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Electronic cigarettes for smoking cessation (Review)

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[Intervention Review]

Electronic cigarettes for smoking cessation

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ABSTRACT

Background

Electronic cigarettes (ECs) are handheld electronic vaping devices which produce an aerosol formed by heating an e-liquid. Some people who smoke use ECs to stop or reduce smoking, but some organizations, advocacy groups and policymakers have discouraged this, citing lack of evidence of efficacy and safety. People who smoke, healthcare providers and regulators want to know if ECs can help people quit and if they are safe to use for this purpose. This is an update of a review first published in 2014.

Objectives

To examine the effectiveness, tolerability, and safety of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

Search methods

We searched the Cochrane Tobacco Addiction Group's Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO to 1 February 2021, together with reference-checking and contact with study authors.

Selection criteria

We included randomized controlled trials (RCTs) and randomized cross-over trials in which people who smoke were randomized to an EC or control condition. We also included uncontrolled intervention studies in which all participants received an EC intervention. To be included, studies had to report abstinence from cigarettes at six months or longer and/or data on adverse events (AEs) or other markers of safety at one week or longer.

Data collection and analysis

We followed standard Cochrane methods for screening and data extraction. Our primary outcome measures were abstinence from smoking after at least six months follow-up, adverse events (AEs), and serious adverse events (SAEs). Secondary outcomes included changes in carbon monoxide, blood pressure, heart rate, blood oxygen saturation, lung function, and levels of known carcinogens/toxicants. We used a fixed-effect Mantel-Haenszel model to calculate the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes, we calculated mean differences. Where appropriate, we pooled data from these studies in meta-analyses.

Main results

We included 56 completed studies, representing 12,804 participants, of which 29 were RCTs. Six of the 56 included studies were new to this review update. Of the included studies, we rated five (all contributing to our main comparisons) at low risk of bias overall, 41 at high risk overall (including the 25 non-randomized studies), and the remainder at unclear risk.

There was moderate-certainty evidence, limited by imprecision, that quit rates were higher in people randomized to nicotine EC than in those randomized to nicotine replacement therapy (NRT) (risk ratio (RR) 1.69, 95% confidence interval (CI) 1.25 to 2.27; I^2 = 0%; 3 studies, 1498 participants). In absolute terms, this might translate to an additional four successful quitters per 100 (95% CI 2 to 8). There was low-certainty evidence (limited by very serious imprecision) that the rate of occurrence of AEs was similar) (RR 0.98, 95% CI 0.80 to 1.19; I^2 = 0%; 2 studies, 485 participants). SAEs occurred rarely, with no evidence that their frequency differed between nicotine EC and NRT, but very serious imprecision led to low certainty in this finding (RR 1.37, 95% CI 0.77 to 2.41: I^2 = n/a; 2 studies, 727 participants).

There was moderate-certainty evidence, again limited by imprecision, that quit rates were higher in people randomized to nicotine EC than to non-nicotine EC (RR 1.70, 95% CI 1.03 to 2.81; I^2 = 0%; 4 studies, 1057 participants). In absolute terms, this might again lead to an additional four successful quitters per 100 (95% CI 0 to 11). These trials mainly used older EC with relatively low nicotine delivery. There was moderate-certainty evidence of no difference in the rate of AEs between these groups (RR 1.01, 95% CI 0.91 to 1.11; I^2 = 0%; 3 studies, 601 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 0.60, 95% CI 0.15 to 2.44; I^2 = n/a; 4 studies, 494 participants).

Compared to behavioral support only/no support, quit rates were higher for participants randomized to nicotine EC (RR 2.70, 95% CI 1.39 to 5.26; I^2 = 0%; 5 studies, 2561 participants). In absolute terms this represents an increase of seven per 100 (95% CI 2 to 17). However, this finding was of very low certainty, due to issues with imprecision and risk of bias. There was no evidence that the rate of SAEs differed, but some evidence that non-serious AEs were more common in people randomized to nicotine EC (AEs: RR 1.22, 95% CI 1.12 to 1.32; I^2 = 41%, low certainty; 4 studies, 765 participants; SAEs: RR 1.17, 95% CI 0.33 to 4.09; I^2 = 5%; 6 studies, 1011 participants, very low certainty).

Data from non-randomized studies were consistent with RCT data. The most commonly reported AEs were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate with continued use. Very few studies reported data on other outcomes or comparisons and hence evidence for these is limited, with confidence intervals often encompassing clinically significant harm and benefit.

