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Review

## Electronic Cigarettes for Smoking Cessation: A Systematic Review

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### Abstract

**Background and Aims:** Electronic cigarettes (e-cigarettes) have been steadily increasing in popularity among smokers, most of whom report using them to quit smoking. This study systematically reviews the current literature on the effectiveness of e-cigarettes as cessation aids.

**Methods:** We searched PubMed, MEDLINE, PsycINFO, CINAHL, ERIC, ROVER, Scopus, ISI Web of Science, Cochrane Library, the Ontario Tobacco Research Unit (OTRU) library catalogue, and various gray literature sources. We included all English-language, empirical quantitative and qualitative papers that investigated primary cessation outcomes (smoking abstinence or reduction) or secondary outcomes (abstinence-related withdrawal symptoms and craving reductions) and were published on or before February 1, 2016.

**Results:** Literature searches identified 2855 references. After removing duplicates and screening for eligibility, 62 relevant references were reviewed and appraised. In accordance with the GRADE system, the quality of the evidence in support of e-cigarettes' effectiveness in helping smokers quit was assessed as very low to low, and the evidence on smoking reduction was assessed as very low to moderate. The majority of included studies found that e-cigarettes, especially second-generation types, could alleviate smoking withdrawal symptoms and cravings in laboratory settings.

**Conclusions:** While the majority of studies demonstrate a positive relationship between e-cigarette use and smoking cessation, the evidence remains inconclusive due to the low quality of the research published to date. Well-designed randomized controlled trials and longitudinal, population studies are needed to further elucidate the role of e-cigarettes in smoking cessation.

**Implications:** This is the most comprehensive systematic evidence review to examine the relationship between e-cigarette use and smoking cessation among smokers. This review offers balanced and rigorous qualitative and quantitative analyses of published evidence on the effectiveness of e-cigarette use for smoking abstinence and reduction as well as important outcomes such as withdrawal symptoms and craving to smoke. While inconclusive due to low quality, overall the existing literature suggests e-cigarettes may be helpful for some smokers for quitting or reducing smoking. However, more carefully designed and scientifically sound studies are urgently needed to establish unequivocally the long-term cessation effects of e-cigarettes and to better understand of how and when e-cigarettes may be helpful.

## Introduction

Tobacco use, particularly cigarette smoking, remains among the top causes of preventable death and disease. More than one-sixth of the world's population (1.1 billion people) currently smokes cigarettes. It is estimated that every year 6 million individuals die worldwide from smoking-related chronic diseases.<sup>1</sup> Although nicotine replacement therapies (NRTs; nicotine gum, patch, lozenges, sprays, and inhalers), bupropion SR, and varenicline have been approved by regulatory drug agencies as safe and efficacious in achieving smoking cessation outcomes, cessation rates remain stubbornly low.<sup>2</sup>

Electronic cigarettes (or e-cigarettes) have become increasingly popular among smokers in recent years.<sup>3</sup> E-cigarettes contain a heating unit that aerosolizes vegetable glycerin and/or propylene glycol mixed with flavorings and various concentrations of nicotine (or no nicotine). Earlier e-cigarette models resemble combustible cigarettes in shape and are disposable, while newer types are rechargeable, use refillable cartridges, and may have variable power settings. Many cigarette smokers report trying e-cigarettes for the purpose of quitting or reducing cigarette smoking.<sup>4</sup> The industry and some advocates claim that e-cigarettes are effective cessation supports with little or no associated risk.<sup>5</sup>

To date, five systematic reviews have been published that investigate the efficacy or effectiveness of e-cigarettes for cessation. Franck et al.<sup>6</sup> reviewed seven studies published before September 2013, of which three were assessed using the Cochrane criteria. They concluded that there remains significant uncertainty about the efficacy of e-cigarettes for cessation due to methodological weaknesses. In 2014, the Cochrane Collaboration published a systematic review that examined 13 completed studies, of which two randomized controlled trials (RCTs) were synthesized in a meta-analysis, and nine ongoing trials. The paper concluded that evidence supporting e-cigarettes' efficacy for smoking cessation was low due to the small number of well-conducted studies on the subject.<sup>7</sup> Rahman et al.<sup>8</sup> reviewed the evidence published up to May 2014 and synthesized data from six studies, only two of which were RCTs and were included in a meta-analysis. Their findings underscored the relative efficacy of nicotine-containing e-cigarettes for smoking cessation and reduction when compared to nicotine-free ones; however, the review could not establish conclusively if e-cigarettes were more efficacious than other cessation methods such as NRTs. Conversely, Kalkhoran and Glantz<sup>9</sup> examined the effects of e-cigarettes use on quitting and reducing smoking in 38 peer-reviewed articles on PubMed and Web of Science until June 17, 2015, and concluded that e-cigarette use was associated with less quitting. The authors included 20 experimental and observational studies with control groups in a random-effects meta-analysis. Notably, a significant amount of variability was present in these studies, jeopardizing the validity of the meta-analysis results. Lam and West<sup>10</sup> searched only three databases in February 2015 to include four RCTs. Based on a qualitative analysis of these studies, the authors concluded that further research is needed to confirm the positive results of single studies.

