

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Electronic Cigarettes for the Reduction or Cessation of Smoking: Clinical Utility, Safety, and Guidelines

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## Research Questions

1. What is the clinical evidence regarding the utility of electronic cigarettes for the reduction or cessation of smoking?
2. What is the clinical evidence regarding the safety associated with electronic cigarettes or other vaping devices?
3. What is the clinical evidence regarding the safety of propylene glycol, glycerin or polyethylene glycol inhalation from electronic cigarettes or other vaping devices?
4. What is the clinical evidence regarding the safety of nicotine inhalation from electronic cigarettes or other vaping devices?
5. What are the evidence-based guidelines regarding the use of electronic cigarettes for the reduction or cessation of smoking?

## Key Findings

One health technology assessment, 14 systematic reviews, and eight randomized controlled trials were identified regarding electronic cigarettes for the reduction or cessation of smoking or regarding the safety of e-cigarettes. Additionally, three evidence-based guidelines were identified.

## Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and August 14, 2017. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients who smoke using an electronic cigarette or vaping device
<b>Intervention</b>	Q1-2: Electronic cigarettes Q3: Propylene glycol, glycerin or polyethylene glycol from electronic cigarettes Q4: Nicotine from electronic cigarettes Q5: Guidelines on electronic cigarettes
<b>Comparator</b>	Q1-4: No comparator or any comparator Q5: No comparator
<b>Outcomes</b>	Q1-4: Efficacy, reduction or cessation of smoking, safety, second-hand smoke exposure Q5: Guidelines and recommendations
<b>Study Designs</b>	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and evidence-based guidelines.

One health technology assessment, 14 systematic reviews, and eight randomized controlled trials were identified regarding electronic cigarettes for the reduction or cessation of smoking or regarding the safety of e-cigarettes. Additionally, three evidence-based guidelines were identified. Due to the large volume of relevant literature, non-randomized studies were moved to the appendix and were not summarized in this report.

Additional references of potential interest are provided in the appendix.

## Overall Summary of Findings

One health technology assessment (HTA),<sup>1</sup> 14 systematic reviews,<sup>2-15</sup> and eight randomized controlled trials (RCTs)<sup>16-23</sup> were identified regarding electronic cigarettes (e-cigarettes) for the reduction or cessation of smoking, or regarding the safety of e-cigarettes. Detailed study characteristics are provided in Table 2.

Overall, the literature was generally inconclusive on the benefit of e-cigarettes for smoking cessation.<sup>2,7,10,13</sup> Some improvements in abstaining from or reducing the number of conventional cigarettes smoked have been found with the use of nicotine e-cigarettes,<sup>2-3,6,8,9,11,14</sup> however, the rates of fully quitting from all nicotine products appears to be lower with the use of e-cigarettes.<sup>2,5</sup> Many abstracts were unclear about the definition of cessation of smoking, and whether “smoking cessation” also includes cessation of the use of e-cigarettes. E-cigarettes which include nicotine in their inhaled vapour appeared to be more effective for the reduction of conventional cigarette smoking than placebo or non-nicotine infused e-cigarettes,<sup>2-3,6,11,20</sup> and equally as effective as other cessation tools, such as nicotine replacement patches.<sup>3,22-23</sup>

The safety of e-cigarettes is also unknown, especially in the long term.<sup>1,10,15</sup> The most prominent acute safety concern is from the potential for lithium battery powered e-cigarettes to explode, causing thermal burns to the user.<sup>1</sup> Other potential harms can occur from acute nicotine poisoning through ingestion of the nicotine cartridge, especially in young children, but this is uncommon.<sup>1</sup> Adverse events were also seen with the use of e-cigarettes, such as throat and respiratory irritation, headache, and dry cough,<sup>1,3,8,10,13-14,18,21</sup> but the rate of adverse events did not appear to differ between nicotine e-cigarettes, placebo e-cigarettes, and other conventional forms of nicotine replacement therapy.<sup>1,6,10,21-23</sup> Overall, e-cigarettes, either nicotine filled or placebo, were seen as less toxic and safer than conventional cigarettes.<sup>1,10,12-13</sup>

Three evidence based guidelines were also identified.<sup>24-26</sup> One guideline<sup>24</sup> by the U.S. Preventive Services Task Force found the evidence for the use of e-cigarettes as a smoking cessation tool in adults, including pregnant women and adolescents, to be insufficient to make a recommendation. A second guideline<sup>25</sup> by The Canadian Paediatric Society does not recommend the use of e-cigarettes as a cessation aid for adolescents, but health care practitioners should instead be educating adolescents on their harm potential. The final guideline for patients with cancer<sup>26</sup> by Alberta Health Services states that there is currently insufficient safety, quality, or efficacy evidence or data to support a recommendation for the use of e-cigarettes as a smoking cessation aid.