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 size of effect, particularly when using modern EC products. Confidence intervals were for the most part wide for data on AEs, SAEs and other safety markers, though evidence indicated no difference in AEs between nicotine and non-nicotine ECs. 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 evidence is limited mainly by 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, this review is now a living systematic review. We run searches monthly, with the review updated when relevant new evidence becomes available. Please refer to the *Cochrane Database of Systematic Reviews* for the review's current status.

PLAIN LANGUAGE SUMMARY

Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose?

What are electronic cigarettes?

Electronic cigarettes (e-cigarettes) are handheld devices that work by heating a liquid that usually contains nicotine and flavorings. E-cigarettes allow you to inhale nicotine in a vapor rather than smoke. Because they do not burn tobacco, e-cigarettes do not expose users to the same levels of toxins that we know can cause smoking-related diseases in people who use conventional cigarettes.

Using an e-cigarette is known as 'vaping'. Many people use e-cigarettes to help them to stop smoking tobacco.

Why we did this Cochrane Review

Stopping smoking lowers your risk of getting lung cancer and other diseases. Many people find it difficult to quit. We wanted to find out if using e-cigarettes could help people to stop smoking, and if people using them for this purpose experienced any unwanted effects.

What did we do?

We searched for studies that looked at the use of e-cigarettes to help people stop smoking.

We looked for randomized controlled trials, in which the treatments people received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment. We also looked for studies in which everyone received an e-cigarette treatment.

We were interested in finding out:

· how many people stopped smoking for at least six months; and
· how many people had unwanted effects, reported on for at least one week.

Search date: We included evidence published up to 1st February 2021.

What we found

We found 56 studies in 12,804 adults who smoked. The studies compared e-cigarettes with:

· nicotine replacement therapy, such as patches or gum;

· varenicline (a medicine to help people stop smoking);
· nicotine-free e-cigarettes;
· behavioral support, such as advice or counseling; or
· no support, for stopping smoking.

Most studies took place in the USA (24 studies), the UK (9), and Italy (7).

What are the results of our review?

More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (3 studies, 1498 people), or nicotine-free e-cigarettes (4 studies, 1057 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioral support only (5 studies, 2561 people).

For every 100 people using nicotine e-cigarettes to stop smoking, 10 or 11 might successfully stop, compared with only six of 100 people using nicotine-replacement therapy or nicotine-free e-cigarettes, or four of 100 people having no support or behavioral support only.

We are uncertain if there is a difference between how many unwanted effects occur using nicotine e-cigarettes compared with nicotine replacement therapy, no support or behavioral support only. There was some evidence that non-serious unwanted effects were more common in groups receiving nicotine e-cigarettes compared to no support or behavioral support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for other comparisons. There is probably no difference in how many non-serious unwanted effects occur in people using nicotine e-cigarettes compared to non-nicotine e-cigarettes.

The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes.

How reliable are these results?

Our results are based on a small number of studies, and in some the measured data varied widely.

We are moderately confident that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy or nicotine-free e-cigarettes. However, these results might change if further evidence becomes available.

We are less confident about how nicotine e-cigarettes compare with no support, or behavioral support, to stop smoking.

Most of our results for the unwanted effects are likely to change when more evidence becomes available.

Key messages

Nicotine e-cigarettes probably do help people to stop smoking for at least six months. They probably work better than nicotine replacement therapy and nicotine-free e-cigarettes.

They may work better than no support, or behavioral support alone, and they may not be associated with serious unwanted effects.

However, we need more, reliable evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery.

Summary of findings 1. Nicotine EC compared to NRT for smoking cessation

Nicotine EC compared to NRT for smoking cessation

Patient or population: People who smoke
Setting: New Zealand, UK, USA
Intervention: Nicotine EC
Comparison: NRT

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with NRT	Risk with Nicotine EC				
Smoking cessation at 6 months to 1 year Assessed with biochemical validation	Study population		RR 1.69 (1.25 to 2.27)	1498 (3 RCTs)	⊕⊕⊕⊖ MODERATE[a]	-
	6 per 100	10 per 100 (8 to 14)				
Adverse events at 4 weeks to 6 months Assessed by self-report	Study population		RR 0.98 (0.80 to 1.19)	485 (2 RCTs)	⊕⊕⊖⊖ LOW[b]	-
	45 per 100	44 per 100 (36 to 53)				
Serious adverse events at 4 weeks to 1 year Assessed via self-report and medical records	Study population		RR 1.37 (0.77 to 2.41)	727 (2 RCTs)	⊕⊕⊖⊖ LOW[b]	One study reported no events; effect estimate based on the one study in which events were reported
	5 per 100	7 per 100 (4 to 13)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on assumed quit rates for NRT assuming receipt of limited behavioral stop-smoking support (as per Hartmann-Boyce 2018a). The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Downgraded one level due to imprecision; small number of events (< 300 overall).
[b]Downgraded two levels due to imprecision; confidence intervals encompass clinically-important harm as well as clinically important benefit.

