E-Cigarette Research Update

Introduction: Research challenges continue

The evidence base on e-cigarettes continues to grow at an impressive rate. However, owing to a number of factors, there are still significant gaps in our understanding of the impacts of these products on individual and public health. For every study that is published indicating one thing, there seems to be another showing the opposite effect. Part of the problem stems from a lack of standardization for definitions and research methods, along with various methodological flaws and study biases. For example, measures of "regular use" of e-cigarettes often erroneously capture experimentation which inflates the numbers. The lack of standardization has also led to findings that do not reflect real-world e-cigarette use or conditions. For example, an e-cigarette puffed by a machine can be over-heated and emit dangerous levels of toxins. However, over-heating causes "dry puff" which is unpleasant and not tolerated by humans. Another issue is with the rapid evolution in vapour technology: it's hard for scientists to replicate studies to either confirm or refute findings when the particular models of e-cigarettes used in earlier studies are obsolete and no longer available. All this has not been helped by sensationalist headlines in the media that do not reflect actual scientific findings and which have served to further confuse the public over what is already a controversial and complicated issue.

> *"Reviews to date have typically combined uninformative or methodologically weak studies with well-designed studies, resulting in a lack of clarity and contradictory conclusions."*
>
> ~ Villanti et al, 2018

These problems are starting to be addressed. A group of experts has recently published a paper proposing a minimum set of criteria to encourage consensus to facilitate cross-survey and cross-jurisdictional comparisons of e-cigarette use behaviour.[1] Following a review of the literature in which just 3 of 91 studies passed muster, another group of scientists has recommended a hierarchy of methodological criteria to consider when determining whether or not a study provides sufficient information to answer questions regarding smoking cessation or reduction.[2]

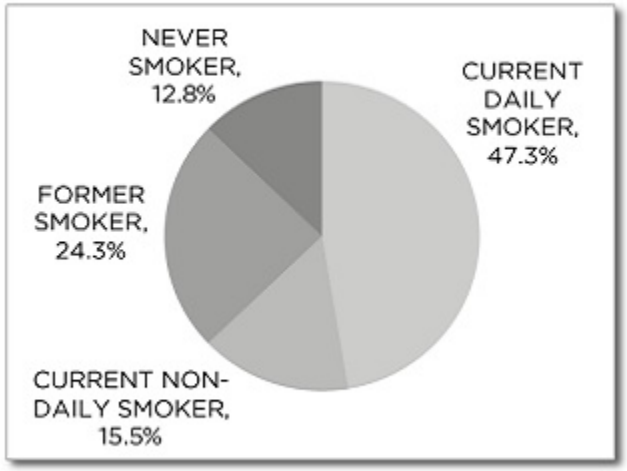
[1] Pearson JL, Hitchman SC, Brose LS et al. Recommended core items to assess e-cigarette use in population-based surveys. Tobacco Control Published Online First: 17 June 2017. doi: 10.1136/tobaccocontrol-2016-053541

[2] Villanti AC, Feirman SP, Niaura RS et al. How do we determine the impact of e-cigarettes on cigarette smoking cessation or reduction? Review and recommendations for answering the research question with scientific rigor. Addiction 2018; 113: 391–404. doi: 10.1111/add.14020.

Low prevalence of use in Canada

New Canadian data have not been released since our last e-cigarette evidence update in 2016. The most recent nationally-representative prevalence data are from 2015 and indicate that:

FIGURE 12.17: SMOKING STATUS OF PAST 30-DAY USERS OF E-CIGARETTES, 2015



DATA SOURCE: CANADIAN TOBACCO, ALCOHOL AND DRUGS SURVEY, 2015

- 13% of all Canadians 15+ reported having "ever tried" an e-cigarette (this includes a single puff, with or without nicotine);
- 3.2%, representing less than a quarter of "ever triers," reported past 30-day use, which is a better proxy for regular use;
    - 6.3% of youth (15-19) and 6.3% of young adults (20-24) reported past 30-day use;
- 1% of all respondents indicated they were daily users (~308,000 people);
- As indicated in the pie graph at right, courtesy of Propel Centre for Population Health Impact, the vast majority (87%) of past 30-day e-cigarette users are daily, occasional or former smokers;
    - 62.8% of these are "dual users" (continue to smoke as well as to vape); and
- Among all "ever triers," 22.8% reported using e-cigarettes to help them quit smoking within the past two years.