This systematic review addresses important gaps in the literature on the effectiveness and efficacy of e-cigarettes as cessation aids. All but one of the previous systematic reviews excluded population cross-sectional studies and were limited to published peer-reviewed literature. To address the rapidly changing landscape of research on e-cigarettes in an environment where high quality evidence remains scarce, we undertook a comprehensive review of both the published peer-reviewed and gray literatures, until February 2016. This review is the most comprehensive to date and includes several

studies published since the Cochrane review and others were completed. It employs a rigorous design to thoroughly assess the evidence from various disciplines and methodological approaches, taking into account methodological weaknesses of individual studies during data synthesis. This design allows for a more careful and balanced understanding of the existing knowledge. This review aims to examine the effectiveness of e-cigarettes as smoking cessation aids in terms of smoking abstinence and reduction, as well as two other important cessation outcomes: alleviation of withdrawal symptoms and urges to smoke.

## Methods

The systematic review protocol followed PRISMA guidelines for best practice in systematic reviews<sup>11</sup> and was prospectively registered with the PROSPERO registry for systematic reviews.<sup>12</sup> The final PRISMA record is shown in Figure 1.

### Identification

Peer-reviewed literature was searched using PubMed, MEDLINE, PsycINFO, CINAHL, ERIC, ROVER, Scopus, ISI Web of Science, Cochrane Library, and the Ontario Tobacco Research Unit (OTRU) library catalogue. Gray literature was searched using Grey Matters, OAIster, Open Grey, the NYAM Web site, the Legacy Library, BIOSIS Previews, Conference Papers Index, ISI Proceedings, Dissertation Abstracts International, CIHI, and Grey Net International. All search metadata were saved. Where possible, searches queried both title and keyword for official and slang terms related to e-cigarettes and smoking cessation.<sup>12</sup> Queries searched publications up to February 1, 2016. Literature searches identified a total of 2855 references, of which 1303 were duplicates.

### Eligibility Screening

The remaining 1552 references and abstracts were screened by two reviewers using DistillerSR, an online software application for systematic reviews. We included any English-language publications that contained original data related to e-cigarettes and smoking cessation (except studies on public awareness only), excluding literature reviews; business reports; commentaries and discussion papers; news articles; fact sheets; and position/policy statements. Authors of abstracts, posters, and presentations were contacted for further information; those who did not respond or showed potential conflict of interest (COI) were excluded. Inclusion required one reviewer, exclusion two reviewers (blind to each other), and conflicts were automatically flagged and resolved through discussion or by a third reviewer. We excluded 1048 records, leaving 504 references for review. Of these, 62 pertained to smoking cessation. Figure 1 illustrates the search strategy for identification and selection of relevant studies.

### Quality Assessment

To accommodate the broad scope and methodological heterogeneity of the literature, references were assessed using a version of Kmet et al.'s<sup>13</sup> QualSyst tool, which we modified for the present review by merging the quantitative and qualitative checklists and revising criteria based on guidelines from the Cochrane Handbook.<sup>14</sup> The resulting tool evaluates 16 indicators of reporting quality, study design and methodology, sample representativeness, instrument validity/reliability, statistical analysis, reflexivity, and risk of bias. For each