Summary of findings 2. Nicotine EC compared to non-nicotine EC for smoking cessation

Nicotine EC compared to non-nicotine EC for smoking cessation

Patient or population: People who smoke cigarettes
Setting: Canada, Italy, New Zealand, UK, USA
Intervention: Nicotine EC
Comparison: Non-nicotine EC

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with non-nicotine EC	Risk with Nicotine EC				
Smoking cessation at 6-12 months Assessed with biochemical validation	Study population		RR 1.70 (1.03 to 2.81)	1057 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a, b]	-
	6 per 100	10 per 100 (6 to 17)				
Adverse events at 1 week to 6 months Assessed via self-report	Study population		RR 1.01 (0.91 to 1.11)	601 (3 RCTs)	⊕⊕⊕⊖ MODERATE[c]	-
	35 per 100	35 per 100 (31 to 38)				
Serious adverse events at 1 week to 1 year Assessed via self-report and medical records	Study population		RR 0.60 (0.15 to 2.44)	494 (4 RCTs)	⊕⊕⊖⊖ LOW[d]	3 studies reported no events; effect estimate based on the one study in which events were reported
	2 per 100	1 per 100 (0 to 4)				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of moderate-intensity behavioral stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomized controlled trial; **RR:** Risk ratio

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]Not downgraded for risk of bias. One of three studies considered high risk of bias; removing this study increased the direction of the effect in favor of the intervention.
[b]Downgraded one level due to imprecision; confidence intervals incorporate no clinically-significant difference as well as clinically-significant benefit.
[c]Downgraded one level due to imprecision: though confidence intervals are narrow, only 3 studies with 601 participants contribute data.
[d]Downgraded two levels due to imprecision: confidence intervals encompass clinically-significant harm as well as clinically-significant benefit.

Summary of findings 3. Nicotine EC compared to behavioral support only/no support for smoking cessation

Nicotine EC compared to behavioral support only/no support for smoking cessation

Patient or population: People who smoke
Setting: Canada, Italy, UK, USA
Intervention: Nicotine EC
Comparison: Behavioral support only/no support

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with behavioral support only/no support	Risk with Nicotine EC				
Smoking cessation at 6 to 12 months Assessed using biochemical validation	Study population		RR 2.70 (1.39 to 5.26)	2561 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[a, b]	-
	4 per 100	11 per 100 (6 to 21)				
Adverse events at 12 weeks to 6 months Assessed via self-report	Study population		RR 1.22 (1.12 to 1.32)	765 (4 RCTs)	⊕⊕⊖⊖ LOW[a]	-
	60 per 100	73 per 100 (67 to 79)				
Serious adverse events at 4 weeks to 6 months Assessed via self-report and medical records	Study population		RR 1.17 (0.33 to 4.09)	1011 (6 RCTs)	⊕⊖⊖⊖ VERY LOW[a, c]	4 of the 6 studies reported no SAEs; MA is based on pooled results from 2 studies
	1 per 100	1 per 100 (0 to 5)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). For cessation, the assumed risk in the control group is based on receipt of limited stop-smoking support. The assumed risk for adverse events and serious adverse events is a weighted mean average of quit rates across control groups in contributing studies.

CI: Confidence interval; **RCT:** randomized controlled trial; **RR:** Risk ratio

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GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

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[a]Downgraded two levels due to risk of bias. Due to lack of blinding and differential support between arms, judged to be at high risk of bias.
[b]Downgraded one level due to imprecision; although confidence intervals are consistent with clinically- important difference, event count is very low (< 100).
[c]Downgraded two levels due to imprecision; confidence intervals incorporate clinically-significant benefit and clinically-significant harm.