**Table 2: Summary of Included Studies on Electronic Cigarettes for the Reduction or Cessation of Smoking or on Safety of Electronic Cigarettes**

First Author, Year	Study Characteristics	Population(s), Intervention(s), Comparator(s)	Outcome(s)	Conclusion(s)
<b>Health Technology Assessments</b>				
HIQA, 2017 <sup>1</sup>	<ul style="list-style-type: none"> <li>HTA</li> <li>Number of included studies NR</li> <li>N = NR</li> </ul>	<ul style="list-style-type: none"> <li>Adults and children</li> <li>Placebo and nicotine ECs</li> <li>NRT patches</li> <li>Conventional cigarettes</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> <li>AEs and SAEs</li> <li>Passive inhalation (second-hand smoke)</li> <li>Pulmonary effects</li> </ul>	<ul style="list-style-type: none"> <li>Most common side effects are temporary throat and respiratory irritation and dry cough which dissipates over time</li> <li>No SAEs in trials, no difference in AEs between NRT patches, placebo, or nicotine ECs</li> <li>E-liquid ingestion by children can cause nausea, vomiting and ataxia</li> <li>Lithium battery explosions and thermal burns a concern</li> <li>Small amounts of chemicals may be released, such as formaldehyde and acetaldehyde and tobacco-specific nitrosamines, but it is lower than in conventional cigarette smoke</li> <li>Toxic substances were 9 to 450 times lower in ECs than in cigarette smoke</li> </ul>

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				<ul style="list-style-type: none"> <li>Aldehyde emissions are small under normal conditions</li> <li>Impurities related to flavourings and preservations are unlikely to be harmful</li> <li>EC or NRT use (but not dual use of cigarettes with either) associated with lower carcinogens and toxins compared with cigarette smoke</li> <li>No evidence that long term use leads to reductions in smoking-related disease, and may increase levels of COPD, cancer and other disease</li> </ul>
<b>Systematic Reviews and Meta-Analyses</b>				
<b>Ei Dib, 2017<sup>2</sup></b>	<ul style="list-style-type: none"> <li>SR &amp; MA</li> <li>3 RCTs and 9 cohorts included</li> <li>N = 14,122</li> </ul>	<ul style="list-style-type: none"> <li>Cigarette smokers on long-term tobacco use</li> <li>ENDS</li> <li>ENNDS</li> <li>Smoking cessation aids</li> </ul>	<ul style="list-style-type: none"> <li>Tobacco cessation</li> <li>Quit rates</li> </ul>	<ul style="list-style-type: none"> <li>Increased tobacco smoking cessation with ENDS compared with ENNDS</li> <li>Reduction in quit rates with use of ENDS compared with no use of ENDS</li> <li>Data is of low certainty and evidence is limited</li> </ul>
<b>Hartmann-Boyce, 2016<sup>3</sup></b>	<ul style="list-style-type: none"> <li>SR &amp; MA</li> <li>3 RCTs and 21 cohort studies included</li> <li>N = &gt;662</li> </ul>	<ul style="list-style-type: none"> <li>Current smokers</li> <li>Placebo and non-placebo EC</li> <li>NRT patch</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> <li>Abstinence from smoking after at least six months</li> </ul>	<ul style="list-style-type: none"> <li>EC users more likely to abstain from smoking than placebo EC users, no difference when compared to NRT patch</li> <li>No SAEs reported</li> <li>AEs reported were throat and mouth irritation, and similar proportion of AEs in all study groups</li> </ul>
<b>Hua, 2016<sup>4</sup></b>	<ul style="list-style-type: none"> <li>SR</li> <li>26 case reports</li> <li>N = 27</li> </ul>	<ul style="list-style-type: none"> <li>Children and adults</li> <li>ECs</li> </ul>	<ul style="list-style-type: none"> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Preexisting conditions and health can be affected negatively by ECs, but it is reversible</li> </ul>
<b>Kalkhoran, 2016<sup>5</sup></b>	<ul style="list-style-type: none"> <li>SR &amp; MA</li> <li>38 studies included</li> <li>N = NR</li> </ul>	<ul style="list-style-type: none"> <li>Adult cigarette smokers</li> <li>ECs</li> </ul>	<ul style="list-style-type: none"> <li>Odds of quitting</li> </ul>	<ul style="list-style-type: none"> <li>The odds of quitting were lower in those using ECs compared to not using ECs</li> </ul>

