Australian National University

Nicotine e-cigarettes for smoking cessation: Evidence to support guideline development

Report prepared for the
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A C K N O W L E D G E M E N T S

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C I T A T I O N

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1. Introduction

The National Centre for Epidemiology and Population Health (NCEPH) at the Australian National University (ANU) was commissioned by the Australian Department of Health to undertake a program of research on electronic cigarettes (e-cigarettes) in the Australian context. This included evidence reviews on: the 'hardening hypothesis'; current smoking prevalence and trends; effects of e-cigarettes on smoking cessation and uptake and health outcomes; and a public health assessment of e-cigarettes.

Building on the body of work on e-cigarettes, this document outlines evidence reviews and technical support for the evidence-to-decision process for updating the e-cigarettes module of the RACGP guidelines for smoking cessation which NCEPH was commissioned to complete.

The evidence review process was conducted independently of the Royal Australian College of General Practitioners (RACGP). As part of this work, a comprehensive updated review of the evidence relating to the use of e-cigarettes for smoking cessation was undertaken, using methods detailed in section 2, below. In line with best practice for guideline development, GRADE (Grading of Recommendations, Assessment, Development and Evaluations) methods were used to reach recommendations on the use of e-cigarettes for smoking cessation. The GRADE process is further described in Section 3. In the GRADE process, the Summary of Findings tables were then used to inform the Evidence to Decision framework, which are found at Section 4. The Framework assisted the guideline module Expert Advisory Group to work through the evidence, and apply it to updating the guidance on electronic cigarettes. Particular consideration was given to whether or not there were compelling reasons to change the 2019 overall recommendation – conditional recommendation for either the intervention or the comparison – in the light of new evidence and whether or not new recommendations needed to be developed.

2. Methods – evidence review process

As the work for the RACGP built upon the evidence review process for the Australian Department of Health, there was slight variation in the methods employed across the different areas, detailed below.

Researchers from NCEPH worked alongside the RACGP to update the Evidence to Decision Framework, which had been undertaken by the Joanna Briggs Institute in 2019. Relevant evidence from the NCEPH body of work for the Australian Department of Health has been incorporated into the framework, particularly in the 'Desirable Effects' and 'Undesirable Effects' sections. In several sections additional research was conducted, as described below. As the framework includes evidence from many and diverse sources, the methodology for each section has been described separately.

2.1 The Problem: tobacco smoking

A rapid literature search was conducted on the health impacts of smoking in Australia, focusing on the most recent and reliable Australian-based data. The previous framework (2019) included data from the Australian Institute of Health and Welfare's 'Australian Burden of Disease Study', published in 2016. An updated dataset of the same study was published in 2019, and it was these data which made up the majority of this section.

2.2 Desirable Effects

Evidence for this section was derived from one of the NCEPH deliverables for the Australian Department of Health work, 'Efficacy of e-cigarettes as aids to cessation of combustible tobacco

smoking: updated evidence review'.[1] Below is a brief summary of the methods used in that systematic review.

A systematic review was undertaken to examine the efficacy of e-cigarettes as a smoking cessation aid. Six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were initially searched between 5 February and 2 March 2020, with an additional search conducted on 27 April 2021 to retrieve papers published since the initial search. There was no date limit on the search and only studies with abstracts published in English were included. The systematic review protocol was published on PROSPERO (CRD42020170692).

The review included randomised controlled trials (RCTs) where current smokers were randomised to intervention groups of e-cigarettes (with or without nicotine used in isolation or in combination with other cessation aids) or other smoking cessation treatments such as approved nicotine replacement therapy (NRT) and behavioural support. Comparison groups included no intervention or usual care, non-nicotine e-cigarettes, counselling, NRT, or a combination of these. Outcomes were biochemically verified sustained cessation (four months or greater) of combustible tobacco smoking and nicotine cessation, determined via biologically confirmed salivary cotinine. Only analyses including nicotine e-cigarettes were considered for the RACGP guidelines.

Papers were imported into an EndNote library, exported to Covidence, and duplicates removed. Two authors independently screened all titles, abstracts and full-texts identified in the searches per the predefined inclusion and exclusion criteria. ANU Library, Web of Science and Scopus were used to complete forward and backward citation searches on included articles.

Two researchers independently extracted data using a pre-specified data extraction template. Relative risks and 95% confidence intervals – by intention to treat – were extracted from each paper or, when possible, calculated from number of events or percentages reported in the published study.

Risk of bias was assessed independently by two authors using the Cochrane Collaboration's tool for assessing risk of bias in randomised trials[2]. The certainty of the evidence, for each comparison, was evaluated using the GRADE approach.[3 4]

The review aimed to summarise the available high-quality, reliable evidence on the efficacy of e-cigarettes for smoking cessation. Avoiding the potential influence of competing interests on research findings is central to this. Research funding and author conflict of interest information was extracted from each study and studies were considered separately if they were funded and/or received contributions in kind from the tobacco or e-cigarette industry, or if their authors currently or previously received funding from the tobacco or e-cigarette industry.

2.3 Undesirable Effects

Four methods were used to compile evidence for this section. First, much of the evidence developed by the Joanna Briggs Institute in 2019 remained relevant and was retained and presented alongside updated evidence. Second, prevalence data from the Australian Institute of Health and Welfare National Drug Strategy Household Survey 2019 was used to inform evidence on patterns of e-cigarette use. Third, evidence on adverse events from RCTs included in *Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review* (detailed methods Section 2.2) was incorporated. Fourth, preliminary findings from another NCEPH deliverable, *'Electronic cigarettes and health outcomes: systematic review of evidence'* (interim report submitted to the Australian Department of Health in August 2021) was included, methods briefly described below.[5]

An umbrella and top-up systematic review was undertaken to examine the primary evidence on the health outcomes associated with e-cigarette use. The umbrella review considered evidence and conclusions from major international reviews, including the 2018 National Academies of Sciences, Engineering, and Medicine (NASEM) review[6], the 2020 Irish Health Research Board literature map,[7] the 2018 Public Health England review[8] with an evidence update in 2020,[9] the literature review by the Commonwealth Scientific and Industrial Research Organisation (CSIRO) of Australia[10], the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) review[11] and the US Preventative Services Task Force (USPSTF) reviews[12].