The Canadian data show that very few ever triers go on to become regular users. This is both comforting from a youth protection perspective and discouraging from a smoking cessation perspective. For the future, Health Canada has advised that it will be surveying Canadians' use of e-cigarettes more frequently and with better and more detailed questions.

Cessation effectiveness: promising but not conclusive

Unfortunately, there continues to be a lack of detailed nationally-representative data on Canadians' use and experiences with e-cigarettes for cessation. A review of the literature undertaken by Public Health Ontario concluded that *"Randomized Control Trials (RCTs) suggest that nicotine-containing e-cigarettes are more effective than placebo e-cigarettes, but are not superior to NRT… It is unclear whether e-cigarettes (with or without nicotine) are an effective smoking cessation device… More research is needed… ."*[3] Literature on the effectiveness of e-cigarettes in helping smokers to quit continues to be mixed, reflecting the comments made in the introduction about methodological problems and study biases. One meta-analysis which has received considerable attention concluded that e-cigarettes

[3] Smoke-Free Ontario Scientific Advisory Committee, Ontario Agency for Health Protection and Promotion (Public Health Ontario). Evidence to guide action: Comprehensive tobacco control in Ontario (2016). Toronto, ON: Queen's Printer for Ontario; 2017. https://www.publichealthontario.ca/en/eRepository/SFOSAC%202016_FullReport.pdf

are associated with significantly less quitting among smokers.[4] This study has been criticized as being grossly misleading, owing to the fact that it only included people who were currently smoking and had used e-cigarettes in the past; people who had already successfully used e-cigarettes to quit smoking were excluded from the analysis!

Public Health England reports that since 2013, e-cigarettes are the most common quitting aid in England with an estimated 50% increase in success rates (from 5% to 7.5%) over and above NRT bought and used without a prescription or professional support. The report also emphasizes that the quit rate in the first half of 2017 was significantly higher than the average for the previous 10 years, and that for the first time in a decade (and possibly ever) parity in quit success rates was achieved between low and high socio-economic groups. The evidence suggests that e-cigarettes have contributed an estimated 22,000 – 57,000 additional quitters in England.[5] Data from the United States paint a similar picture: smoker population surveys suggest that e-cigarette users are more likely than non-users to make a quit attempt (65.1% vs 40.1%), and are more likely to succeed in quitting (8.2% v 4.8%). The overall population smoking cessation rate increased between 2010-2011 (4.5%) and 2014-15 (5.6%), representing approximately 350,000 additional US smokers who quit in 2014-15.[6]

Factors that are associated with the cessation effectiveness of e-cigarettes include:

- **Daily vaping**: people who vape every day compared to those who vape less frequently are more likely to be ex-smokers;
    - If they continue to smoke (dual use), daily vapers are more likely to consume fewer cigarettes and to have a stronger motivation to quit than smokers who vape less frequently;
- **Nicotine**: people who vape e-juice with nicotine are more likely to quit smoking than people who use nicotine-free e-juice;
- **Tank models**: 3rd and 4th generation modifiable e-cigarettes with rechargeable batteries and refillable cartridges typically deliver nicotine more effectively than "cig-a-like" models and are more likely to satisfy users' needs;[7] and
- **Experience:** knowledgeable vapers using later generation models can self-dose or "titrate" nicotine levels more effectively than naïve users.

[4] Kalkhoran S & Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Respir Med 2016; 4: 116–28.
[5] McNeill A, Brose LS, Calder R, et al. (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf
[6] Zhu SH, Zhuang YL, Wong S, et al. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ Brit Med J. 2017;358:j3262.
[7] Technology is changing quickly. Note that "Juul," a newer 'closed system' device employs small single-use cartridges that contain the same amount of nicotine as a pack of cigarettes. The Juul website states, "Our JUULsalts™ e-liquid contains nicotine salts found in the tobacco leaf, rather than free-base nicotine used in most e-cigarettes and vaporizers. Together with temperature-regulated vapor technology, this proprietary chemistry enables JUUL to deliver a vapor experience like no other."