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First Author, Year	Study Characteristics	Population(s), Intervention(s), Comparator(s)	Outcome(s)	Conclusion(s)
<b>Khoudigian, 2016<sup>6</sup></b>	<ul style="list-style-type: none"> <li>• SR &amp; MA</li> <li>• 5 studies included</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• Adult smokers</li> <li>• Placebo and non-placebo ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Efficacy for smoking cessation</li> <li>• Withdrawal symptoms</li> <li>• AEs</li> </ul>	<ul style="list-style-type: none"> <li>• Stopping smoking cigarettes more likely with nicotine ECs compared to placebo ECs</li> <li>• Rate of depression, irritability, or AEs were not significantly different between placebo ECs and ECs</li> </ul>
<b>Malas, 2016<sup>7</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• 62 studies included</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• Smokers</li> <li>• ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Withdrawal symptoms</li> <li>• Cravings</li> <li>• Smoking abstinence or reduction</li> </ul>	<ul style="list-style-type: none"> <li>• In laboratory settings, ECs could alleviate withdrawal symptoms and cravings</li> <li>• Evidence on relationship between ECs and cessation is inconclusive due to low quality research</li> </ul>
<b>Gualano, 2015<sup>8</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• 6 experimental and 6 cohort studies included</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• ECs</li> </ul>	<ul style="list-style-type: none"> <li>• AEs</li> <li>• Efficacy</li> </ul>	<ul style="list-style-type: none"> <li>• After use of ECs, smoking was reduced at week 12 and 52.</li> <li>• There was a reduction in number of CPD after EC use</li> <li>• AEs reported included mouth and throat irritation, nausea, headache and dry cough</li> </ul>
<b>Lam, 2015<sup>9</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• 4 studies included</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• ENDS</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking abstinence or reduction</li> </ul>	<ul style="list-style-type: none"> <li>• ENDS are an effective smoking cessation tool</li> </ul>
<b>Patnode, 2015<sup>10</sup></b>	<ul style="list-style-type: none"> <li>• Overview of reviews with supplementary SR</li> <li>• 2 RCTs included</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• ENDS</li> <li>• NRT patches</li> <li>• Conventional cigarettes</li> </ul>	<ul style="list-style-type: none"> <li>• Safety</li> <li>• SAEs, AEs</li> <li>• Smoking abstinence or reduction</li> </ul>	<ul style="list-style-type: none"> <li>• No SAEs related to ENDS, no difference in SAEs or AEs between ENDS and NRT patches</li> <li>• Evidence is very limited for use as a cessation tool and may be of no benefit</li> <li>• Toxicity and safety hard to determine due to variability in manufacturing</li> <li>• Among brands tested, toxicity is lower than in conventional cigarettes</li> <li>• Long term harms of ENDS not known</li> </ul>
<b>Rahman, 2015<sup>11</sup></b>	<ul style="list-style-type: none"> <li>• SR &amp; MA</li> <li>• 6 studies included</li> <li>• SR; N = 7,551</li> </ul>	<ul style="list-style-type: none"> <li>• Nicotine and non-nicotine ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking abstinence or reduction</li> <li>• Efficacy</li> </ul>	<ul style="list-style-type: none"> <li>• Nicotine ECs more effective than non-nicotine ECs</li> <li>• Use of nicotine ECs associated with smoking cessation and reduction in number of cigarettes used</li> </ul>