The top up review was of studies published since the NASEM review. Six databases (PubMed, Scopus, Web of Science, PsycINFO (Ovid), MEDLINE (Ovid), and Cochrane) were searched for published, peer-reviewed original research articles published between July 2017 and July 2020. Studies were restricted to evidence published from July 2017 to July 2020, to capture evidence published since the NASEM review search date commencing 1 February 2017, with continuing inclusion of studies up to 31 August 2017. Studies examining e-cigarettes delivering tetrahydrocannabinol were excluded, since these were considered out of scope by the Australian Department of Health. The systematic review protocol was published on PROSPERO (CRD42020200673).

In addition to the systematic review of primary research articles, a supplementary search to identify systematic reviews/meta-analyses, screened alongside the primary evidence, was completed. These studies, in addition to the major international reviews listed above[6-8 10-13], were used to identify studies that were not identified via the database search.

Papers were imported into an EndNote library, exported to Covidence, and duplicates removed. Two authors of the review independently screened all titles, abstracts and full-texts per the predefined inclusion and exclusion criteria. Discrepancies were resolved through consensus or by a third author. Forward and backward reference search using ANU Library, Web of Science and Scopus was performed on included articles (primary and systematic reviews).

One researcher independently extracted data from the primary research articles using a pre-specified, piloted data extraction Microsoft Excel template. Extracted data was checked by a second researcher. Discrepancies were resolved through consensus or by a third researcher.

Risk of bias for each included study was independently assessed by two researchers using the Joanna Briggs Institute suite of critical appraisal tools. Disagreements were resolved through consensus or by a third researcher. The quality of the body of evidence for health outcomes was evaluated using the GRADE approach[4], adopting the modification for the assessment of a public health intervention[14]. GRADE was applied only to clinical and subclinical outcomes; surveillance reports, case studies and case reports were excluded from GRADE assessments.

As this review aimed to summarise the available high-quality, reliable evidence on the health outcomes of e-cigarettes it was important to consider whether the authors of the studies under review held any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes. As such, information on the source of research sponsorship or external involvement was extracted. Where authors or studies declared funding from the tobacco or e-cigarette industry, the risk of bias was noted in the GRADE assessment.

The highest quality data were prioritised, depending on the health outcome, in the following order:

- Randomised control trials (including randomised cross-over)
- Prospective cohort studies
- Case-control studies

- Non-randomised clinical trials (with comparison group or compared to baseline).

For health outcomes where epidemiological studies were not available or were not relevant, and where these types of evidence were likely to be informative, other forms of evidence listed below were considered:

- Cross-sectional studies
- Case studies and case series (particularly for exposure-dependent health outcomes, for example, burns and injuries)
- Evidence from surveillance systems (usually in grey literature/reports).

Findings from the previous reviews[7 8 10-13], including NASEM[6], and the top up review were then integrated to summarise the evidence and draw conclusions regarding the likely health effects of e-cigarettes.

2.4 Balance of effects

A literature search was conducted to locate all recent major international reviews on e-cigarettes, combustible tobacco cessation and health outcomes. These findings were then considered alongside the evidence on desirable and undesirable effects.

2.5 Certainty of evidence

Information in this section expands upon the GRADE evidence found in the 'Desirable Effects' section.

2.6 Values

There have been no changes to this section since the first framework developed in 2019.

2.7 Acceptability (patient and clinician)

Compared with the 2019 framework, this section was significantly re-worked to align with the legal/regulatory changes currently occurring in Australia. As such, a large portion of the regulatory information was sourced from the Australian Therapeutic Goods Administration (TGA).

2.8 Feasibility (patient and clinician)

This section was updated to reflect changes in the regulatory landscape and their implications for patients and clinicians.

3. Methods - GRADE process

The GRADE process is a widely recognised framework for assessing evidence, preparing summaries and following a systematic approach for making recommendations to guide clinical practice. There is extensive information elsewhere about its development and application, including in the GRADE Handbook.[4] It begins by asking a specific question presented using the PICO model. That is, it specifies:

Patient, Population or Problem

Intervention, Prognostic Factor or Exposure

Comparison or Intervention (if appropriate)

Outcome to be measured or achieved

In this case, the PICO question was:

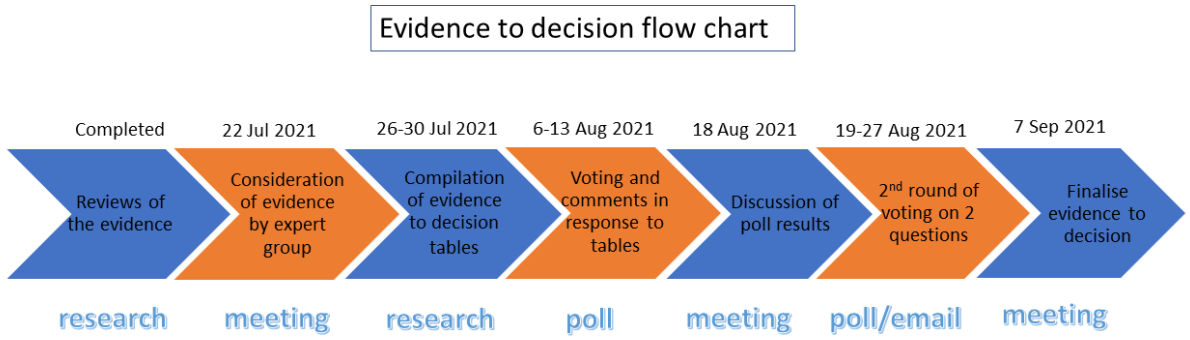
Should nicotine e-cigarettes be recommended for smoking cessation?

Comprehensive systematic reviews, as described in Section 2, are then conducted to address the specific questions:

1. Is the problem a priority?
2. How substantial are the desirable anticipated effects?
3. How substantial are the undesirable anticipated effects?
4. Does the balance between desirable and undesirable effects favour the intervention or the comparison?
5. What is the overall certainty of the evidence of effects?
6. Is there important uncertainty about or variability in how much people value the main outcomes?
7. Is the intervention acceptable to key stakeholders?
8. Is the intervention feasible to implement?

During the 2019 review of the evidence by the Joanna Briggs Institute, the questions about acceptability and feasibility were split into patient and clinician perspective. For consistency, this split was carried forward into the 2021 review.

Figure 1: Summary of evidence to recommendation process



The results of the evidence review described in Section 2 were placed into a Summary of Findings table, which is reproduced in Section 4. This was then sent to the guideline panel. Each member of the panel voted independently on their judgement for each of the questions.