Dual use

Over 60% of Canadians who reported vaping in the past 30 days are dual users: they continue to smoke as well. Unfortunately, very little is known about dual use in Canada including smokers' motivations, beliefs, types of device used and concentrations of nicotine, as well as the breakdown of smoking vs vaping (mostly vaping with the occasional cigarette is a very different scenario from smoking with the occasional vape). Although the evidence shows that smokers must completely switch from cigarettes to e-cigarettes to benefit from reduced exposure to harmful and potentially harmful compounds, evidence from the UK also suggests that dual use could be an important transient phase of heightened motivation to quit that leads to exclusive e-cigarette use. For the first time since 2012 when data were first collected, there are now more ex-smokers (1.5 million) in the UK who use e-cigarettes than dual users (1.3 million). Over half (52%) of e-cigarette users are now ex-smokers and 45% are smokers (dual users).[8]

Toxicity and health effects

The American National Academies of Sciences, Engineering & Medicine recently undertook a review of the literature and came to the following conclusions:

There is **conclusive evidence** that:

- Completely substituting e-cigarettes for regular cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes;
- Other than nicotine, the number, quantity, and characteristics of potentially toxic substances emitted from e-cigarettes is highly variable and depends on product characteristics and how the device is operated.

There is **substantial evidence** that:

- Except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with regular cigarettes;
- E-cigarette aerosol contains metals. The origin of the metals could be the metallic coil used to heat the e-liquid, other parts of the device, or e-liquids. Product characteristics and patterns of use may contribute to differences in the actual metals and metal concentrations measured in aerosol;
- E-cigarette aerosols can affect the blood vessels that line the arteries, although the long-term consequences and outcomes from long-term term exposure are uncertain.

[8] Action on Smoking and Health UK. Fact sheet: Use of e-cigarettes (vapourisers) among adults in Great Britain. May 2017. http://ash.org.uk/download/use-of-e-cigarettes-among-adults-in-great-britain-2017/

The Dose Makes the Poison

One study comparing biomarkers of toxins in the urine and saliva of NRT users compared to e-cigarette users found very similar profiles.

This is important, as many studies have raised the alarm regarding the presence of toxins found in e-juice and/or aerosol. Measured absolute levels are a much more important determinant of toxicity than simply detecting their presence.

In its review of the evidence up to and including March 2017, the Cochrane Tobacco Addiction Review Group asserted that for smokers of conventional cigarettes, switching to e-cigarettes is likely to lead to significant health improvements.[9] A recent review of the evidence by Public Health England concluded that new studies since its last review in 2015 do not demonstrate substantial new risks and its assessment that e-cigarettes are substantially less harmful than cigarettes stands.[10] However, the "95% less harmful" statistic continues to be controversial internationally and the long-term health impacts for users remain unknown. Given that most e-cigarette users are current or former smokers, pinpointing the health effects of vaping separately from those of smoking tobacco is challenging.

Concerns have been raised regarding the use of e-cigarettes among pregnant women. While it is correct that use of nicotine during pregnancy may pose risks to the fetus, it depends on the source of delivery. For example, in the UK, NRT is widely prescribed to pregnant women who smoke and find it difficult to stop. A recent UK longer-term study of a trial of NRT in pregnant smokers followed up the infants of women who had stopped smoking using NRT. It identified that NRT is safe to use during pregnancy and that the priority is to support women to not smoke.[11] We cannot extrapolate from the NRT evidence and apply it to e-cigarettes but need to be cautious about assuming that the evidence on nicotine use during pregnancy from smoking would be directly applicable to the use of e-cigarettes.

Perceived harm

In Great Britain, despite a favourable regulatory environment and a strongly supportive public health community, public perceptions regarding e-cigarettes remain inaccurate, with only 13% of the public in 2017 understanding that vaping e-cigarettes is a lot less harmful than smoking cigarettes. Among smokers, perceptions are becoming worse, with only 20% accurately believing in 2017 that using e-cigarettes is a lot less harmful than smoking, down from 31% in 2015. Also of concern is smokers' understanding of nicotine and the relative harms of NRT, which have recently become more

[9] Cochrane Tobacco Addiction Review Group. Written evidence submitted to the UK Parliament Science and Technology Committee inquiry into the health, regulatory and financial implications of e-cigarettes. http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/ecigarettes/written/75240.pdf

[10] McNeill A, Brose LS, Calder R, et al. (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf

[11] Cooper S, Taggar J, Lewis S et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. Lancet Respir Med. 2014; Sep;2(9):728-37. doi: 10.1016/S2213-2600(14)70157-2. Epub 2014 Aug 10.