BACKGROUND

Throughout this review, we discuss (1) conventional cigarettes and; (2) electronic cigarettes, defined as handheld electronic vaping devices that produce aerosol for inhalation formed by heating an e-liquid. In this review, all mention of smoking, smoking cessation, cigarette use, smoke intake, etc. concern combustible tobacco cigarettes. When the text concerns electronic cigarettes we use the abbreviation 'ECs'. EC users are sometimes described as vapers, and EC use as vaping. We refer to ECs that do not contain nicotine as non-nicotine ECs; these can also be conceptualized as placebo ECs, but we are using the term non-nicotine EC, as they can be conceptualized as an intervention in themselves. This review does not address the use of vaping devices to inhale substances other than nicotine, such as cannabis.

Description of the condition

Stopping smoking is associated with large health benefits. Despite most people who smoke wanting to quit, many find it difficult to succeed in the long term. Almost half who try to quit without support will not manage to stop for even a week, and fewer than five per cent remain abstinent at one year after quitting (Hughes 2004).

Behavioral support and medications such as nicotine patches or gum increase the chances of quitting through providing nicotine to help alleviate withdrawal symptoms, but even with this additional support long-term quit rates remain low (Cahill 2016; Hartmann-Boyce 2018b; Hartmann-Boyce 2019). One of the limitations of current treatments is that, despite substituting nicotine delivery, none adequately addresses the sensory, behavioral and social aspects of smoking that ex-smokers miss when they stop smoking (e.g. holding a cigarette in their hands, taking a puff, enjoyment of smoking, feeling part of a group). ECs may offer a way to overcome this limitation (Notley 2018b).

There is no doubt that people become dependent on tobacco, and find it difficult to stop smoking, primarily because of nicotine and its actions on the brain's reward system (Balfour 2004). However, other factors also contribute to tobacco dependence (Benowitz 2010; Rose 2006). Sensory and behavioral cues provide additional reinforcement of smoking behavior (Rose 1993; Rose 2000) and over time become almost as rewarding as nicotine. There are several lines of evidence to support this. Firstly, people who smoke appear to have a preference for cigarette smoke compared to other forms of nicotine delivery. This is partly related to the speed of nicotine delivery through smoke inhalation. However, even when nicotine is administered intravenously it does not provide the same level of satisfaction or reward as smoking (Rose 2000; Westman 1996). Secondly, the local sensory effects of smoking (e.g. the ‘scratch’ in the back of the throat) may be important for enjoyment and reward. Numbing the sensations of cigarette smoke by anaesthetizing the upper and lower respiratory tract leads to less enjoyment of smoking (Rose 1985). Conversely, products that mimic the sensory effects of smoking on the mouth and throat (such as citric acid, black pepper, and ascorbic acid) reduce craving and some withdrawal symptoms, at least in the short term (Levin 1993; Rose 1994; Westman 1995). Thirdly, very low nicotine content cigarettes (VLNCs) which have a very low content of nicotine (e.g. 0.08 mg instead of the normal 1 mg) and so have negligible or no central effects, have also been investigated for their role in aiding smoking cessation (Przulj 2013). Despite delivering low levels of nicotine, VLNCs are satisfying over the initial few days of abstinence from nicotine (Donny 2007; Donny 2015; Pickworth 1999; Rose 2000). They also reduce tobacco withdrawal symptoms, including urges to smoke and low mood (Barrett 2010; Donny 2009; McRobbie 2016; Perkins 2010; Rose 2000), and have been shown to improve long-term continuous abstinence rates in one study (Walker 2012). Social aspects of smoking, such as feeling part of a like-minded group, or including smoking behavior as part of one's social identity are also key elements of cigarette smoking that people who smoke report to be key aspects of cigarette dependence (Notley 2018a).

Considering the other factors that contribute to tobacco dependence, there is interest in developing smoking-cessation products that would not only help relieve the unpleasant effects of nicotine withdrawal but would also act as an effective substitute for smoking behavior and the rituals and sensations that accompany smoking, without the health risks associated with the inhalation of tobacco smoke. Until recently the only pharmaceutical treatments available that had some of these characteristics were the nicotine inhalator and nicotine oral spray. However, these do not have greater cessation efficacy than the other nicotine replacement therapy (NRT) products (Hajek 1999; Hartmann-Boyce 2018a). This may in part be due to the considerable effort (e.g. 20 minutes of continuous puffing) needed to provide nicotine blood concentrations consistent with other NRTs (Schneider 2001). Adherence to correct use of the inhalator is low compared to other NRTs (Hajek 1999). It is therefore possible that any advantage of sensorimotor replacement is diminished by low nicotine delivery and limited similarities between inhalator use and sensations of smoking (Bullen 2010). A nicotine inhaler using pressurized air has recently been approved as a smoking cessation aid in the UK. The nicotine delivery is substantially lower than from cigarettes, and also lower than from the nicotine inhalator (Romeu 2020).