NCEPH provided the panel with summary results from the voting and facilitated a meeting to discuss the judgements and the overall recommendations. There was consensus on most judgements, however the panel decided to split the question about undesirable effects into short-term and long-term effects and then to re-vote. It also sought to re-vote on the question of acceptability to patients where there were wide variations in views.

NCEPH then facilitated a second vote and summarised the results. The guideline panel met again and agreed on final judgements, recommendations and conclusions, which are summarised at pp. 27-28 of this report.

4. Results

2021 Evidence to decision framework: Electronic Cigarettes module

4.1 Question

SHOULD NICOTINE E-CIGARETTES BE RECOMMENDED FOR SMOKING CESSATION?	
Population:	Efficacy: current smokers of combustible tobacco Safety: current smokers, non-smokers, general Australian population
Intervention:	Nicotine e-cigarettes alone, or in addition to standard nicotine replacement therapy, for the purpose of smoking cessation
Comparison:	Nicotine replacement therapy, usual care, non-exposed
Main outcomes:	Efficacy: Biochemically validated sustained smoking cessation of 4 months or more Safety: Wide range of short-term and long-term health outcomes
Setting:	Australian population
Perspective:	The patient in which this recommendation will be made, the clinician who might be making this recommendation and populations affected by broader safety considerations
Conflict of interest:	Nil declared

4.2 Assessment

4.2.1 Problem

Is the problem a priority?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement ○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Overall, 11% of the Australian population aged 14 and over were current daily smokers in 2019.[15] Smoking causes a higher burden of disease than any other behavioural risk factor in Australia, representing 9.3% of the total burden of disease in 2015[16]. In 2015, the use of tobacco contributed to 13% of deaths, 14% of the fatal burden and 5% of the non-fatal burden[16]. Up to two thirds of current smokers will die from their habit if they do not quit.[17] Critically, there are socioeconomic disparities that exist, with the lowest socioeconomic group having a smoking-related burden 2.6 times greater than the highest socioeconomic group in Australia (the highest rate ratio of all risk factors)[16]. In addition, while the majority of Aboriginal and Torres Strait Islander people do not smoke, in 2018-19, 40.4% of Indigenous Australians aged 18 and over were current daily smokers.[18] Smoking is estimated to cause around one third of all deaths in Aboriginal and Torres Strait Islander people and half of deaths in these populations at age 45 and over. The use of tobacco is associated with a range of different diseases, contributing to the burden of nine disease groups. Below are the estimated percentages of the burden attributable to tobacco use for different disease groups, in 2015[16]: - 41% of respiratory diseases - 22% of cancers - 12% of cardiovascular diseases - 7% of infections - 4% of endocrine disorders Smoking is a significant health and economic issue for the Australian community. It was estimated that the net cost of smoking in Australia in 2015-16 - both tangible and intangible - was $136.9 billion.[19] Smoking prevalence continues to fall in Australia driven by smoking cessation in established smokers, and, increasingly, by reduced uptake in young people. Supporting smokers to quit is an important component in addressing the enormous economic and health burden that tobacco use inflicts on Australia.	

4.2.2 Desirable Effects

How substantial are the desirable anticipated effects?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement ○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Comparison 1: Nicotine e-cigarettes (nicotine concentration >0.01mg/mL) versus nicotine replacement therapy for smoking cessation**	The overall judgement regarding how "substantial the desirable effects are" was made following review of all six comparisons included in this section. One panel member noted that one comparison was with previously effective therapy, which may mean that the anticipated benefits are moderate since it is a small benefit over NRT. Following discussion, the group unanimously decided to make the judgement **Small**.

According to the evidence review, there is limited evidence that nicotine e-cigarettes (nicotine concentration >0.01mg/mL) may be more effective than nicotine replacement therapy for smoking cessation. In absolute terms, for every 1000 people treated, 56 more (from 21 more to 104 more) may achieve biochemically validated smoking cessation using a nicotine e-cigarette compared to nicotine replacement therapy.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with Nicotine Replacement Therapy	Risk difference with Nicotine E-Cigarettes
Smoking Cessation assessed with: Biochemically Validated (Expired Carbon Monoxide) Follow up: range 26 weeks to 52 weeks	1468 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.67** (1.21 to 2.28)	Study population	
				81 per 1,000	**55.2 more per 1,000** (17.3 more to 105.4 more)

Some issues in overall risk of bias (assessment ROB2 tool) and consideration of potential competing interest

Confidence Intervals are somewhat imprecise, ranging from a potentially small effect to a large effect (1.21 -2.28). However, there are a low number of events, with 161 events not meeting the Optimal Information Size threshold.

Comparison 2: Nicotine e-cigarettes versus non-nicotine e-cigarettes for smoking cessation

According to the evidence review, there is insufficient evidence as to whether nicotine e-cigarettes are more, less or equally effective as non-nicotine e-cigarettes for smoking cessation. In absolute terms, for every 1000 people, 32 more

(from 1 fewer to 94 more) could potentially achieve biochemically validated smoking cessation using a nicotine e-cigarette compared to a placebo e-cigarette.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with Placebo E-Cigarettes	Risk difference with Nicotine E-Cigarettes
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide) Follow up: range 24 weeks to 52 weeks	1057 (4 RCTs)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.61** (0.98 to 2.65)	Study population	
				43 per 1,000	**32.0 more per 1,000** (1.1 fewer to 93.6 more)

Significant issues in overall risk of bias (assessment ROB2 tool) and consideration of potential competing interest
Confidence intervals are somewhat imprecise (0.94 – 2.65). There are also few events, 82 events does not meet the Optimal Information Size threshold.

<u>Comparison 3:</u> Nicotine e-cigarettes versus no intervention or usual care for smoking cessation

According to the evidence review, there is limited evidence that nicotine e-cigarettes may be more effective than no active-intervention or usual for smoking cessation. In absolute terms, for every 1000 people, 11 more (from 2 fewer to 35 more) could potentially achieve biochemically validated smoking cessation using a nicotine e-cigarette compared to no active intervention or usual care.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with No Intervention or Usual Care	Risk difference with Nicotine E-Cigarettes
				Study population	

Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide) Follow up: range 16 weeks to 52 weeks	2549 (5 RCTs)	⨁◯◯◯ VERY LOW[a,b,c]	**RR 2.30** (1.19 to 4.42)	77 per 1,000	**10.6 more per 1,000** (2.0 more to 35.3 more)

Significant issues in overall risk of bias (assessment ROB2 tool) and consideration of potential competing interest
Widely differing estimates of treatment effect and confidence intervals.
Confidence Intervals are wide (1.19 – 4.42). Low number of events, 42 events does not meet the Optimal Information Size threshold.

