participants, median age 41 years, 61% men, 705 former smokers
• Learned about the survey from different websites</td></tr>
</table>

First Author, Publication Year, Country	Main Findings
	• 58% of participants had university diploma, income above average • 83.5% were e-cigarettes users, 15.2% never users, 1.3% past users <u>Daily users versus never users of e-cigarettes</u> • Men: 65% vs. 46%, P < 0.001 • Former smokers: 77% vs. 42%, P < 0.001 • Have ever used bupropion: 30% vs. 19%, P < 0.001 • Nicotine therapy: 70% vs. 64%, P < 0.001 • Number of cigarettes smoked among current smokers: 13 vs. 16 cigarettes/day, P < 0.001 • Before started using e-cigarettes: 25 vs. 16 cigarettes/day, p≤0.001 • Trying to quit smoking: 71% vs. 51%, P < 0.001 • Trying to reduce tobacco use: 96% vs. 72% • More confident in their ability to quit ('very sure'): 17% vs. 6%, P < 0.001 • COPD questionnaire: 1.25 vs. 1.79, P < 0.001 • Duration of smoking abstinence among former smokers: 105 days vs. 150 days, P = 0.001 <u>Utilization</u> • Most-used brands varied by countries • Among daily users, the median duration was 3 months, but 15% had been using for one or more years. • Daily users drew an average of 120 puffs per day • Median capacity of refill bottles was 20 ml, median nicotine concentration was 18 mg.ml • Daily users used 2 bottles of refill liquid per months, refilled their e-cigarettes 5 times a day, each refill or cartridge lasted 2 hours • The average price per kit was 60 $US, and Daily users spent 33 $US per month for their e-cigarettes (including refill liquid and cartridges, batteries, components) • 96% bought e-cigarettes on the internet • 45% intended to continue using them for another year or more • Mainly used at home (98%), in their car (90%), and at work (71%), but less frequent in cafes/restaurants/bars/discos (43%), in public transport (15%) or during business meeting (13%) <u>Satisfaction</u> • 92% of current smokers reported that e-cigarettes helped them to reduce smoking • 96% of former smokers reported that e-cigarettes helped them to quit smoking • 89% of users said that it was easy to abstain from smoking while using e-cigarettes • 94% of users are willing to recommend to a friend • 10% still experienced the urge to smoke while using the e-cigarettes • 79% of former smokers feared that they would relapse to smoking if they stopped using it • 91% like the taste and sensation of the e-cigarettes • 22-26% reported that it burned the throat or gave a dry mouth or dry throat • There were concerns that e-cigarettes might be toxic (6%), or could lead to dependence (8%) • 83% feared that it might one day be banned by authorities <u>Reasons for use</u> • 84% perceived that e-cigarettes were less toxic than tobacco • 77% used it to quit smoking or avoid relapsing • 79% used it to deal with craving for tobacco • 67% used it to deal with tobacco withdraw symptoms • 57% though that e-cigarettes were cheaper than smoking <u>Reasons for stop using</u> • 47 individuals stopped using e-cigarettes because they did not need them anymore, thought they would not relapse to smoking if they stopped, product's poor quality, did not reduced graving, relapse to smoking, did not help them to quit smoking, feared its side

First Author, Publication Year, Country	Main Findings
	effects or replaced with a smoking cessation Withdrawal symptoms • 90% felt that e-cigarettes helped to relieve craving to smoke Use to inhale other substance • 0.9% reported having used e-cigarettes to inhale other substances (cannabis, vitamins, flavors, and vodka) Comparing current and former tobacco smokers • Former smokers were more likely than current smokers to use the e-cigarettes and to have ever used smoking cessation medications • Former smokers used e-cigarettes longer than current smokers • Former smokers took more puffs per day, were less likely to use tobacco flavor, and spent more per month • Former smokers were more likely to say that the e-cigarette helped them to quit or reduce their smoking
Authors' Conclusions: "E-cigarettes were used mainly by former smokers as an aid to quit smoking and avoid relapse. These products were perceived as satisfactory, useful and efficacious, and almost all users preferred nicotine-containing e-cigarettes. Despite its limitations, this study adds to the still small body of knowledge about e-cigarettes and provides valuable additional information for smokers, clinicians, regulators and policy makers. Further research should address the safety and efficacy of using e-cigarettes to deliver nicotine and other substances, and assess their effectiveness as an aid to quitting and relapse prevention." p.2027	
Foulds et al. 2011[19] USA	**Q1: Efficacy / utility** Demographics: • Heavy smokers (25 cigarettes per day) • Had tried to quit smoking an average of nine times before using e-cigarettes • 2/3 had tried to quit smoking using FDA-approved smoking cessation medication E-cigarettes use history: • Used e-cigarettes at least a year, and used on a daily basis • Number of uses per day: 10 min or 10-20 puffs • 73% started e-cigarettes with the intention to quit smoking • 99% felt that the e-cigarettes had help them to succeed in quitting smoking • 2/3 used e-cigarettes liquid with a medium to high concentration of nicotine (≥13 mg / cartridge) • Majority of experienced e-cigarettes users did not use the most widely sold e-cigarettes ('NJOY' and 'Smoking Everywhere'), but used models that were larger in size, with higher voltage battery power **Q2: Safety / harms** Not reported
Authors' Conclusions: "Until we have more evidence on the safety and efficacy of e-cigarettes for smoking cessation, smokers should be advised to use proven treatments (e.g. counseling and FDA-approved medicines). However, for those who have successfully switched to e-cigarettes, the priority should be staying off cigarettes, rather than quitting e-cigarettes." p.1037	
McQueen et al. 2011[20] USA	**Q1: Efficacy / utility** Learning about e-cigarettes • Learned about e-cigarettes from friends, advertisements, and internet sites Learning curve to vaping • New users must learn to get the right device, to get enough liquid in advance, and to operate the e-cigarette efficiently. Motives and perceived benefits of using e-cigarettes • Most of e-cigarettes users were heavy smokers who hope that e-cigarettes will reduce their health risks • Vaping was usually perceived to be less expensive than smoking • Used e-cigarettes to get nicotine and not tars, or to quit smoking • Reported benefits included sense of taste and smell, ability to be physically active, and