Description of the intervention

ECs are electronic vaping devices that are handheld and produce an aerosol formed by heating an e-liquid, designed for inhalation by the user (E-cigarette ontology 2021). The e-liquid, usually comprising propylene glycol and glycerol, with or without nicotine and flavors, is stored in disposable or refillable cartridges or a reservoir or 'pod'. The commonly-used term for this aerosol is vapor, which we use throughout the review. In many countries, ECs are marketed as consumer products. Although routes are in place for licensing them as a medicine in some areas, no country yet has a licensed, medicinal EC.

ECs provide sensations similar to smoking a cigarette. They provide taste and throat sensations that are closer to smoking than those provided by the nicotine inhalator (Barbeau 2013). The vapor that looks like tobacco smoke is only visible when the user exhales after drawing on the mouthpiece, not when the device is being held. In qualitative studies users report a sense of shared identity with other users, similar to tobacco smoking identity, and also report pleasure and enjoyment of use, suggesting that ECs may be viewed less as a medical cessation aid but rather as an acceptable alternative to tobacco smoking (Cox 2017; Notley 2018a).

There are many different brands and models of EC available. Variation exists both in the device ('product') and consumable (e-liquid used). There is a wide variation in the composition of e-liquids (nicotine content, flavors and other components) (Goniewicz 2012; Goniewicz 2014), with some users choosing to mix their own e-liquids (Cox 2019b). Initial studies showed that early

models of EC delivered very low amounts of nicotine to naïve users (Bullen 2010; Eissenberg 2010; Vansickel 2010). Later studies that have measured nicotine pharmacokinetics in both experienced and naïve EC users have found that some EC users can achieve blood nicotine levels similar to those achieved with smoking, albeit more slowly, and that their ability to do so often improves over time (Hajek 2015b; Vansickel 2012; Vansickel 2013; Yingst 2019a; Yingst 2019b).

Early on in their development, ECs looked like cigarettes and used disposable cartridges. These models were often called 'cig-a-likes'. The nicotine delivery from these products was low, and even the modern versions of EC devices that use pre-filled cartridges, generally produced by the tobacco industry, for the most part have only low nicotine delivery (Hajek 2017). The later refillable, or 'tank', products have a larger battery and a transparent container that users fill with an e-liquid of their choice, and usually provide faster and more efficient nicotine delivery, allow a wider choice of flavors and nicotine concentrations, and are typically used by experienced vapers who manage to switch to vaping completely (ASH 2019; Dawkins 2013b; Farsalinos 2014). Observational evidence suggests people who smoke are more likely to successfully quit using tank models than with cig-a-likes (Chen 2016; Hitchman 2015). EC types are also often grouped by 'generation': first-generation devices are typically cig-a-likes; second-generation devices are usually tank models, sometimes referred to as 'vape pens'; and third-generation devices are tank models which, unlike second-generation devices, allow users to adjust the power (wattage) level of the product (see NCSCT EC briefing for further information and images of different product types). More recently, smaller 'pod' devices, such as Juul, appeared that use nicotine salt. This nicotine formulation reduces irritant effects and allows the delivery of higher nicotine levels that closely mimic the pharmacokinetic profile of nicotine delivery from cigarettes, despite the low battery power of the device (Hajek 2020). Juul has now become the most popular EC in the USA (Huang 2019). The EU Tobacco Products Directive (European Parliament 2014) does not allow sales of e-liquids with nicotine content higher than 20 mg/ml, and so the US version of Juul (59 mg/nl nicotine) is not available within the EU (Huang 2019; Talih 2020).

The different device types (cig-a-like, refillable and pods using high nicotine content salts) may differ significantly in their efficacy in helping people who smoke to quit, as they differ in delivery of nicotine, the active ingredient. Nicotine itself, when delivered through mechanisms and doses similar to that delivered in traditional NRT, is not considered harmful (Hartmann-Boyce 2018a). The safety profile of the different types of EC may be similar as they use the same constituents, although within the generic range of EC types, there is some evidence to suggest EC providing less nicotine may pose higher risks. This is because low-nicotine delivery devices need to be puffed with higher intensity to provide users with the nicotine levels that they seek, and more intensive puffing is accompanied by increased inhalation of potential toxicants (Dawkins 2016; Dawkins 2018; Smets 2019). Throughout this review we refer to a nicotine-containing EC as ‘nicotine EC’ and to nicotine-free EC as 'non-nicotine EC', which can also be considered 'placebo EC'. The 'placebo' comparison is a test just of the nicotine effect and not of the potential sensorimotor or behavioral and social replacement that the EC may provide.