<u>Comparison 4:</u> Nicotine e-cigarettes and NRT versus non-nicotine e-cigarettes and NRT for smoking cessation

According to the evidence review, there is insufficient evidence that nicotine e-cigarettes combined with nicotine replacement therapy are more effective than placebo e-cigarettes combined with nicotine replacement therapy for smoking cessation. In absolute terms, for every 1000 people, 33 more (from 3 more to 82 more) could potentially achieve biochemically validated smoking cessation using a nicotine e-cigarette combined with NRT compared to a placebo e-cigarette combined with NRT.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with Placebo E-Cigarettes and NRT	Risk difference with Nicotine E-Cigarettes and NRT
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide) Follow up: range 24 weeks to 26 weeks	1039 (2 RCTs)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.77** (1.07 to 2.94)	Study population	
				42 per 1,000	**33 more per 1,000** (3 more to 82 more)

Significant issues in overall risk of bias (assessment ROB2 tool) and consideration of potential competing interest
Very low number of events: 61 events does not meet the Optimal Information Size threshold.

<u>Comparison 5:</u> Nicotine e-cigarettes and NRT versus NRT alone for smoking cessation

According to the evidence review, there is insufficient evidence as to whether nicotine e-cigarettes combined with NRT are more, less or equally effective as NRT alone at achieving smoking cessation. In absolute terms, for every 1000

people, 46 more (from 2 fewer to 200 more) could potentially achieve biochemically validated smoking cessation using combination e-cigarettes and NRT compared to NRT alone.

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
				Risk with NRT Alone	Risk difference with Nicotine E-Cigarettes and NRT
Smoking Cessation assessed with: Biochemical Validation (Expired Carbon Monoxide Concentrations) Follow up: mean 26 weeks	625 (1 RCT)	⨁◯◯◯ Very LOW[a,b]	**RR 2.92** (0.91 to 9.33)	Study population	
				24 per 1,000	**46 more per 1,000** (2 fewer to 200 more)

Significant issues in overall risk of bias (assessment ROB2 tool) and consideration of potential competing interest
Very low number of events, 38 events does not meet the optimal information size threshold

Evidence regarding the most appropriate nicotine concentration is limited. All trials used freebase nicotine, at concentrations of 24mg/mL or lower. Two trials have demonstrated a significant benefit of nicotine e-cigarettes for smoking cessation compared to best practice NRT. One of these trials – Hajek et al[20]– was included in the systematic review and the other – Myers-Smith et al 2021[21] – was published after the search date. Both were conducted within UK smoking cessation services and hence were limited by UK regulations to nicotine concentrations of ≤20mg/mL – effectively 18mg/mL or lower. The first commenced with those randomised to e-cigarettes given a second generation refillable e-cigarette with one bottle of 18mg/mL nicotine e-liquid, with a recommendation to purchase further e-liquids of a flavour and strength of their choice.[20] The second involved smokers who had not been able to quit with conventional therapy.[21] Those randomised to nicotine e-cigarettes used a device and e-liquid of their choice, up to the UK limit of 20mg/mL.[21] The median nicotine concentration in use in the early phases of the trial was 10mg/mL and at 6 month follow-up it was 6mg/mL.

4.2.3 Undesirable Effects

How substantial are the undesirable anticipated effects?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement **Short-term** ○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know 2021 Judgement **Long-term** ○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	Comparison 1: Nicotine e-cigarettes (nicotine concentration >0.01mg/mL) versus nicotine replacement therapy for smoking cessation Comparison 2: Nicotine e-cigarettes versus non-nicotine e-cigarettes for smoking cessation Comparison 3: Nicotine e-cigarettes versus no intervention or usual care for smoking cessation Comparison 4: Nicotine e-cigarettes and NRT versus non-nicotine e-cigarettes and NRT for smoking cessation Comparison 5: Nicotine e-cigarettes and NRT versus NRT alone for smoking cessation **Health outcomes** While RCT evidence is required to establish the efficacy of e-cigarettes for smoking cessation, evidence regarding adverse events requires consideration of RCTs, observational and other evidence types. It should be noted that the available RCTs are small and limited in duration, devices considered and nicotine concentrations (all freebase ≤24mg/mL) used, as well as the populations included. They are therefore able to provide evidence on common short term adverse events relevant to these exposures. The preliminary findings from the review of health outcomes and findings from the review of smoking behaviour in relation to e-cigarettes are that there is: • Conclusive evidence that intentional or accidental exposure to e-liquids related to e-cigarettes can lead to poisoning, and that poisonings can be severe and can result in death. • Conclusive evidence that a significant number of poisonings occur in children under the age of six (8,296 between 2012 and 2017 in the United States alone). • Conclusive evidence that the use of e-cigarettes is related to burns and injuries, and that burns and injuries can be severe and can result in death. There is evidence that that the incidence of e-cigarette-associated burns and injuries has increased over time as use has increased (national	Discussion focused on the lack of data on long-term adverse effects as well as strong or moderate evidence for less common but potentially serious outcomes such as poisoning and injuries. It was also unclear how factors such as duration of use and dose are related to the short-term adverse effects. Some undesirable effects were large whereas others were uncertain. The group noted that it was difficult to consider all of the effects together and initially the majority of the group had voted or **Don't Know** and **Varies**" for the overall effects. The panel then decided to split this question into two parts, short-term and long-term. The group then voted again. The supplementary voting returned unanimous agreement that the long-term adverse effects were **Don't Know**. For the short-term adverse effects, the most frequent vote was for **Small**, which was the same as the 2019 judgement. After email exchanges, the group therefore made

