Contrasting Adverse Effects Associated With Low And High Nicotine Concentration Electronic Cigarettes (EC): A Systematic Review Meta-analysis

Mr. Aathavan Shanmuga Anandan1,2, Dr. Daniel Stjepanovic1, Dr. Gary Chan1
National Centre for Youth Substance Use Research1, Faculty of Medicine, The University of Queensland 2

INTRODUCTION
The use of alternative forms of nicotine delivery as an aid for tobacco cessation is the current mainstream approach to harm reduction and smoking cessation. The role of electronic cigarettes (ECs) as a tool for quitting tobacco is contentious with safety and adverse effects (AEs) commonly cited as criticisms against its use.

This systematic review compares the adverse effects associated with a low nicotine concentration (LNC) (<6mg/mL) versus high nicotine concentration (HNC) (>6mg/mL) in ECs. The use of the 6mg/mL threshold was chosen as this is considered the standard minimum concentration of nicotine in a conventional tobacco cigarette.

METHODS
- Studies reporting quantitative data on common AEs were included in final data extraction
- Database search for EC adverse effects was executed on PubMed, Web of Science & PsycINFO
- Database search resulted in 2850 unique entries (post-duplicate removal) with 25 papers included in final analysis
- Studies were subsequently differentiated into low nicotine concentration (LNC) (<6mg/mL) and high nicotine concentration (HNC) (>6mg/mL) sub-groups
- Ultimately, of the 25 articles, 9 reported LNC AEs and 16 reported HNC AEs

RESULTS

<table>
<thead>
<tr>
<th>Odds Ratio (OR)</th>
<th>Low Nicotine Concentration (LNC)</th>
<th>High Nicotine Concentration (HNC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Irritation</td>
<td>–</td>
<td>2.09</td>
</tr>
<tr>
<td>Cough</td>
<td>–</td>
<td>1.65</td>
</tr>
<tr>
<td>Vertigo</td>
<td>–</td>
<td>1.86</td>
</tr>
<tr>
<td>Nausea</td>
<td>–</td>
<td>2.86</td>
</tr>
<tr>
<td>Headache</td>
<td>0.52</td>
<td>–</td>
</tr>
</tbody>
</table>

Figure 2: Comparison of the joint adverse effects (AEs) between low nicotine concentration (LNC) electronic cigarettes (EC) and high nicotine concentration (HNC) electronic cigarette (EC). Symptoms Prevalence (Frequency).

Overall, results indicate that HNC ECs were associated with a greater incidence of:
- Nausea (OR = 2.86)
- Vertigo (OR = 1.86)
- Oral Irritation (OR = 2.09)
- Cough (OR = 1.65)

Contrarily, LNC ECs induced a greater incidence of:
- Headache (OR = 0.52)

HNC ECs were associated with a greater reported side effect incidence of vertigo, nausea, cough and oral irritation. These symptoms are explainable by the elevated nicotine concentration, replicating common nicotine exposure symptoms.

LNC ECs noted a greater incidence of headache. The apparent increase in incidence of headache in LNC ECs was likely attributed to the effects of nicotine withdrawal in smokers attempting cessation therapy. Headache/migraines are an established AE of nicotine withdrawal, and the lack of supplemental nicotine in LNC ECs may have likely resulted in the experience of withdrawal.

Ultimately, optimising adherence to cessation is associated with both minimising the adverse effects associated with withdrawal and the adverse effects of supplemental nicotine within electronic cigarettes. Reaching an equilibrium, where the impedance of both categories of adverse effects are minimised would lead to the greatest adherence to long-term tobacco cessation, and thus, improved health outcomes.

The current systematic review noted two key limitations. Firstly, the review did not adjust for covariates and thus reported unadjusted odds ratios (OR). Furthermore, the review contained EC users which were a mix between never tobacco smokers, ex-smokers and current tobacco smokers. The variation in experience of smoke inhalation may have led to variation in results and reduced generalisability to the general population.

This research provides an effective benchmark to understand the AEs associated LNC and HNC in electronic cigarettes. To further compound on this research, clinical trials investigating the optimal concentration of nicotine to minimise adverse effects could be conducted. Additionally, trials noting the nicotine concentration associated with the greatest adherence to tobacco cessation therapy would provide high practical relevance.

CONCLUSION
In summary, the current review provided an understanding of the influence that varying concentrations of nicotine within electronic cigarettes had on adverse effects. Through this, we can further investigate the implications the reported adverse effects have on adhering to cessation therapy. By determining the nicotine concentration associated with the greatest adherence to tobacco cessation, the burden of disease this drug places on society can be alleviated.