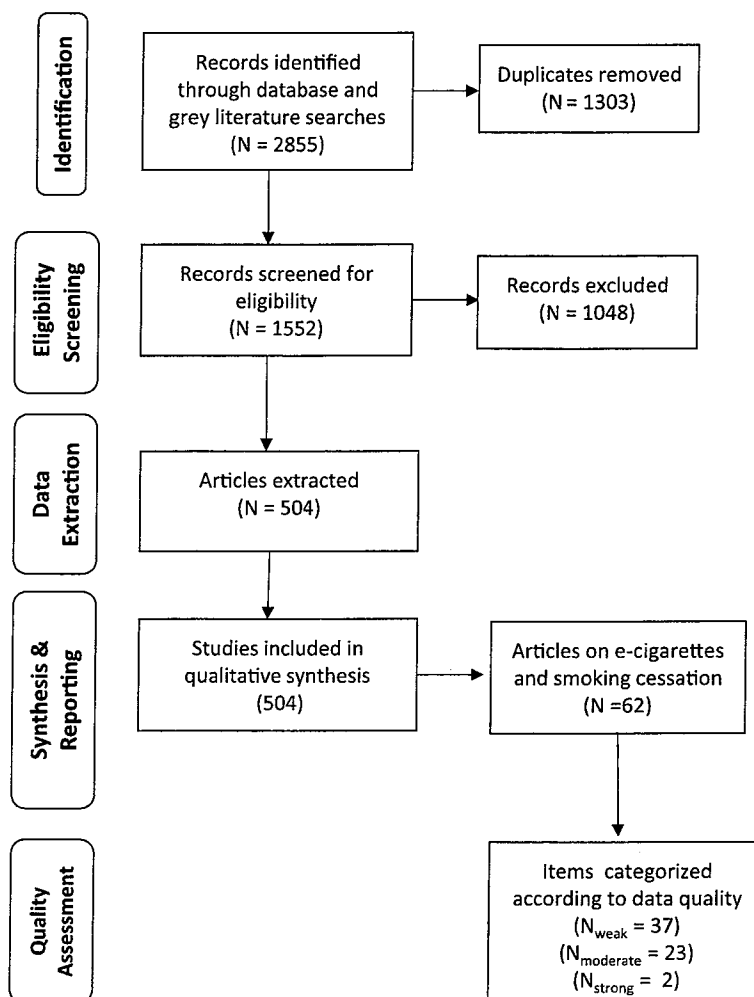


Figure 1. PRISMA flowchart showing search strategy for identification and selection of relevant studies.

article, the tool generates a summary score value between 0 and 1 and a resulting rating of *weak* (0.00–0.49), *moderate* (0.50–0.74), or *strong* (0.75–1.00). Ratings were calibrated to maximize interrater agreement on a sample of 29 reviewed articles.<sup>13</sup> Quality was assessed by one reviewer; when a quality rating was overruled, a second, blinded reviewer provided a second assessment. COI was appraised separately but informed reviewers' quality assessments; a separate form on DistillerSR was created to document (COI), while a question on the quality assessment form was used to evaluate the potential influence of a present researcher bias. Disagreements and final scores/ratings were decided through interreviewer discussion.

The intention of our quality assessment strategy was to ensure that studies were evaluated on their own merit and not against each other. In other words, a cross-sectional study with a large representative sample and strong analytical design (eg, Brown et al.<sup>15</sup>) and a well-designed RCT could receive a quantitative score with an equivalent assessment of strong. Downgrading a final score was considered when a single flaw in the methodological (eg, sampling bias) or analytical approach (eg, choice of statistical test or lack thereof) or limitations in the design cumulatively compromised the validity of the findings and hence warranted lowering the score (see Supplementary Appendix A for examples of studies whose quality scores were downgraded and why).

Interrater agreement was tested using the intraclass correlation coefficient (ICC)<sup>16</sup> on a random selection of 10% of references at the beginning, midpoint, and end of the review. In test 1, the two reviewers showed *good* agreement<sup>17</sup> on 10 articles,  $ICC(2,1) = .687, P < .01$ , 95% confidence interval (CI): 0.190, 0.910. In test 2, the two reviewers showed *excellent* agreement on 10 articles,  $ICC(2,1) = .875$ , 95% CI: 0.570, 0.967. The review team was then joined by a third researcher, so the final test sample size was increased to 20 articles, resulting in *good* interrater agreement,  $ICC(2,1) = .602$ , 95% CI (0.353, 0.800). Overall agreement was *good*.

Due to the small number of studies added in the second phase of data collection and inclusion which preceded the publication of this manuscript ( $N = 15$ ), we could not conduct an interclass correlation analysis of interrater agreement. Instead, the two researchers compared their quality assessment scores for five random studies (31% of sample), showing a score difference range of 0–0.16. The researchers agreed on the final quality assessment for all five studies (ie, weak, moderate, or strong), demonstrating confidence in the consistency of quality assessment.

### Data Analysis and Synthesis

This review examines four smoking cessation-related outcomes: two primary (smoking abstinence and reduction) and two secondary

(withdrawal symptoms and urges to smoke) outcomes. Abstinence outcome measures are 7-day point prevalence, 30-day point prevalence, or continuous abstinence for the duration of the study. Due to substantially higher relapse rates associated with short-term abstinence from smoking,<sup>2</sup> our analysis focuses only on abstinence and reduction outcomes measured at follow-up points of at least 30 days. Relevant findings relating to primary outcomes from moderate and strong papers were synthesized using summary tables where appropriate. The body of evidence related to primary and secondary cessation outcomes was assessed using the GRADE system adopted by the Cochrane Collaboration for evidence quality evaluation.<sup>14</sup> Findings from weak studies were excluded from the analysis but are presented in data tables in Supplementary Appendices B and C. However, those with potentially interesting hypothesis-generating findings are also discussed.