	estimates from the United States indicate an increase from no cases between 2007-2012 to 726 in 2017). • Conclusive evidence that use of e-cigarettes can result in nicotine toxicity from inhalation, including seizures. • Conclusive evidence that e-cigarettes can cause e-cigarette, or vaping, product use-associated lung injury (EVALI), with many surveillance reports reporting the use of THC and/or vitamin E acetate. Cases of EVALI with reported use of ENDS without THC or vitamin E acetate have been reported. • Insufficient evidence on the relationship of ENDS to other clinical respiratory outcomes in smokers and non-smokers, including asthma, bronchitis and COPD. • Moderate evidence that e-cigarette use results in dependence on e-cigarettes among non-smokers and limited evidence that e-cigarettes results in dependence on e-cigarettes among smokers. • Strong evidence that use of e-cigarettes among non-smokers, particularly youth, increases the risk of progressing to current smoking of combustible tobacco around 3-fold.[22 23] • Limited evidence on reproductive outcomes, including effects on pregnancy outcomes. • No available evidence regarding the effects of nicotine e-cigarettes on clinical outcomes relating to cardiovascular disease, cancer, mental health, reproduction, development in children and adolescents, sleep, wound healing, cancer, neurological disease and endocrine, olfactory, optical, allergic and haematological outcomes. **Adverse events from RCTs** As reported in the systematic review by Hartmann-Boyce et al. (2021)[24], "The most commonly reported AEs were throat/mouth irritation, headache, cough, and nausea…. Very few studies reported data on other outcomes or comparisons and hence evidence for these is limited, with confidence intervals encompassing clinically significant harm and benefit." the most commonly reported adverse events (AEs) were mouth and throat irritation during the trial period. Adverse events were recorded and reported narratively in all but one (Halpern et al. 2018)[25] of the studies that have contributed to the above summary of findings tables and additional trial evidence included in Hartmann-Boyce (2021) are also considered here.[24] Overall, the most common adverse events associated with e-cigarette use were cough; dry/irritated mouth/throat; headache and nausea. These were all reported during the duration of the trial and there was no evidence on long term NRT use within these studies. Details of the specific trials presenting evidence are below. Adriaens et al. (2014),[26] recorded AEs through self-reporting in online diaries. The only complaint that was unique to the e-cigarette group was related to technical problems with the e-cigarette unit.	the judgement **Small,** noting variation in the views of the committee.

	Otherwise, there was no significant difference in the proportion of AEs between the e-cigarette and the CC groups. The AEs common to both groups included bad taste; dry/irritated mouth/throat; dizziness; headache; nausea; increased heart rate; increased weight and shortness of breath. Bullen et al. (2013)[27] did not provide descriptive information about the type of AE experienced in the study, but categorised AEs as 'serious' or 'non-serious'. There were no significant differences in the proportion of participants experiencing either a serious or non-serious AE between treatment groups, and no serious adverse event was related to product use. Caponnetto et al. (2013)[28] presented AE data combined between groups (nicotine versus placebo e-cigarette). Overall 26% of the study participants experienced cough; 22% shortness of breath; 20% throat irritation and 17% experienced a headache. Whilst no difference was found between the frequency and distribution of AEs among study groups at any time point, there was a decrease in reported AEs over time, compared to baseline. Of the participants randomised to receive the nicotine e-cigarette in the study by Carpenter et al. (2017)[29], 52% (24mg/ml) and 36% (16mg/ml) experienced at least one AE over the trial period. Combining e-cigarette nicotine concentration groups, 32% of all e-cigarette assigned participants experienced cough, 24% experienced nausea and 16% experienced mouth/throat irritation. In the control group receiving no intervention the most common AEs were headache (24%), cough (21%), and mouth/throat irritation (17%). No AE resulted in study termination. In their RCT of very low nicotine concentration e-cigarettes (0.01mg/mL) versus nicotine gum, Lee et al (2019)[30] reported no serious AEs. AEs were significantly less common in the ENDS group compared to the nicotine gum group (6.7% vs 17.3%, P=0.044). The most common AEs in both groups were oral pain, cough, dry mouth, headache, and nausea/vomiting in both groups. The AEs were considered of mild to moderate intensity and none led to withdrawal from the study. Cravo et al. (2016)[31] present comprehensive data on the number and type of AEs reported in e-cigarette using, or conventional cigarette using participants. Overall, AEs considered to be 'mild' were reported by 29.6% of the e-cigarette using participants, moderate AEs were experienced by 54.6% of the participants and 15.8 % experienced severe AEs. These were not significantly different when compared to the AEs reported by the conventional cigarette group. A greater percentage of participants in the e-cigarette group reported oropharyngeal pain (27.8%) compared to the conventional cigarette group (8.8%) and cough (17.0% vs. 7.8%), however all other AEs remained relatively stable. Hajek et al. (2019)[20] report AE data for nausea, sleep disturbances and throat/mouth irritation (pre-specified in study protocol). Nausea was more common in the participants randomised to receive NRT	

(37.9%) compared to those receiving the e-cigarette (31.3%). Throat/mouth irritation was more common in the e-cigarette group (65.3% vs. 51.2%). Sleep disturbances were common in both groups (65% for e-cigarette vs. 68% for NRT). The authors state that there were 27 serious adverse events in the e-cigarette group, and 22 in the NRT group. Of these, there were 5 respiratory events in the e-cigarette group and 1 respiratory event in the NRT group. No serious adverse event was classified by the trial clinician as being related to product use.

Holliday et al. 2019[32] reported no serious AEs among 80 smokers with periodontitis participating in their trial. There were 56 largely oral or dental AEs reported: 35 in the ENDS group and 20 in the control group.

At 3 month follow up, Lucchiari et al (2019)[33] reported throat irritation in 5.7% of participants in the ENDS group and 2.9% of the ENNDS group and cough in 10% of the ENDS group and 2.9% of the ENNDS group. At 6 months, 15.9% of the ENDS group and 5.6% of the ENNDS group reported throat irritation and 5.8% and 2.8%, respectively, reported cough.

Lee et al.[34] report that the common AEs to both NRT and e-cigarettes use were headaches (40% vs. 20%, respectively); nausea (10% vs. 25%); cough (10% vs. 30%) and throat irritation (30% vs 25%), however there were no significant differences in the rate of AE occurrence.

Tseng et al. (2016)[35] provide narrative description only as to the type of AEs that were common to both the nicotine e-cigarettes and placebo e-cigarettes, being mouth/throat irritation, cough, insomnia, abnormal dreams, headache and fatigue. The authors report that there was no difference in AEs between groups (34.1% for intervention and 17.5% for placebo group at week 1, P = .09; 22.5% for intervention and 10.3% for placebo group at week 3, P = .14; chi-square test).Eisenberg et al. (2020)[36] found AEs were common among 376 study participants. AEs were commonly reported among the 376 participants, including cough (242, 64%), dry mouth (201, 54%), rhinitis (188, 50%), and headache (185, 49%). Cough was reported by 95 nicotine e-cigarettes plus counselling participants (74%), 81 nonnicotine e-cigarettes plus counselling participants (64%), and 66 counselling alone participants (55%). Occurrence of other AEs was comparable between the nicotine and nonnicotine e-cigarettes plus counselling groups, but more frequent compared with the counselling alone group. During the 12 week treatment period there was 1 participant experiencing an SAE in the ENDS group, 4 in the ENNDS group and 2 in the counselling alone group. There were 2, 2, and 2 participants affected by SAEs in the corresponding groups during the 12-24 week follow up period.