First Author, Publication Year, Country	Main Findings
	less coughing and breathlessness Reduced nicotine tolerance and dependence • Using lower nicotine concentrations overtime • Some planned to use non-nicotine liquids in the future • Some can wait longer period without vaping Users' interest in research and advocacy • E-cigarette users are vocal about potential bans • Vapers demonstrated enthusiasm for research and advocacy by citing studies they have read • eagerly offering to help with any future studies • Encouraging other smokers to try vaping • Actively voicing their support of e-cigarettes to government authorities. **Q2: Safety / harms** Not reported
Authors' Conclusions: "We did not have to interview many vapers to learn that vaping is not like smoking. Vapers follow a learning curve that involves selecting among numerous devices, components, liquids, and techniques. Additionally, vaping involves adapting to evolving products and maintenance issues and changing personal needs and preferences. The complexities of vaping have important implications for novice users, retailers, scientists, and policy makers. Experienced users report health gains typical for smoking cessation despite continued vaping and appears to be willing research participants. Independent research on the first- and second-hand effects of e-cig aerosols is urgently needed to inform use and regulation of e-cigs as well as determine the utility of conducting further studies to assess the safety and efficacy of e-cigs as smoking cessation aid. Additionally, research is needed to assess the effects on health if e-cigs are used long term. Future research will require transdisciplinary efforts, which may be better informed by tapping the expertise of experienced vapers." p. 865	
Regan et al. 2011[21] USA	**Q1: Efficacy / utility** Awareness • Doubled from 16.4% in 2009 to 32.2% in 2010 (P < 0.001) • Largest increase in awareness were current smokers (20.7% in 2009 to 49.6% in 2010); and adults between 35 and 44 years of age (16.4% in 2009 to 37.1 in 2010) • Ever use of e-cigarettes (0.6% in 2009 to 2.7% in 2010, P < 0.01) • Men had heard about e-cigarettes more often than women (OR 1.34, 95% CI 1.17 – 1.53) • Men were less likely to try e-cigarettes than women (OR 0.59, 95% CI 0.40 – 0.86) • Those with less than high school education were less likely to heard about e-cigarettes (OR 0.67, 95% CI 0.47 – 0.96), but they were more likely to try e-cigarettes (OR 2.90, 95% CI 1.13 – 7.45), and more likely to have used e-cigarettes in the past month (OR 3.47, 95% CI 1.15 – 10.46) than those who earned a college degree or higher education. • No difference in awareness between adults of different incomes, or between races • Current cigarette smokers were more likely to heard about e-cigarettes (OR 2.50, 95% CI 2.09 – 3.00), more likely to have tried (OR 5.71, 95% CI 3.72 – 8.76), and more likely to have used e-cigarettes in the past month (OR 3.06, 95% CI 1.72 – 5.42) than never-cigarettes smokers • Tobacco users were more likely to try e-cigarettes (OR 5.55, 95% CI 3.80 – 8.11), and more likely to use e-cigarettes in the past month (OR 4.21, 95% CI 2.35 – 7.01) compared to non-tobacco users • Among current cigarette smokers, the plans to quit smoking were similar between those who tried e-cigarettes and those who had never tried e-cigarettes **Q2: Safety / harms** Not reported
Authors' Conclusions: "Given the large increase in awareness and ever use of e-cigarettes during this 1-year period and the unknown impact of e-cigarettes use on cigarette smoking behaviors and long-term health, continued monitoring of these products is needed." p.1	
Siegel et al.	**Q1: Efficacy / utility**