## Results

This review identified 62 articles that investigated primary (smoking abstinence or reduction at the longest follow-up point reported) and/or secondary (withdrawal symptoms and craving or urges to smoke) outcomes related to e-cigarettes' efficacy or effectiveness as a smoking cessation aid. According to our quality assessment criteria, these articles consisted of 37 weak studies, 23 moderate studies, and only 2 with a strong quality assessment result (see Table 1 for a breakdown of included papers).

### Primary Outcomes: Smoking Abstinence and Reduction

This section examines two primary outcomes for cessation, abstinence and smoking reduction at various long-term follow-up points beyond 30 days. Our review identified 15 relevant studies that were individually assessed as moderate or strong. Three relevant studies were excluded from the analysis for various reasons. One RCT comparing the cessation outcomes of e-cigarettes with inhalers within a 3-day study period is excluded from the analysis as it measured abstinence within a period of less than 7 days.<sup>18</sup> Two other studies by Copp et al.<sup>19</sup> and by Kalkhoran et al.<sup>20</sup> are also excluded from this analysis, as they did not examine the cessation outcomes under study. Three other studies examined specific populations or smoker groups, such as patients with schizophrenia or cancer, or smokers enrolled in a cessation program,<sup>21-23</sup> and are discussed in Supplementary Appendix A. One study examined the association between e-cigarette use duration and smoking cessation.<sup>24</sup> Synthesized results from the

remaining 11 studies (using smokers from the general population) are expressed as ranges of values according to each reported outcome measures (see Tables 2-5). Refer to Supplementary Appendix A for a narrative assessment of each study.

Two studies compared the use of e-cigarettes with NRTs in terms of smoking abstinence and reduction outcomes found that e-cigarettes with nicotine may be more effective than NRTs for smoking cessation. A well-designed cross-sectional study of 5863 English smokers by Brown et al.<sup>15</sup> rated as strong found that e-cigarette users were 1.63 times more likely than NRT users to quit smoking, even after adjusting for age, sex, socioeconomic status, quit attempts in the past year, urges to smoke, and year of the survey. In addition, an RCT by Bullen et al.<sup>33</sup> compared cessation outcomes of two groups of smokers attempting to quit using nicotine e-cigarettes versus NRT, respectively, demonstrating higher abstinence and larger reduction in cigarettes smoked per day in the e-cigarette group (7.3% vs. 5.8%). The results from the latter study lacked statistical significance—one of the limitations that resulted in downgrading the study's quality from strong to moderate. Despite the high quality scores of these two studies, due to a lack of other comparative studies, evidence for e-cigarettes' cessation aid effectiveness as compared to NRT remains weak and inconclusive.

While the majority of the moderate to strong studies included in this analysis of primary outcome measures yielded results supporting e-cigarettes, two studies did not. First, a cross-sectional survey by Christensen et al.<sup>28</sup> showed that use of e-cigarettes was negatively associated with quitting (adjusted odds ratio [AOR]: 0.10; 95% CI: 0.05, 0.22). These results, however, are difficult to interpret as e-cigarette users may have still been in the process of quitting while the survey was conducted. Another study by Grana et al.<sup>29</sup> found that e-cigarette users at baseline were less likely to have quit smoking 1 year later. This result was based on a small subsample of 88 smokers who used e-cigarettes (including only eight quitters) and was not statistically significant.

A study of moderate quality by Lechner et al.<sup>24</sup> whose results were not quantitatively synthesized, investigated the effects of e-cigarette use duration on smoking and found a positive association: increased duration of e-cigarette use slightly increased the likelihood of being an ex-smoker (OR: 1.003;  $P = .012$ ) and was associated with a greater reduction in smoking ( $P < .001$ ). Another moderate study by the same research team<sup>25</sup> confirmed this finding: among 215 vape store customers smoking abstinence was five times more likely among prolonged e-cigarette users (OR: 4.9; 95% CI: 2.11, 11.16;  $P < .001$ ).

Based on a GRADE analysis of the synthesized results from 10 moderately to strongly rated studies, the overall evidence supporting the effectiveness of e-cigarettes as a smoking cessation or reduction aid was found to be weak. Specifically, the GRADE score for evidence of abstinence was very low to low and was very low to moderate for smoking reduction. Although 11 of the 14 studies individually rated as moderate or strong provide some evidence suggesting e-cigarettes' effectiveness for smoking abstinence and reduction, it is not possible to draw reliable conclusions from the complete body of evidence due to serious methodological limitations, such as design weaknesses (eg, predominance of cross-sectional surveys and paucity of controlled studies), high risk of bias (eg, sampling problems and inadequate blinding), and low reliability of results (eg, wide CIs or lack of statistical significance). Refer to Supplementary Appendix A for a discussion of the limitations of moderate and strong study.