Finally, Walele et al. (2016)[37] report that no participant reported a moderate or serious AE and no AEs lead to study withdrawal. The most common reported AEs were once again, cough; mouth/throat irritation; fatigue and headache. In Part 2 of the study, 58.3% of the participants reported a total of 13

AEs, all of which were evaluated as mild. The authors state that while no clear product trend was observed, most AEs occurred with the products the greater concentrations of nicotine.

Overall, nicotine e-cigarette use is associated with the occurrence of some mild AEs. The most common of which include coughing; dry/irritated mouth/throat; nausea and insomnia. However, the occurrence of these AEs are comparable to the rates of AEs experienced when participants were using either NRT, CC or placebo e-cigarettes. As reported by Caponetto et al. (2013) AEs related to e-cigarette use have the potential to decrease over time, however more study data is needed to validate this claim.

Dual use of e-cigarettes and combustible cigarettes

The commonest pattern of use of e-cigarettes in Australia is dual use, with 54% of current e-cigarette users in 2019 also being smokers.[1 15 23] Greater availability of e-cigarettes to smokers is likely to result in increased dual use, if a quit attempts fail, or if e-cigarettes were obtained without the intention of quitting.

Use of e-cigarettes in non-smokers, particularly youth

In 2019, around 16% of current e-cigarette users are never smokers and use of e-cigarettes in non-smokers is becoming increasingly common in young people.[1 15 23] Overall, among people in Australia aged 15-24, 22.3% report ever having used electronic cigarettes and 4.5% report recent use. Over half of these recent users (n=38,500) are estimated to be non-smokers (our calculations).[15] Greater availability of e-cigarettes in the community is likely to increase use in non-smokers (see below) and may also contribute to legitimising or normalising use as “safe”.

Diversion

Wider availability of e-cigarettes on prescription is likely to result in diversion, in keeping with observed behaviours regarding other prescription medications such as opiates. In contrast with opiates, there are no planned activities to reduce potential for diversion, such as real-time prescription monitoring (“anti Dr shopping” measures).

4.2.4 Balance of effects

Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement ○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ● Probably favours the intervention ○ Favours the intervention	Combustible tobacco smoking is highly damaging to health and quitting carries significant health benefits. The above evidence demonstrates limited evidence of efficacy of e-cigarettes for smoking cessation, along with evidence of specific individual and population health impacts, as well as considerable uncertainties for important clinical outcomes. Given the overwhelming negative health impacts of tobacco, any health benefits of ENDS are likely to be greater if they support complete quitting of combustible cigarettes, rather than dual use. The conclusions of recent major international reviews of the evidence are summarised below. The US Preventive Services Task Force review is particularly relevant as it considers the balance of benefits and harms within the clinical context. From an Australian standpoint, the Therapeutic Goods Administration notes that "Unlike Nicotine Replacement Therapy (NRT) products, which have been approved by the Therapeutic Goods Administration (TGA) for use as aids in withdrawal from smoking, no assessment of electronic cigarettes has been undertaken. This means the quality, safety and efficacy of electronic cigarettes is not known."[38] Based on our searches, ENDS are not registered as therapeutic products for smoking cessation with the US Food and Drug Administration, the EU EMEA, the UK MHRA or any other national drug regulatory body. The recent Scheduling decision by the TGA on ENDS aimed primarily at avoiding use in non-smokers, due to evidence of harm in this group.[39] **International Review** / **Conclusion** European Union Scientific Committee on Health, Environmental and Emerging Risks (April 2021)[11] — There is **weak evidence** for the support of electronic cigarettes' effectiveness in helping smokers to quit. The US Preventive Services Task Force (Jan 2021)[40] — The evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is **insufficient**, and the balance of benefits and harms cannot be determined.	In the initial voting, the vast majority of panel members voted for **Probably favours the intervention**. Two panel members commented that whilst it probably favours the intervention at the individual level, it does not favour the intervention at the population level. After panel discussion, the consensus remained **Probably favours the intervention.**

US Surgeon General (2020)[41]	The evidence is **inadequate** to infer that e-cigarettes, in general, increase smoking cessation. However, the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e-cigarettes not containing nicotine.	
Irish Research Board (June 2020)[42]	The systematic review and network meta-analysis of electronic nicotine delivery systems (e-cigarettes) versus therapies usually given for smoking cessation showed that there is **no evidence** of a difference in effect on incidences of smoking cessation. There is a low-level of certainty in these results.	
National Academies of Science, Engineering and Medicine (2018)[6]	Overall, there is **limited evidence** that e-cigarettes may be effective aids to promote smoking cessation. There is **moderate evidence** from randomised controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation. There is **insufficient evidence** from randomised controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration–approved smoking cessation treatments.	
Australian Commonwealth Scientific and Industrial Research Organisation (2018)[10]	The effectiveness of this method compared with other smoking cessation methods is **not known.**	

4.2.5 Certainty of evidence

What is the overall certainty of the evidence of effects?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement ○ Very low ● Low ○ Moderate ○ High ○ No included studies	**<u>Comparison 1:</u> Nicotine e-cigarettes versus nicotine replacement therapy for smoking cessation**	Although the GRADE ratings of the comparisons were low or very low, the most frequent initial response in the voting was for the judgement to be **Low,** emphasising the comparison with NRT. After discussion, the panel agreed to the final judgement as **Low**, which was the same as the 2019 judgement.
	Of the two studies for this comparison, one was judged to be at a low risk of bias[20] and the other to have some concerns.[27] The GRADE rating for this comparison was low and was driven by serious concerns in risk of bias (which also took potential competing interests into consideration) and imprecision.	
	<u>Comparison 2:</u> Nicotine -cigarettes versus non-nicotine e-cigarettes for smoking cessation	
	Of the four studies for this comparison, two were assessed as having a high risk of bias due to missing outcome data[28 36] and two were considered to raise "some concerns" due to deviations from the intended intervention and missing outcome data.[27 33] The GRADE rating for this comparison was very low and was driven by very serious concerns in the risk of bias assessment (which also took potential competing interests into consideration) and serious concerns in imprecision.	
	<u>Comparison 3:</u> Nicotine e-cigarettes versus no intervention for smoking cessation	
	Four out of the five studies included in this comparison were assessed as having a high risk of bias, one was judged to be at high risk for measurement of the outcome[28] and the other three judged high risk for missing outcome data[25 32 36]. One study was found to have some concerns and had concerns in two domains – deviations from intended intervention and missing data.[33] The GRADE rating for this comparison was very low and was driven by very serious concerns in the risk of bias assessment (which also took potential competing interests into consideration) and serious concerns in imprecision.	
	<u>Comparison 4:</u> Nicotine e-cigarettes and NRT versus non-nicotine e-cigarettes and NRT for smoking cessation	
	Both studies were judged to be at high risk of bias due to missing outcome data.[43 44] The GRADE rating for this comparison was very low and was driven by very serious concerns in the risk of bias assessment (which also took potential competing interests into consideration), serious concerns in indirectness and very serious concerns in imprecision.	