There is no one agreed classification system for EC devices, and product development has moved so quickly that the definitions used within trials of the devices tested may no longer be necessarily fit for purpose. In this review, the definitions used are based on those drawn from the included trials. We currently label three different types of EC as 'cartridges' for devices with disposable cartridges and - typically, but not always - low nicotine delivery (e.g. cig-a-likes); refillable ECs for devices that vapers fill with their own choice of e-liquids; and pods for the small devices that use nicotine salts. We may review this categorization system in future versions of the review as new trials and devices emerge.

Why it is important to do this review

Since ECs appeared on the market in 2006 there has been a steady increase in their use. In the UK the ASH 2019 survey found 19.4% of the adult population have ever tried vaping, but only 7.2% were current vapers. EC use remains slightly more common among men compared with women, although the difference is small. EC use is most prevalent in current (19.9%) and former (11.6%) smokers. Less than one per cent of never-smokers report regular EC use. Prevalence data from the USA in 2019 showed that 4.4% of adults were current EC users (Du 2020). Data from lower-income countries suggest similar levels of EC use and awareness (Besaratinia 2019; Jiang 2016; Palipudi 2016).

Particular concern has been raised about the increased use of EC in young people, especially among never-smokers. Data for 2019 from Canada, England, and the USA show regular use (≥ 20 days in the last 30 days) among 16- to 19-year-olds to be 5.7%, 2.7% and 6.7%, respectively. There appear to be some regional differences in the change in the prevalence of EC use. For example, in North America the rates of regular EC use among 16- to 19-year-old never-smokers has significantly increased between 2017 and 2019, compared to England where there has not been any significant change (0.2% to 0.3%) (Hammond 2020). However, as with adults, regular use is greatest among those who are also smoking and lowest among never-smokers (1.0%, 0.3%, and 1.8% for Canada, England and USA, respectively).

Regulatory approaches being used for ECs currently vary widely, from no regulation to partial and complete bans (McNeill 2021). Within the USA, for example, the Food and Drug Administration (FDA) has classified them as tobacco products and there are a range of laws that include prohibition of EC use indoors, require retailers to have a license to sell, and prohibit sales to minors. Laws prohibiting sales to minors apply nationwide, but other laws vary by state (Du 2020). The European Union includes ECs in their Tobacco Products Directive, except where therapeutic claims are made or in instances where they contain over 20 mg/nl of nicotine, when they will require medicines authorization (European Parliament 2014).

Categorical statements about the toxicity of ECs are not possible because of the large number of devices and liquids available and the frequent addition of new products to the market. In 2019, cases of severe lung injury associated with EC use were reported in the USA, and by February 2020 there were around 2800 hospitalized cases or deaths (CDC 2020). This illness was termed E-cigarette or Vaping-Associated Lung Injury (EVALI) and caused concern throughout the world (Hall 2020), and a negative change in people's perception of the risks of EC use compared to smoking (Tattan-Birch 2020). These cases were somewhat at odds with data from trials and cohort studies, and it was later found that these injuries were related to use of tetrahydrocannabinol (THC)-containing EC, and in

particular THC products adulterated with vitamin E acetate (Blount 2020; Hartnett 2020). Among those brands of nicotine EC that have been tested, levels of toxins have been found to be substantially lower than in cigarettes (Hajek 2014; McNeill 2021). Long-term effects beyond 12 months are unknown, although based on what is known about liquid and vapor constituents and patterns of use, a report from the UK's Royal College of Physicians has concluded that using an EC is likely to be considerably safer than smoking (RCP 2016). The US National Academies of Sciences, Engineering, and Medicine (NASEM) concluded that ECs are likely to be far less harmful than continuing to smoke cigarettes, with the caveat that the long-term health effects of e-cigarette use are not yet known (NASEM 2018).