**Table 1.** Overview of Included Studies According to Quality Assessment and Methodological Approach

Overview of included articles on smoking cessation (N = 62)				
Primary outcomes, N = 45; secondary outcomes, N = 19				
Study type	Quality assessment			Total
	Strong (S)	Moderate (M)	Weak (W)	
RCT	0	5	5	10
Experimental	1	7	8	16
Longitudinal	0	5	13	18
Cross-sectional	1	6	12	19

RCT = randomized controlled trial.

**Table 2.** Synthesized Results From Four Moderate and Strong Studies With Abstinence Outcomes (Duration Not Reported)

Outcome 1: abstinence—duration not specified (N = 5)									
Abstinence (% , OR, or AOR ranges)									
Comparator	% of study participants (P value; 95% CI)	OR (P value; 95% CI)	AOR (P value; 95% CI)	Study types	References	Cumulative sample size (# of studies)	Device used	Individual quality score(s)	GRADE quality score
No control	11% (NR)–74% (NR) abstinence rate			Longitudinal; cross-sectional	Refs. <sup>(4,25-27)</sup>	7673 (4)	Newer generation device (28)	M (4)	Very low <sup>a</sup>
Compared to NRT		2.23 (95% CI: 0.70, 2.93; P < .001)	1.63 (95% CI: 1.17, 2.27; P < .01)	Cross-sectional	Ref. <sup>(15)</sup>	5863 (1)	Not specified	S	Low <sup>b</sup>
Compared to no aid		1.38 (95% CI: 1.08, 1.76; P < .05)	1.61 (95% CI: 1.19, 2.18; P < .01)	Cross-sectional	Ref. <sup>(15)</sup>	5863 (1)	Not specified	S	Low <sup>c</sup>

AOR = adjusted odds ratio; CI = confidence interval; M = moderate; NR = not reported; NRT = nicotine replacement therapy; OR = odds ratio; P = P value; S = strong.

<sup>a</sup>Downgraded two levels to very low due to imprecision of results and the presence of high risk of bias from survey design limitations.

<sup>b</sup>Assessed as low due to the small number of studies for this outcome measure.

<sup>c</sup>Assessed as low due to the small number of studies for this outcome measure.

**Table 3. Synthesized Results From Six Moderate Studies With Abstinence Outcomes Reported at 6-Month Follow-up or Longer**

Outcome 1: abstinence—at 6-month follow-up or longer (N = 6)									
Abstinence (% , OR, or AOR ranges)									
Comparator	% of study participants (P value; 95% CI)	OR (P value; 95% CI)	AOR (P value; 95% CI)	Study types	References	Cumulative sample size (# of studies)	Device used	Individual quality score(s)	GRADE quality score
No control	13.1% (95% CI: 7.3, 22.3)–36% (NR)	0.08 (95% CI: 0.04, 0.16)– 0.71 (95% CI: 0.35, 1.46; P = .35)	0.10 (95% CI: 0.05, 0.22)–6.07 (95% CI: 1.11, 33.18)	RCT; experimental; longitudinal; cross-sectional	Refs. <sup>(28–32)</sup>	11 398 (5)	Second generation (2/5 studies); not specified by other studies	M (5)	Low <sup>a</sup>
Compared to NRT	7.3% vs. 5.8% (nonsignificant)			RCT	Ref. <sup>(33)</sup>	657 (1)	First generation	M	Low <sup>b</sup>
Compared to placebo	7.3% vs. 4.1% (nonsignificant)			RCT	Ref. <sup>(33)</sup>	657 (1)	First generation	M	Low <sup>c</sup>

AOR = adjusted odds ratio; CI = confidence interval; M = moderate; NR = not reported; NRT = nicotine replacement therapy; OR = odds ratio; P = P value; RCT = randomized controlled trial.

<sup>a</sup>Downgraded one level to low due to imprecision of results and limitations in study implementation.

<sup>b</sup>Downgraded one level to low due to imprecision of results (only one RCT and problems with statistical significance due to insufficient power).

<sup>c</sup>Downgraded one level to low due to imprecision of results (only one RCT and problems with statistical significance due to insufficient power).