	<u>Comparison 5:</u> Nicotine e-cigarettes and NRT versus NRT alone for smoking cessation	
	The study was judged to be at high risk of bias due to missing outcome data.[43] The GRADE rating for this comparisons was very low and was driven by very serious concerns in the risk of bias assessment (which also took potential competing interests into consideration), serious concerns in indirectness and very serious concerns in imprecision.	

4.2.6 Values

Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	Most smokers of conventional cigarettes have a nominal understanding of the health risks associated with smoking. Whilst most smokers might understand the presence of increased health risks, the extent to which they are aware of the magnitude of such health risks is unclear.	The panel considered that smokers were largely aware of the risks of smoking and that most would like to quit. The vast majority of panel members voted for **Probably no important certainty or variability**. One member commented that it is unclear to what extent typical users of e-cigarettes even want to quit smoking, given the very low overall quitting rates in users – both in real life and in studies. After group discussion, the panel agreed that the judgment would remain **Probably no important certainty or variability.**

4.2.7 Acceptability

Is the intervention acceptable to key stakeholders?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement **Patient Perspective** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know **Clinician Perspective** ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	In 2019, after discussion with the guideline panel, it was unanimously decided that the acceptability of a recommendation for e-cigarettes needs to be separated into a patient and clinician perspective **Patient perspective** E-cigarettes vary in their acceptability among patients and the community. In countries where they are available as consumer goods, they are used by a minority of smokers, including in an estimated 12.7% of UK quit attempts from 2006-2018.[45] In Australia in 2019, 9.7% of current tobacco smokers reported current or recent e-cigarette use and 38.7% reported ever having used them.[15] Uncertainties about their long term health effects and the relatively recent EVALI outbreak in the US **Clinician perspective** From the clinician perspective, acceptability of the product is related to its quality, safety and efficacy and whether or not it is registered in Australia as a therapeutic good. As outlined above, e-cigarettes are not currently registered as therapeutic goods with the TGA (see below). The limited evidence on efficacy, highly variable devices and products, evidence on acute adverse effects and harms, and lack of evidence on long term effects of e-cigarette use means that clinicians may feel that this is an unacceptable treatment to offer their patients. Furthermore, products imported via the Personal Importation Scheme are not required to meet TGO 110 standards for labelling – including warning labels – and child resistant packaging. Since clinicians are not able to mandate where the prescription for e-cigarettes is filled, this it also likely to influence their acceptability to clinicians. **Research Evidence** Research evidence regarding the likely health impacts of e-cigarettes is given above. **Current regulation** A scheduling decision announced by the Australian Therapeutic Goods Administration in December 2020 clarified that consumers will require a valid Australian medical prescription to access nicotine e-cigarettes and certain other nicotine products from 1 October 2021. In Australia, e-cigarettes are not currently registered as therapeutic goods with the TGA. A person holding a prescription for nicotine e-	In the initial round of voting on the patient perspective, the majority were in favour of the judgement being **Yes**, however group discussion raised important differences in viewpoint. E-cigarettes are likely to be acceptable to patients who present to their GP asking for a prescription, and the rise in use of ENDS indicates that it is acceptable to a range of people. However, some panel members doubted that an unapproved therapy would be acceptable for the average patient. The group agreed to re-vote. In Round 2, the voting was evenly split between **Yes**, **Probably Yes** and **Varies**. On assessing this question, the panel noted the GRADE process recommends that the previous judgement only be changed when there is a compelling reason to do so, and the division in the voting would indicate that the reasons were not compelling. The panel agreed to make this judgement on patient perspective **Probably Yes.**

	cigarettes can either have this dispensed at an Australian pharmacy or can purchase them via the Personal Importation Scheme. Products dispensed at an Australian pharmacy must meet TGO 110 standards, including appropriate labelling and child-resistant packaging. The table below outlines these requirements. Products imported directly by consumers from overseas suppliers via the Personal Importation Scheme are not subject to the packaging and labelling requirements in TGO 110, although people using the Personal Importation Scheme are still encouraged to check if their product has compliant labelling and packaging. These products are also exempt from the record-keeping requirements in TGO 110. The TGO 110 ingredient requirements will continue to apply to these products.	In the voting on the clinician perspective, panel members were initially split between **Varies** and **Probably No,** which was the 2019 judgement. Panel members noted that there were potentially varying views among clinicians in rural and metropolitan settings, and in the type of general practice. There were also concerns that many practitioners would not be comfortable with prescribing an unapproved medicine and would preference NRT and other registered options. Whilst recognising that several in the panel still felt that **Probably No** was the best judgement, the panel decided that the lack of agreement itself indicated that **Varies** was a better judgement.

TGO 110 requirement	Products supplied in Australia (including products imported for supply in Australia) *	Products imported via Personal Importation Scheme
Labelling requirements (information to be provided on container, primary pack or in information sheet)		
Ingredient list	✓	✗
Nicotine concentration (mg/mL)	✓	✗
Warning statements	✓	✗

TGO 110 requirement	Products supplied in Australia (including products imported for supply in Australia) *	Products imported via Personal Importation Scheme
Packaging requirements		
Child-resistant packaging	✓ (except FDA PMTA marketing order compliant products)	✗
Ingredient requirements		
Nicotine (base and/or salt form(s)) the only active ingredient	✓ (except FDA PMTA marketing order compliant products)	✓ (except FDA PMTA marketing order compliant products)
Nicotine concentration/ content within 90 – 110% of what (if anything) is stated on the label	✓ (except FDA PMTA marketing order compliant products)	✓ (except FDA PMTA marketing order compliant products)
Nicotine (or equivalent base form) concentration ≤ 100 mg/mL	✓ (except FDA PMTA marketing order compliant products)	✓ (except FDA PMTA marketing order compliant products)
No prohibited ingredients added to product	✓ (except FDA PMTA marketing order compliant products)	✓ (except FDA PMTA marketing order compliant products)
Record-keeping obligations for Australian sponsors		
Maintain records demonstrating conformance with TGO 110	✓ (except FDA PMTA marketing order compliant products)	✗

* Packaging and labelling requirements can be met *after* importation into Australia (e.g. a sponsor may import a product with non-compliant labelling and then over-sticker the product in Australia prior to supply to a wholesaler or directly to pharmacy or other health practitioner). Ingredient and record-keeping requirements must be complied with at the time of importation.