Despite general acknowledgement that EC use exposes the user to fewer toxicants and at lower levels than smoking cigarettes (McNeill 2021; NASEM 2018; RCP 2016), there remains some hesitancy in making these products available to people who smoke as a harm reduction tool or smoking cessation aid (e.g. McDonald 2020). Lack of quality control measures, possible harms of second-hand EC vapor inhalation, concerns that the products may be a gateway to smoking initiation or may prolong continued dual-use of tobacco, concerns that ECs may undermine smoke-free legislation if used in smoke-free spaces, concerns about the involvement of the tobacco industry, and concerns that the long-term effects of EC use on health are not yet known are often cited. Recently, a report from the US Preventive Services Taskforce concluded "that the current evidence is insufficient to assess the balance of benefits and harms of electronic cigarettes (e-cigarettes) for tobacco cessation in adults" (USPFTS 2021). However, others suggest that potential benefits outweigh potential disadvantages (Farsalinos 2014; Hajek 2014; McNeill 2021; NASEM 2018; RCP 2016).

People who smoke, healthcare providers and regulators are interested to know if ECs can help smokers quit and if it is safe to use them to do so. In particular, healthcare providers have an urgent need to know what they should recommend for people who want to stop smoking. The largest health gains are achieved from stopping smoking completely, as opposed to reducing cigarette consumption, and as such this review focuses on the effectiveness of ECs in aiding smoking cessation.

This review was first published in 2014, and updated in 2016 and 2020.

Following the publication of the 2020 update of this review, we are maintaining it as a living systematic review (Brooker 2019). This means we are continually running searches and incorporating new evidence into the review. For more information about the living systematic review methods being used, see Appendix 1. A living systematic review approach is appropriate for this review, for three reasons. First, the review addresses an important public health issue; the role of ECs in enabling people who smoke to stop smoking, with potential for substantial ongoing individual and societal benefits if effective. Secondly, there remains uncertainty in the existing evidence; more studies are needed to confirm the degree of benefit for different comparisons and product types, and there is considerable uncertainty about adverse events and other markers of safety. Thirdly, we are aware of multiple ongoing trials on this topic that are likely to have an important impact on the conclusions of the review.

OBJECTIVES

To examine the safety, tolerability and effectiveness of using electronic cigarettes (ECs) to help people who smoke achieve long-term smoking abstinence.

METHODS

Criteria for considering studies for this review

Types of studies

We include randomized controlled trials (RCTs) and randomized cross-over trials in which people who smoke are randomized to ECs or to a control condition. RCTs are the best available primary evidence, but the continued paucity of RCTs in this area requires that we also include uncontrolled intervention studies in which all participants are given an EC intervention.

We include studies regardless of their publication status or language of publication.

Types of participants

People defined as currently smoking cigarettes at enrolment into the studies. Participants could be motivated or unmotivated to quit.

Types of interventions

Any type of EC or intervention intended to promote EC use for smoking cessation, including studies which did not measure smoking cessation but provided ECs with the instruction they be used as a complete substitute for cigarette use. ECs may or may not contain nicotine.

Types of comparators

We compare nicotine ECs with non-nicotine ECs, ECs versus alternative smoking cessation aids, including NRT or no intervention, and ECs added to standard smoking cessation treatment (behavioral or pharmacological or both) with standard treatment alone.

Types of outcome measures

Primary outcomes

- Cessation at the longest follow-up point, at least six months from the start of the intervention, measured on an intention-to-treat basis using the strictest definition of abstinence, preferring biochemically-validated results where reported
- Number of participants reporting adverse events or serious adverse events at one week or longer (as defined by study authors)

Secondary outcomes

Changes in the following measures at one week or longer:

- Carbon monoxide (CO), as measured through breath or blood
- Blood pressure
- Heart rate
- Blood oxygen saturation
- Lung function measures
- Known toxins/carcinogens, as measured through blood or urine (toxicant names and abbreviations are listed in Appendix 2)

Studies had to report one of the primary or secondary outcomes above to be eligible for inclusion.

Search methods for identification of studies

Electronic searches

For this update we searched the following databases on 1st February 2021:

- Cochrane Tobacco Addiction Group Specialized Register
- Cochrane Central Register of Controlled Trials (CENTRAL)
- MEDLINE (OVID SP)
- Embase (OVID SP)
- PsycINFO (OVID SP)
- ClinicalTrials.gov
- WHO International Clinical Trials Registry Platform (ICTRP: www.who.int/ictrp/en/)

At the time of the search, the Register included the results of searches of the Cochrane Central Register of Controlled trials (CENTRAL), issue 1, 2021; MEDLINE (via OVID) to update 20210104; Embase (via OVID) to week 202101; PsycINFO (via OVID) to update 20201228. See the Tobacco Addiction Group website for full search strategies and a list of other resources searched.