inaccurate.[12] Public Health England reports that in 2017, only 13.5% of adult smokers correctly thought that none or a very small part of the risk of smoking comes from nicotine, whereas 6% thought that it was nearly all the risk and one quarter did not know. Similar findings among young people have also been reported in Great Britain.[13]

Public health effects

E-cigarettes are controversial for a few reasons, one being their potentially negative impact on public health. While these devices may assist some smokers in quitting, there are concerns that e-cigarettes could interfere with others' quit attempts (*"why quit when I can vape in smoke-free places?"*) and attract past smokers back to nicotine, or worse—entice non-smokers, particularly youth, to start. However, it is important to understand that the population health impact depends critically upon whether the never smoker who tries e-cigarettes would have tried and gone on to smoke combustible cigarettes in the absence of e-cigarettes. It should also be noted that in high income countries like Canada, as many as 40% of smokers make a quit attempt each year, but only 3–5% remain abstinent for more than 6 months, indicating that many smokers who try to quit soon relapse to smoking.[14]

A study in the United States looking at the potential health impact from an endgame strategy directed at replacing all or most cigarette smoking with e-cigarette use over a 10-year period compared different scenarios on overall initiation, cessation and switching and their population health outcomes. Compared with the status quo, even under a pessimistic scenario in which e-cigarettes are assumed to be 60% less harmful than cigarettes, 1.6 million premature deaths could be averted with 20.8 million fewer life years lost, the largest gains being realized among younger cohorts.[15] It is imperative that the government strike the right regulatory balance to maximize the benefits and minimize risks to both individuals and public health. Much can be done to educate Canadians on the health and safety aspects of e-cigarettes and to incentivize smokers to choose less harmful alternatives through various policy levers including price, taxation, packaging, labelling, and advertising and promotion.

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[12] Action on Smoking and Health UK. Fact sheet: Use of e-cigarettes (vapourisers) among adults in Great Britain. May 2017. http://ash.org.uk/download/use-of-e-cigarettes-among-adults-in-great-britain-2017/

[13] McNeill A, Brose LS, Calder R, et al. (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf

[14] Levy DT, Cummings MK, Villanti AC et al. A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products. Addiction 2017;112:8–17, doi:10.1111/add.13394

[15] Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. Tobacco Control 2018;27:18-25.

Gateway theory remains controversial and might never be proved

In its review of the evidence, the National Academies of Sciences, Engineering & Medicine concluded that in never smokers, e-cigarettes *may* lead to ever smoking, but found no evidence that e-cigarette use leads to *regular* smoking. On this issue, scientists emphasize that it is difficult to establish causality because all available studies are observational (i.e. not performed under lab conditions where variables can be controlled) with confounding factors that are challenging to avoid. Because of the impossibility of conducting experiments in young non-users, gateway theories may never be provable and may always remain controversial.[16] There is definitely an association between teen e-cigarette use and smoking; however, the reason is most likely explained by "common liability"—the things that cause young people to vape are the same personal characteristics and social circumstances that cause them to smoke.

Conclusion

Despite the development of an impressive body of research on e-cigarettes in recent years, significant gaps persist. Scientific proposals to standardize definitions and research methods will make it easier to compare studies and draw reliable conclusions. Health Canada has announced the intention to improve surveillance of e-cigarette use in Canada which will shed light on Canadians' perceptions of vapour devices, their dual use and the role that e-cigarettes play with respect to smoking reduction and cessation. However, it will take time before better data are available, and longer still for causal relationships to emerge from longitudinal studies.

With respect to cessation, the research to date suggests that e-cigarettes are as effective as NRT. This is significant, as the technology could provide another tool in the public health arsenal against the tobacco epidemic. Further, these studies used first generation "cig-a-like" devices which are now largely obsolete due to their poor delivery of nicotine. The Cochrane Collaboration has identified more studies for a future review of the evidence which should provide a more robust endorsement of the cessation utility of e-cigarettes generally, and later models specifically.

[16] Etter JF. E-cigarettes and the obsolescence of combustion. Expert Review of Respiratory Medicine 2018; doi: 10.1080/17476348.2018.1453809. https://www.tandfonline.com/doi/pdf/10.1080/17476348.2018.1453809