First Author, Publication Year, Country	Main Findings
2011[22] USA	Cessation or reduction of tobacco after e-cigarette use • 66.8% respondents reported having reduced the number of cigarettes smoked per day after trying e-cigarettes • 49.3% reported reducing nicotine use • 48.8% indicated that they quit smoking for a period of time after trying e-cigarettes E-cigarette use patterns and 6-month smoking status • 31% of respondents were not smoking in 6 months (95% CI 24.8% - 37.2%) • Of those were not smoking at 6 months, 56.7% were using e-cigarettes, 9.0% were using tobacco free nicotine products, and 34.3% were completely nicotine-free • Those respondents using e-cigarettes more than 20 times per day had quit rate of 70.0% **Q2: Safety / harms** Not reported
Authors' Conclusions: "Findings suggest that e-cigarettes may hold promise as a smoking-cessation method and that they are worthy of further study using more-rigorous research designs." p.472	
McCauley et al., 2012[23] USA	**Q1: Efficacy / utility** Not reported **Q2: Safety / harms** Physical examination Her physical examinations were normal except for bilateral rales Laboratory tests and imaging findings • WBC count of 18.0 x 10^3 with a normal differential and hemoglobin level of 11.2 g/dL • Chemistry panel and brain natriuretic peptide levels were normal • Chest radiographic: new multifocal bilateral opacities • CT images: extensive bilateral upper- and lower-lobe patchy ground glass pulmonary opacities in a "crazy paving" pattern • HIV test: negative • Nasal *pertussis* PCR swab: negative • Urine *Legionella* antigen and serum *Mycoplasma* IgG and IgM tests: negative • Hypersensitivity pneumonitis panel, extracted nuclear panel, and tests for antinuclear antibody, cyclic citrullinated peptide, and rheumatoid factor: negative • Bird fancier's panel: trace reactivity to pigeon and parrot droppings • Bronchoscopy and BAL: 48% neutrophils, 8% lymphocytes, 43% monocytes, and 1% eosinophils • All bacterial and viral cultures: negative • Fungal culture: light growth of *Candida* • Viral DFA panel: *Pneumocyctis jeroveci* DFA and *Legionella* antigen tests were negative • Bronchoalveolar lavage cytological examination: abundant lipid-laden macrophages Diagnosis Exogenous lipoid pneumonia due to e-cigarette use Clinical course The patient was instructed to avoid the use of e-cigarettes, and, subsequently, her symptoms improved. A follow-up chest radiograph was normal, and pulmonary function testing showed mild diffusion impairment but no obstructive or restrictive defects.
Authors' Conclusions: "most cases of exogenous lipoid pneumonia are associated with aspiration of mineral oil or lipid-based preparations…To our knowledge, there are no prior published cases of exogenous lipoid pneumonia due to the use of glycerin-based e-cigarettes. Importantly, this case highlights harm caused by the nicotine-solution carrier and the delivery system of the e-cigarette…, the risk of lipoid pneumonia adds another dimension to the supercharged social, political, and medical debate surrounding the regulation and legality of e-cigarette use." p1112-1113	

First Author, Publication Year, Country	Main Findings
Caponnetto et al. 2011[24] Italy	**Q1: Efficacy / utility** Patient 1: 47-year old Caucasian male lawyer, smoked 32 cigarettes per day, CO reading at baseline was 31 ppm. He was prescribed nicotine patches and bupropion with smoking cessation counseling, but relapsed a month after treatment. He started using e-cigarette (7.2 mg nicotine per cartridge) two years ago, was able to stop tobacco smoking a few weeks later, and stopped using e-cigarettes a few months later. He has been abstinence from tobacco smoking for approximately 6 months (CO = 4 ppm). Patient 2: A 38-year-old Caucasian female social worker, smoked 28 cigarettes per day, CO reading at baseline was 29 ppm. He was prescribed nicotine patches and bupropion with smoking cessation counseling. Her last relapse occurred two years ago. He started using e-cigarette (7.2 mg nicotine per cartridge) two years ago, was able to stop tobacco smoking three months later, kept using e-cigarette with high nicotine concentration for another month, then switched to mentholated cartridges, and now uses frequently during social events. He has been abstinence from tobacco smoking for approximately 7 months (CO = 2 ppm), with no reported lapse or relapse. Patient 3: A 65-year-old Caucasian male pharmacist with COPD, smoked nearly 50 years, smoked 30-40 cigarettes per day (CO=34.9 ppm at baseline), had past history of alcohol abuse, was prescribed nicotine patches and attended group counseling sessions, and was lost to follow-up. He started using e-cigarette (loaded with nicotine cartridge) two years ago, was able to stop tobacco smoking two months later, continue using e-cigarette on a regular basis. Abstinence from tobacco smoking was confirmed (CO=5 ppm). **Q2: Safety / harms** Patient 2: The e-cigarette was well tolerated with occasional dry cough. Patients 1 and 3: The e-cigarette was well tolerated with no reported adverse events.
Authors' Conclusions: "This is the first time that objective measure of smoking cessation are reported for smokers who quit successfully after using an E-cigarette. This was accomplished in smokers who repeatedly failed in previous attempts with professional smoking cessation assistance using the usual nicotine dependence treatments and smoking cessation counseling." p.1	