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First Author, Year	Study Characteristics	Population(s), Intervention(s), Comparator(s)	Outcome(s)	Conclusion(s)
	MA; N = 1,242			
<b>Farsalinos, 2014<sup>12</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• Number of included studies NR</li> </ul>	<ul style="list-style-type: none"> <li>• ECs</li> <li>• Conventional cigarettes</li> </ul>	<ul style="list-style-type: none"> <li>• Safety</li> </ul>	<ul style="list-style-type: none"> <li>• ECs are less harmful than conventional cigarettes</li> </ul>
<b>Harrell, 2014<sup>13</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• Number of included studies NR</li> </ul>	<ul style="list-style-type: none"> <li>• ECs</li> <li>• Conventional cigarettes</li> </ul>	<ul style="list-style-type: none"> <li>• Safety</li> <li>• Smoking abstinence</li> </ul>	<ul style="list-style-type: none"> <li>• ECs are lower in toxicity, AEs, and secondhand smoke exposure than conventional cigarettes</li> <li>• Use of ECs for cessation is inconclusive</li> </ul>
<b>Orr, 2014<sup>14</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• 6 studies included</li> </ul>	<ul style="list-style-type: none"> <li>• ECs</li> <li>• NRT patches</li> </ul>	<ul style="list-style-type: none"> <li>• Smoking abstinence or reduction</li> <li>• CO levels</li> <li>• AEs</li> <li>• Desire to smoke</li> <li>• Number of CPD</li> </ul>	<ul style="list-style-type: none"> <li>• Most common AEs are temporary throat irritation, headache, and cough</li> <li>• Higher adherence and fewer AEs with ECs compared to NRT patches</li> <li>• Acute cessation of cigarettes occurred with ECs but was not maintained in the long term</li> </ul>
<b>Pisinger, 2014<sup>15</sup></b>	<ul style="list-style-type: none"> <li>• SR</li> <li>• 76 studies included</li> </ul>	<ul style="list-style-type: none"> <li>• ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Safety</li> <li>• AEs</li> </ul>	<ul style="list-style-type: none"> <li>• Inconclusive on the safety of ECs</li> </ul>
<b>Randomized Controlled Trials</b>				
<b>D’Ruiz, 2017<sup>16</sup></b>	<ul style="list-style-type: none"> <li>• RCT</li> <li>• N = 105</li> </ul>	<ul style="list-style-type: none"> <li>• Smokers</li> <li>• ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Systolic and diastolic blood pressure and heart rate</li> <li>• Pulmonary function (FVC, FEV1, and exhaled CO and NO)</li> <li>• AEs</li> </ul>	<ul style="list-style-type: none"> <li>• Use of ECs for 5 days did not result in higher BP or HR, lower pulmonary function or AEs</li> <li>• BP and HR lowered, and potential pulmonary benefits in individuals who switched to ECs completely</li> </ul>
<b>Cibella, 2016<sup>17</sup></b>	<ul style="list-style-type: none"> <li>• RCT</li> <li>• N = NR</li> </ul>	<ul style="list-style-type: none"> <li>• Smokers</li> <li>• ECs</li> </ul>	<ul style="list-style-type: none"> <li>• Spirometric indices</li> <li>• Respiratory symptoms</li> </ul>	<ul style="list-style-type: none"> <li>• Smoker who switched completely to ECs improved in pulmonary function and had normalization of peripheral airways function</li> </ul>
<b>Cravo, 2016<sup>18</sup></b>	<ul style="list-style-type: none"> <li>• RCT</li> <li>• N = NR</li> <li>• Parallel group</li> </ul>	<ul style="list-style-type: none"> <li>• Smokers</li> <li>• ECs</li> <li>• Conventional cigarettes</li> </ul>	<ul style="list-style-type: none"> <li>• AEs</li> </ul>	<ul style="list-style-type: none"> <li>• Adverse events were more frequent during the first week of switching to ECs</li> <li>• Headache, sore throat, desire to</li> </ul>