	E-cigarettes are not currently subsidised by the Pharmaceutical Benefits Scheme.	

4.2.8 Feasibility

Is the intervention feasible to implement?

Judgement	Research evidence updated to 2021	Additional considerations
2021 Judgement **Patient perspective** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know **Clinician perspective** ○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	**Patient perspective** It is likely to be feasible for a patient to attend their doctor and receive a prescription. There is the potential for confusion regarding appropriate devices and nicotine concentrations. **Clinician perspective** Recent changes in regulation are likely to improve feasibility. However, nicotine e-cigarettes are not on the register of therapeutic goods in Australia. There are also issues associated with prescribing an e-cigarette product, such as standard prescription forms for nicotine e-liquids, uncertainties regarding appropriate starting doses and the lack of standard, approved, recommended devices. Medical indemnity considerations are also likely to be part of clinician considerations.	Issues were raised regarding the feasibility of prescribing an unapproved medicine and the lack of clarity regarding doses and devices, as well as safety concerns regarding supply through the Personal Importation Scheme. Legal concerns were also raised. The final judgement was **Probably Yes** from both patient and clinician's perspective.

4.3 Summary of judgements

	Judgement						
Problem	No	Probably no	Probably yes	**Yes**		Varies	Don't know
Desirable effects	Trivial	**Small**	Trivial	Large		Varies	Don't know
Undesirable effects (short-term)	Trivial	**Small**	Trivial	Large		Varies	Don't know
Undesirable effects (long-term)	Large	Moderate	Small	Trivial		Varies	**Don't know**
Balance of effects	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	**Probably favours the intervention**	Favours the intervention	Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
Acceptability (Patient)	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Acceptability (Clinician)	No	Probably no	Probably yes	Yes		**Varies**	Don't know
Feasibility (Patient)	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Feasibility (clinician)	No	Probably no	**Probably yes**	Yes		Varies	Don't know

4.4 Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

4.5 Conclusions

Recommendation
For people who have tried to achieve smoking cessation with TGA-approved pharmacotherapies combined with behavioural intervention but failed and are still motivated to quit smoking, e-cigarettes may be a reasonable intervention to recommend. However, this needs to be preceded by an evidence-informed shared-decision making process, whereby the patient is aware of the following caveats: 1. Due to the lack of available evidence, the long-term health effects of e-cigarettes are unknown. 2. E-cigarettes are not registered therapeutic goods in Australia and therefore their safety, efficacy and quality have not been established. 3. There is a lack of uniformity in delivery devices and e-liquid constituents which increases the uncertainties associated with their use. 4. TGO 110 permits extremely high concentrations of liquid nicotine to be prescribed and dispensed so, if prescribed, the patient must fully understand the potential consequences of high concentration liquid nicotine and take steps to minimise risk. 5. In order to maximise possible benefit and minimise risk of harms, dual use should be avoided and long-term use should be minimised.
Justification
This process compared e-cigarettes to NRT and usual care, not nicotine e-cigarettes to tobacco smoking. There is some limited evidence that, in the clinical context, nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care. However, the balance of risks, safety and efficacy of e-cigarettes needs to be considered in clinical decision-making about their use for smoking cessation. RCTs show that nicotine e-cigarettes can result in prolonged exposure to nicotine through ongoing exclusive e-cigarette use or dual use if smoking continues. Identified risks of e-cigarettes include: intentional and accidental poisoning; injuries and burns; immediate nicotine toxicity, including seizures; addiction; diversion; increased uptake of smoking in non-smokers; indoor air pollution; fires; and waste. The long-term effects on major clinical outcomes - such as cardiovascular disease, cancer, mental health, reproductive health; child and adolescent development; sleep, wound healing, cancer, neurological disease and endocrine, olfactory, optical, allergic and haematological disease – is not known.

Subgroup considerations
This recommendation may be more effective for smokers who are dependent on the behavioural or social components of smoking. Risks related to unintentional e-liquid poisoning are likely to be greater in people living in households with children and those with limited safe storage facilities. The likelihood of intentional poisoning using e-liquids is higher for those at risk of self-harm.
Implementation considerations
Registration with the TGA (Therapeutic Goods Administration) would encourage further standardisation and regulation of e-cigarette availability and use. Clinicians might be more accepting of recommending e-cigarettes with TGA testing and regulation. The current legislation and regulation of e-cigarettes varies state by state and this needs to be considered. Guideline implementation needs to address identified risks, including those relating to high nicotine concentration e-liquids.
Research priorities
More research is needed to investigate the efficacy of e-cigarette use for smoking cessation and the health risks associated with long term e-cigarette use. Potentially serious adverse effects such as respiratory events also need further investigation.

5. Summary

The GRADE process calls for changes to recommendations for existing clinical guidelines to be made only when there are compelling reasons to do so. For the 2021 update, all judgements were the same as the 2019 judgements, with the following exceptions:

- In 2021, the panel split the question about adverse effects into short-term and long-term. In 2019 the judgement on the question of adverse effects was *Don't Know*. In 2021, short-term effects were judged *Small* overall, although several panel members felt that *Moderate* was more appropriate. Long-term effects were judged *Don't Know*.

- In 2019, the question on acceptability to the clinician was judged as *Probably No*. In 2021, the panel judged it as *Varies*, to reflect the wide range of views amongst clinicians.

Consistent with the similarity in judgements, the overall recommendation remains the same as for 2019: *Conditional recommendation for either the intervention or the comparison.* It is important to re-iterate that the comparison in this case is nicotine e-cigarettes versus nicotine replacement therapy and/or usual care, not tobacco smoking.

The Conclusions, including recommendation, justification, sub-group considerations, implementation considerations and research priorities were updated and/or re-written in 2021.

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