Setting the agenda for tobacco harm (reduction) research

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The Virtual E-Cigarette Summit 2020
Setting the agenda for tobacco harm (reduction) research

WHO set(s) the agenda?

• Self-appointed special interests (children; anti-tobacco/nicotine industries), including agenda-driven scientists and some authoritative organizations.

• Not the majority of scientists interested in tobacco and nicotine – laggards.

• FDA/regulatory bodies – also play catch up.

• Tobacco/nicotine industries – follow FDA/regulatory bodies.
What was/is the agenda?

Zombie theories (cannot be killed by evidence, refuse to die)

• Use of e-cigarettes (and all alternative nicotine products) *causes* naïve users (esp. youth) to smoke cigarettes – The Gateway Hypothesis.

• Use of e-cigarettes (and all alternative nicotine products) *causes* smokers to fail quitting (attempting or succeeding), or it doesn’t help them to quit.

• Use of e-cigarettes (and all alternative nicotine products) *causes* biological (and other) harms.
Use of e-cigarettes (and all alternative nicotine products) causes naïve users (esp. youth) to smoke cigarettes – The Gateway Hypothesis.

NASEM (2018):

Conclusion 16-1. There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.

Causal conclusion
Across the studies, a wide range of covariates were adjusted for that spanned a number of sociodemographic, interpersonal, environmental, and intrapersonal factors, including use of other substances (see Table 16-1), which the committee considered a comprehensive selection of confounding factors...

By contrast, ecological trends in e-cigarette use and smoking prevalence in youth across time failed to provide confirmatory support that e-cigarette use causes smoking initiation, and, if anything, are more consistent with the notion that e-cigarette use is associated with reduced smoking. However, ecological studies of trends going back a decade found that the rate of reduction of smoking in U.S. youth has remained consistent and has not accelerated in recent years when e-cigarettes have become popular.”
Breathtaking “scientific” interpretation and inference
Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation

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National Centre for Youth Substance Use Research, University of Queensland, Brisbane, QLD, Australia; Discipline of Psychiatry, University of Queensland, Brisbane, QLD, Australia; and School of Public Health, University of Queensland, Brisbane, QLD, Australia.
There is a longitudinal association between adolescent vaping and smoking initiation; however, the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders.

*All but one study were rated as having critical or serious risk of bias*; this finding was inconsistent with previous reviews, which rated most of the studies as having a low risk of bias.

The US National Academies of Sciences and Medicine have stated that: ‘Across the studies, a wide range of covariates were adjusted for that spanned a number of sociodemographic, interpersonal, environmental, and intrapersonal factors, including use of other substances, which the committee considered a comprehensive selection of confounding factors’ (p. 533). *However, our analysis demonstrates that this was not the case.*
Recommendations

Please stop. But if you must study the gateway hypothesis, do a better job of measuring confounding factors, and use proper causal inference methods (minimum bar).

Youth population surveillance studies are probably adequate for most purposes, but report (and release) all of the data. Who uses these products and why? - CONTEXT
Use of e-cigarettes (and all alternative nicotine products) causes smokers to fail quitting (attempting or succeeding), or it doesn't help them to quit.
Findings—38 studies (of 577 studies identified) were included in the systematic review; all 20 studies with control groups (15 cohort studies, three cross-sectional studies, and two clinical trials) were included in random effects meta-analysis and sensitivity analyses. Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (odds ratio [OR] 0·72, 95% CI 0·57–0·91).

Interpretation—As currently being used, e-cigarettes are associated with significantly less quitting among smokers.
Crucially, this group of studies (the longitudinal surveys) share a serious limitation. As these studies only recruited current smokers, they excluded those people from the same population who tried ECs and stopped smoking (e.g. if 100 smokers tried ECs and 50 stopped smoking, these studies would only recruit the 50 who continued to smoke). Following up ‘treatment failures’ is likely to show a low treatment effect, even for treatments that are highly effective. To assess the effects of ECs on smoking, participants need to be recruited prior to initiating EC use. In future versions of this review, as higher-quality data become available, we will no longer include this group of studies.
Prevalent User Bias

A is initiation of a drug, V1 is continued use, and S is selection into a study of prevalent users. Common causes V2 of continued use and the outcome Y, such as underlying health conditions, could lead to selection bias if not taken into account.

“As these studies only recruited current smokers, they excluded those people from the same population who tried ECs and stopped smoking (e.g. if 100 smokers tried ECs and 50 stopped smoking, these studies would only recruit the 50 who continued to smoke). Following up ‘treatment failures’ is likely to show a low treatment effect, even for treatments that are highly effective. To assess the effects of ECs on smoking, participants need to be recruited prior to initiating EC use.”

Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E-Cigarettes (N = 438)</th>
<th>Nicotine Replacement (N = 446)</th>
<th>Primary Analysis: Relative Risk (95% CI)†</th>
<th>Sensitivity Analysis: Adjusted Relative Risk (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: abstinence at 52 wk — no. (%)</td>
<td>79 (18.0)</td>
<td>44 (9.9)</td>
<td>1.83 (1.30–2.58)</td>
<td>1.75 (1.24–2.46)‡</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence between wk 26 and wk 52 — no. (%)</td>
<td>93 (21.2)</td>
<td>53 (11.9)</td>
<td>1.79 (1.32–2.44)</td>
<td>1.82 (1.34–2.47)‡</td>
</tr>
<tr>
<td>Abstinence at 4 wk after target quit date — no. (%)</td>
<td>192 (43.8)</td>
<td>134 (30.0)</td>
<td>1.45 (1.22–1.74)</td>
<td>1.43 (1.20–1.71)¶</td>
</tr>
<tr>
<td>Abstinence at 26 wk after target quit date — no. (%)</td>
<td>155 (35.4)</td>
<td>112 (25.1)</td>
<td>1.40 (1.14–1.72)</td>
<td>1.36 (1.15–1.67)‡</td>
</tr>
<tr>
<td>Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)</td>
<td>44/345 (12.8)</td>
<td>29/393 (7.4)</td>
<td>1.75 (1.12–2.72)</td>
<td>1.73 (1.11–2.69)∥</td>
</tr>
</tbody>
</table>
Electronic cigarettes for smoking cessation (Review)


Authors' conclusions

There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the degree of effect, particularly when using modern EC products. Confidence intervals were wide for data on AEs, SAEs and other safety markers. Overall incidence of SAEs was low across all study arms. We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.

The main limitation of the evidence base remains imprecision due to the small number of RCTs, often with low event rates. Further RCTs are underway. To ensure the review continues to provide up-to-date information for decision-makers, this review is now a living systematic review. We will run searches monthly from December 2020, with the review updated as relevant new evidence becomes available. Please refer to the Cochrane Database of Systematic Reviews for the review's current status.
Observational research study strengths and limitations

Strength:

• Population-level inferences – external validity – but estimates can be “off”.

Limitations:

• Abstract – Removed from reality (e.g., past 30 day use).

• Provisional – Always lagging (some things change quickly).

• Incomplete – Measurement is usually superficial and error-prone; what is meaningful to people, not just to researchers, regulators, special interests, etc.?

• Exposures/interventions poorly defined and ad hoc (MSU).
Observational research study strengths and limitations

Limitations:

• Outcomes: Multidetermined – Isolating single causes mangles reality. How much is a little, a lot (p-values don’t tell us)? Unobserved confounders.

• Causal inference – Not impossible, but difficult. Seeing, not doing. Proper causal inferential methods are required (minimum bar). Population samples do not mitigate confounding or selection biases.
Addressing unmeasured confounding in comparative observational research

Xiang Zhang, Douglas E. Faries, Hu Li, James D. Stamey, Guido W. Imbens

Real-world evidence to support regulatory decision-making for medicines: Considerations for external control arms

Mehmet Burcu, Nancy A. Dreyer, Jessica M. Franklin, Michael D. Blum, Cathy W. Critchlow, Eleanor M. Perfetto, Wei Zhou
Recommendations

• RCTs: Full steam ahead

• What’s the question? Quitting smoking cigarettes, reduction, switching, reduced harms compared to smoking?

• What’s the intervention? What’s plausible and how is it related to what people really do or can do in their ordinary lives? Compared to what (e.g., therapeutic options)? Real-world RCTs?

• Observational studies: Fit for purpose? Use proper causal inference methods; don’t “select” subpopulations.
Use of e-cigarettes (and all alternative nicotine products) causes biological (and other) harms.
eFigure 2. Patterns of Change in NNAL, CO, and Cotinine for e-Cigarette Trajectory Groups
**Respiratory symptoms improve**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>E-Cigarettes (N = 315)</th>
<th>Nicotine Replacement (N = 279)</th>
<th>Relative Risk (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>52 Weeks</td>
<td>Baseline</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>120 (38.1)</td>
<td>66 (21.0)</td>
<td>92 (33.0)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>102 (32.4)</td>
<td>74 (23.5)</td>
<td>86 (30.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>173 (54.9)</td>
<td>97 (30.8)</td>
<td>144 (51.6)</td>
</tr>
<tr>
<td>Phlegm</td>
<td>137 (43.5)</td>
<td>79 (25.1)</td>
<td>121 (43.4)</td>
</tr>
</tbody>
</table>

* Symptoms were assessed by asking whether participants had the symptom (yes or no).
† Relative risk was calculated by means of logistic regression. Symptoms at 52 weeks were regressed onto trial group, with adjustment for baseline symptoms and trial center.
Pulmonary function improves in switchers with COPD
Recommendations

• Pay attention to research with human beings

• Switching studies and, to a much lesser extent, known group comparisons (must include cigarette smokers)

• Biomarker and symptom studies for short-term effects

• More health outcome studies (except for observational studies which are riddled with potential confounding, e.g., disentangling smoking and e-cig use histories of exposure)
You've got to accentuate the positive
Eliminate the negative
And latch on to the affirmative
Don't mess with Mister In-Between

You've got to spread joy up to the maximum
Bring gloom down to the minimum
Have faith or pandemonium's
Liable to walk upon the scene