**Table 4.** Synthesized Results From One Moderate Study With Smoking Reduction Outcomes (Duration Not Reported)

Outcome 2: smoking reduction—duration not specified (N = 2)								
Comparator	% of study participants (P value; 95% CI)	Decrease in CPD (P value; 95% CI)	Study types	References	Cumulative sample size (# of studies)	Device used	Individual quality score(s)	GRADE quality score
No control	14% (NR)	Mean decrease of 14.6 CPD (P < .001)	Cross-sectional survey	Refs. <sup>(25,26)</sup>	1555 (2)	Newer generation device (28)	M (2)	Very low <sup>a</sup>

CI = confidence interval; CPD = cigarettes per day; M = moderate; NR = not reported; P = P value.

<sup>a</sup>Downgraded two levels to very low due to imprecision of results (one cross-sectional survey) and the presence of high risk of bias from design limitations.

Thirty-one articles with primary cessation outcomes were rated as weak according to our quality assessment tool. Of these, one RCT comparing the use of nicotine versus nonnicotine e-cigarettes is excluded from the analysis as it measured outcomes within a shorter than 30-day timeframe.<sup>34</sup> Seven longitudinal, one experimental, and two cross-sectional studies showed positive results in terms of abstinence and/or reduction in cigarettes smoked per day. However, these studies shared several weaknesses and limitations, including small sample sizes ranging from 17 to 48 participants, with the exception of three studies with 477<sup>35</sup> and 1656 participants, respectively.<sup>36,37</sup> A number of these did not test or report the statistical significance of results (see Supplementary Appendix B for study results and limitations). In addition, several studies demonstrated substantial risk of bias resulting from poor sampling techniques or recruitment methods. Four studies of the general population<sup>38–41</sup> suggested that e-cigarettes did not help smokers quit or reduce smoking. Many of these studies relied on surveys with a high risk of selection (and researcher) bias due to convenience sampling and/or recruitment from e-cigarette-related Web sites and forums frequented by e-cigarette aficionados. Another common limitation was low internal validity, due to poorly designed analyses that failed to adjust for baseline differences and other potential confounds. Some of these studies did not support their results with appropriate statistical testing. As a result, the following 31 weakly rated studies were excluded from our analysis of primary outcome measures: three RCTs,<sup>34,42,43</sup> four experimental studies,<sup>44–47</sup> 13 longitudinal studies,<sup>35,39–41,48–56</sup> and 11 cross-sectional survey studies.<sup>36–38,57–64</sup>

### Secondary Outcomes: Urges to Smoke and Withdrawal Symptoms

Nineteen studies that investigated secondary outcomes related to cigarette smoking withdrawal symptoms and cravings or urges to smoke were identified. Using our quality assessment tool, only one of these included studies was rated as *strong*, nine were rated as *moderate*, and nine as *weak* (excluded from analysis and only discussed briefly in this paper).

Overall, nine of the included studies demonstrated results suggesting that e-cigarettes are useful in alleviating withdrawal symptoms and reducing urges to smoke. The consistency of results across these studies provides some evidence suggesting that e-cigarettes may reduce symptoms and cravings. However, the quality of the overall body of evidence relating to these secondary outcomes was rated as *low* (GRADE score), primarily due to the consistent presence of risks of bias within individual studies. The main findings are discussed below (see Supplementary Appendix C for individual study limitations). Eight experimental studies, including three RCTs, found that e-cigarettes helped reduce both smoking-related

withdrawal symptoms and urges to smoke in users.<sup>30,65–71</sup> Adriaens et al.<sup>30</sup> in their RCT observed an immediate decrease in withdrawal symptoms and smoking-related cravings following 5 minutes of using a second-generation e-cigarette. The decrease in withdrawal symptoms in the e-cigarette groups was comparable to that observed in the cigarette-only (control) group. Another RCT by Dawkins et al.<sup>68</sup> found that nicotine and placebo e-cigarettes reduced the desire to smoke and some withdrawal symptoms 20 minutes after use. Males in the nicotine e-cigarette group experienced better outcomes than their counterparts in the placebo group, but this effect was not seen among females. This study also utilized a second-generation device. Comparable findings were reported by Dawkins et al.<sup>65</sup> whose RCT found that using a first-generation e-cigarette with and without nicotine helped alleviate reported withdrawal symptoms and cravings with similar effects. A more recent experimental study by Dawkins et al.<sup>67</sup> found that second-generation e-cigarettes with nicotine reduced reported anxiety and smoking cravings more substantially than placebo e-cigarettes. Two other experimental studies also reported reductions in cravings and some withdrawal symptoms, particularly anxiety and restlessness, after using a second-generation e-cigarette device for 10 puffs or *ad libitum*.<sup>69,71</sup> A strongly rated experimental study by Vansickel et al.<sup>70</sup> found that two different brands of first-generation e-cigarettes reduced both withdrawal symptoms and cravings in naïve users; however, smoking one's own combustible cigarette brand resulted in a larger reduction in the same outcomes.