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				<ul style="list-style-type: none"> <li>smoke and cough the most frequent AEs</li> <li>6% of AEs were related to ECs</li> </ul>
<b>O'Connell, 2016<sup>19</sup></b>	<ul style="list-style-type: none"> <li>RCT</li> <li>N = 105</li> </ul>	<ul style="list-style-type: none"> <li>Smokers</li> <li>ECs</li> <li>Dual use ECs and conventional cigarettes</li> <li>Conventional cigarettes alone</li> </ul>	<ul style="list-style-type: none"> <li>Levels of urinary biomarkers</li> </ul>	<ul style="list-style-type: none"> <li>Individuals who switched to ECs either partially or completely over 5 days had lower levels of urinary biomarkers for HPHCs</li> </ul>
<b>Tseng, 2016<sup>20</sup></b>	<ul style="list-style-type: none"> <li>RCT</li> <li>Double-blind</li> <li>N = 99</li> </ul>	<ul style="list-style-type: none"> <li>Young adult smokers who smoke <math>\geq 10</math> CPDs living in New York City</li> <li>Placebo or non-placebo ECs</li> </ul>	<ul style="list-style-type: none"> <li>Number of smoked CPD</li> </ul>	<ul style="list-style-type: none"> <li>Reduction of CPD for both placebo and non-placebo EC groups, however higher reduction in non-placebo EC group observed.</li> <li>Using higher number of ECs associated with achieving a 50% reduction in CPD</li> </ul>
<b>Walele, 2016<sup>21</sup></b>	<ul style="list-style-type: none"> <li>RCT</li> <li>Crossover trial</li> <li>N = NR</li> </ul>	<ul style="list-style-type: none"> <li>Smokers</li> <li>Flavoured and unflavoured ECs</li> <li>Conventional cigarettes</li> <li>Nicotine inhaler</li> </ul>	<ul style="list-style-type: none"> <li>AEs</li> <li>Vital signs</li> <li>CO exhalation</li> <li>Smoking urges</li> <li>Withdrawal symptoms</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Only mild AEs were reported</li> <li>No difference in AEs between the nicotine inhaler and the ECs</li> <li>No increase in CO levels for any intervention, only with conventional cigarettes</li> <li>Smoking urges and nicotine withdrawal decreased with all products</li> <li>Short term safety of nicotine inhaler and ECs were similar</li> </ul>
<b>O'Brien, 2015<sup>22</sup></b>	<ul style="list-style-type: none"> <li>RCT</li> <li>Secondary analysis of ASCEND trial</li> <li>N = 657 in trial, N = 87 analyzed for report</li> </ul>	<ul style="list-style-type: none"> <li>Dependent adult smokers motivated to quit, with mental illness</li> <li>16 mg nicotine EC</li> <li>21 mg NRT patch</li> <li>0 mg nicotine EC</li> </ul>	<ul style="list-style-type: none"> <li>Smoking abstinence or reduction</li> <li>AEs</li> <li>Relapse rates</li> <li>Treatment compliance and acceptability</li> </ul>	<ul style="list-style-type: none"> <li>There was no difference in quitting rates, AEs, acceptability, reduction of smoking, or treatment compliance at 6 months between individuals with mental illness and those without, for ECs alone and all intervention pooled together</li> <li>There was no difference in cessation, AEs, or relapse rates between interventions</li> <li>ECs were more accepted, and had higher levels of treatment compliance and smoking reduction</li> </ul>
<b>Bullen, 2013<sup>23</sup></b>	<ul style="list-style-type: none"> <li>RCT</li> <li>Superiority trial</li> <li>N = 657</li> </ul>	<ul style="list-style-type: none"> <li>Adult smokers motivated to quit</li> <li>ECs</li> </ul>	<ul style="list-style-type: none"> <li>Smoking abstinence or reduction</li> </ul>	<ul style="list-style-type: none"> <li>No difference in adverse event between interventions</li> <li>ECs had a modest effectiveness at</li> </ul>

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		<ul style="list-style-type: none"> <li>• NRT patches</li> </ul>	<ul style="list-style-type: none"> <li>• AEs</li> </ul>	assisting in quit efforts, similar rate of abstinence between ECs and NRT patches

Abbreviations: AE = adverse event; BP = blood pressure; CO = carbon monoxide; COPD = chronic pulmonary obstructive disease; CPD = cigarettes per day; EC = electronic cigarette; ENDS = electronic nicotine delivery systems; ENNDS = electronic non-nicotine delivery systems; HIQA = Health Information and Quality Authority; HPHC = harmful or potentially harmful constituents; HR = heart rate; HTA = health technology assessment; MA = meta-analysis; NR = not reported; NRT = nicotine replacement therapy; QoL = quality of life; RCT = randomized controlled trials; SAE = serious adverse event; SR = systematic review.

## References Summarized

### Health Technology Assessments

1. Health technology assessment (HTA) of smoking cessation interventions [Internet]. Dublin (Ireland): Health Information and Quality Authority (HIQA); 2017 Mar 22 [cited 2017 Sep 1]. Available from: <https://www.hiqa.ie/sites/default/files/2017-04/Smoking%20Cessation%20HTA.pdf>

### Systematic Reviews and Meta-analyses

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