One cross-sectional survey study by Dawkins et al.<sup>26</sup> investigated the effects of e-cigarette use on cravings among other behavioral outcomes in e-cigarette users. An overwhelming majority of users in their survey (91% of a sample of 1347) reported a reduction of urges to smoke after using e-cigarettes, although these findings are markedly limited by the risk of sampling bias (participants were recruited from Web sites linked to e-cigarette companies), and lack of biochemical verification of smoking abstinence.

Only one study of moderate quality reported neutral or negative secondary outcomes. An experimental study by Norton et al.<sup>72</sup> found that e-cigarettes did not significantly reduce participants' urges to smoke conventional cigarettes, whereas smoking cigarettes showed a significant positive effect on cravings. This study relied on the use of first-generation devices and involved significant noncompliance with protocols—limitations that weaken the reliability of the results.

Findings from weak studies (two RCTs, six experimental, and one cross-sectional survey) are generally in agreement with the results discussed above.<sup>44,46,47,58,73–77</sup> However, two of these studies did not report a positive relationship between e-cigarette use and reduction in symptoms or cravings. Both of these studies utilized a first-generation device.<sup>46,73</sup> One noteworthy study by Lechner et al.<sup>76</sup>

**Table 5.** Synthesized Results From Four Moderate Studies With Smoking Reduction Outcomes Reported at 6-Month Follow-up or Longer

Outcome 2: smoking reduction—at 6-month follow-up or longer (N = 4)										
Smoking reduction (# CPD, % participants, % reduction, % ≥50% ranges)										
Comparator	Decrease in CPD ( <i>P</i> value; 95% CI)	% reduction in mean CPD ( <i>P</i> value; 95% CI)	% reduction in median CPD ( <i>P</i> value; 95% CI)	% participants ≥50% reduction	Study types	References	Cumulative sample size (# of studies)	Device used	Individual quality score(s)	GRADE quality score
No control	20 CPD ( <i>P</i> < .001)	60% decrease in CPD ( <i>M</i> = 7.66, <i>SD</i> = 7.72)	80% reduction in CPD (NR)	30% ( <i>P</i> < .001)	RCT; experimental	Refs. <sup>(30,31)</sup>	98 (2)	Second generation	M (2)	Moderate
Compared to NRT	A larger decrease in e-cigarette group by 2 CPD ( <i>P</i> = .002)			57% compared to 41% ( <i>P</i> = .0002)	RCT	Ref. <sup>(33)</sup>	657 (1)	First generation	M	Low <sup>a</sup>
Compared to Placebo				57% compared to 45% ( <i>P</i> = .08)	RCT	Ref. <sup>(33)</sup>	657 (1)	First generation	M	
Compared to nonusers	A larger decrease in e-cigarette group by 1.9 CPD (3.78 compared to 1.85; <i>P</i> < .05)				Longitudinal	Ref. <sup>(4)</sup>	5939 (1)	Not specified	M	Low <sup>b</sup>

CI = confidence interval; CPD = cigarettes per day; M = moderate; NR = not reported; NRT = nicotine replacement therapy; *P* = *P* value; RCT = randomized controlled trial; *SD* = standard deviation.

<sup>a</sup>Downgraded one level to low due to imprecision of results (only one RCT and problems with statistical significance).

<sup>b</sup>Downgraded one level to low due to imprecision of results (only one study).



compared the efficacy of a second- and a first-generation e-cigarette in reducing withdrawal symptoms in a randomized crossover design. Mean reduction of scores on the Mood and Physical Symptoms Scale (MPSS) was 5.73 after using the second-generation device, compared to 3.14 with the first-generation device. Although the study failed to account for differences in baseline MPSS scores, the findings highlight the potential superiority of second-generation devices in reducing withdrawal symptoms experienced by users.

## Discussion

The results of this systematic review lead us to conclude that evidence for the effectiveness of e-cigarettes as a cessation aid is inconclusive. There is too much uncontrolled variation to allow for any general conclusion to be made. Studies are only beginning to account for important variables related to the product (e-cigarette device, fluid, nicotine content, nicotine delivery), characteristics of users (cigarette use profile, quitting history, health status, demographics), and patterns of use (frequency, duration, time period, inhalation). The study of e-cigarettes as cessation aids is still in its infancy, and at present there are simply too few well-designed studies to establish a strong body of evidence.

The state of the evidence in support of e-cigarettes as effective aids that may help smokers quit is currently assessed as *very low to low*. This is primarily because of methodological weaknesses, such as a lack of randomized trials, survey design limitations, and sampling problems, and imprecision of results—both statistically and due to a small number of relevant studies. What limited evidence there is seems to point to e-cigarettes as potentially useful in helping some smokers quit cigarette smoking. Evidence of a positive association between e-cigarette use and smoking reduction is slightly better, but also weak as indicated by a GRADE assessment of *very low to moderate*. Our findings are supported by a Cochrane review, in which GRADE result was also *low* and which forms the basis for a recent Public Health England review.<sup>7,78</sup>

There is a small amount of evidence suggesting that second-generation e-cigarettes may be more effective than first-generation devices in helping smokers to quit or smoke less. This is supported by the existing evidence on apparent superiority of second-generation e-cigarettes in reducing abstinence-related withdrawal symptoms and cravings and could be explained by their increased control over vapor production and nicotine delivery as compared to first-generation models. An important caution is that lab efficacy studies do not always translate into symptom and craving reduction in the real world and over time.

The long-term effectiveness of e-cigarettes to reduce withdrawal symptoms and cravings in real-life settings remains uncertain. RCTs and longitudinal studies that examine the effectiveness of e-cigarettes outside lab settings and provide insight into contextual and behavioral mechanisms are needed. Moreover, it remains unclear whether e-cigarettes are only beneficial for certain types of smokers and whether their efficacy is enhanced or hampered when used in tandem with other cessation aids such as counseling or NRT. Research has demonstrated increased benefits of cessation aids such as NRTs when coupled with behavioral support.<sup>2</sup> Future studies should examine the potential role of behavioral support or counseling programs in order to have a better understanding of contextual factors that may contribute to better cessation outcomes.

Our findings have some limitations. Firstly, the lack of standardized outcome measures reported by the included studies made

it difficult to quantitatively synthesize individual findings. It is possible that assessing the body of evidence per primary outcome measure resulted in an underestimation of the overall strength of the evidence, as grouping pooled measures may better demonstrate consistency between results, increase the precision of findings, and thereby the level of confidence in the results.<sup>14</sup> Our review may have benefited from a meta-analysis of some included studies. However, due to the heterogeneity of outcome measures and methodological approaches included in the review, it was impractical to combine the data quantitatively.<sup>14</sup> Secondly, to limit the scope of the study, our analysis did not examine adverse health effects related to e-cigarette use for cessation or how abstinence rates differed between e-cigarette users who reported an intention to quit and those users who were only experimenting. Thirdly, our review employed a comprehensive search strategy that included conference proceedings and ongoing RCTs; however, we may have missed some unpublished results. Nonetheless, our study possesses several strengths that support the reliability of our findings. First, and unlike other reviews on the subject, our literature search strategy employed numerous search engines and both peer-reviewed and gray literature sources, ensuring that the review included virtually all relevant evidence to date and resulting in the most comprehensive to date, examining 62 studies. Second, a committee of experts in public health and tobacco policy oversaw the development of the study protocol, including assessment and data extraction tools, in order to establish comprehensive and stringent review criteria. Third, interrater agreement was rigorously tested and validated at several stages of the review. Fourth, implementing two stages of quality assessment when possible—the first using a tool specially designed to assess a highly heterogeneous body of evidence, the second to rate specific categories of evidence (GRADE)—allowed us to carefully and stringently parse and evaluate the evidence, with the weakest studies excluded from our analysis. These measures bring a degree of rigor to the study not seen in other systematic reviews on e-cigarette cessation aid effectiveness and should bolster confidence in our results. Lastly, in addition to the qualitative analysis, and recognizing the impracticality of conducting a meta-analysis, this review provides a broad quantitative synthesis of studies of fair quality regardless of study design to help stakeholders understand the state of current evidence on e-cigarettes as cessation aids. Further research employing robust randomized controlled designs and population sampling strategies is needed to enhance the current evidence and enrich our understanding of how e-cigarettes may be utilized by smokers to reduce their consumption of cigarettes or quit smoking. Such studies should use devices that have been well characterized with effective nicotine delivery and other effects and would benefit from more rigorous validation methods of cessation such as biochemical verification. Although, the development of RCTs using e-cigarettes that have been shown to match the nicotine delivery profile of a tobacco cigarette is presently impractical in countries where the use of nicotine e-cigarettes is banned (eg, Canada) or where standard devices need to be approved (eg, the United States). Such studies may help to elucidate the role of these products in helping smokers remain abstinent and smoke less.

## Supplementary Material

Supplementary Appendices A–C can be found online at <http://www.ntr.oxfordjournals.org>

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## Declaration of Interests

None declared.

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