For the first version of the review we also searched CINAHL (EBSCO Host) (2004 to July 2014). We did not search this database from 2016 onwards as it did not contribute additional search results to the first version of the review. The search terms were broad and included e-cig$ OR elect$ cigar$ OR electronic nicotine. The search for the 2016 update added the terms vape or vaper or vapers or vaping. The 2020 searches added further terms, including the MESH heading 'Electronic Nicotine Delivery Systems' and terms to limit by study design. Our search strategy for MEDLINE (Ovid SP) is listed in Appendix 3. The previously-used search strategy is shown in Appendix 4. The search date parameters of the original searches were limited to 2004 to the present, due to the fact that ECs were not available before 2004.

Searching other resources

We searched the reference lists of eligible studies found in the literature search and contacted authors of known trials and other published EC studies.

Data collection and analysis

Selection of studies

Two review authors (for this update from: JHB, NL, CN, RB, PH, NR, ARB, HMR) independently prescreened all titles and abstracts obtained from the search, using a screening checklist, and then independently screened full-text versions of the potentially relevant papers for inclusion. We resolved any disagreements by discussion or with a third review author.

Data extraction and management

Two review authors (for this update from: CN, ARB, AT, HMR) extracted data from the included studies using a pre-piloted data extraction form, and checked them against each other. We resolved any disagreements by discussion or with a third review author. We extracted data on:

- Author
- Date and place of publication
- Study dates
- Study design
- Inclusion and exclusion criteria
- Setting
- Summary of study participant characteristics
- Summary of intervention and control conditions
- Number of participants in each arm
- Smoking cessation outcomes
- Type of biochemical validation (if any)
- Adverse events (AEs), serious adverse events (SAEs), and relevant biomarkers
- Assessment time points
- Study funding source
- Author declarations of interest
- Risk of bias in the domains specified below
- Additional comments

We adopted a broad focus to detect a variety of adverse events.

One review author (JHB) then entered the data into Review Manager 2020 software for analyses, and another checked them (AB for this update).

Assessment of risk of bias in included studies

Two review authors (for this update from: CN, ARB, AT, HMR) independently assessed the risks of bias for each included study, using the Cochrane 'Risk of bias' Tool v1 (Higgins 2011). This approach uses a domain-based evaluation that addresses seven different areas: random sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential sources of bias. We assigned a grade (low, high, or unclear) for risk of bias for each domain. We resolved disagreements by discussion or by consulting a third review author.

Specific considerations about judgments for individual domains in this review are outlined below:

- Random sequence generation/allocation concealment: We rated all non-randomized studies at high risk in these domains;
- Blinding of participants and personnel: We did not evaluate this domain for non-randomized studies, as we considered it not to be applicable. For randomized studies which did not use blinding, we considered studies to be at low risk in this domain if the intervention was compared to an active control of similar intensity, as we judged performance bias to be unlikely in this circumstance. If studies were unblinded and the comparator group was a minimal-intervention control or of lower intensity than the intervention group, we considered the study to be at high risk of bias in this domain;
- Following standard methods of the Cochrane Tobacco Addiction Review Group, we considered studies to be at low risk of detection bias (blinding of outcome assessment) if our primary outcome was objectively measured or if the intensity of intervention was similar between groups, or both. For studies where cessation was measured, our judgment was based on

whether cessation was biochemically verified. For other studies, we judged this domain based on adverse or serious adverse events;

- Again following standard methods of the Cochrane Tobacco Addiction Group, we rated studies at high risk of attrition bias if loss to follow-up was greater than 50% overall or if there was a difference in follow-up rates of more than 20% between study arms.

We judged studies to be at high risk of bias overall if they were rated at high risk in at least one domain, and at low risk of bias overall if they were judged to be at low risk across all domains evaluated. We judged the remaining studies to be at unclear risk of bias overall.

Measures of treatment effect

We analyzed dichotomous data by calculating the risk ratio (RR). For cessation, we calculated the RR as ((number of events in intervention condition/intervention denominator) / (number of events in control condition/control denominator)) with a 95% confidence interval (CI), using data at the longest follow-up period reported.

We analyzed continuous data (other measures of tobacco exposure) by comparing the difference between the mean change from baseline to follow-up in the intervention and comparator groups. For outcomes other than cessation where data were reported at multiple time points, we used data at the longest follow-up point at which ECs were still being provided.

Unit of analysis issues

In the case of trials with multiple arms, we do not combine data between arms unless this is the way it has been presented by study authors. We note in our analyses where this is the case.

For all but one study, the unit of assignment was the individual. Dawkins 2020 assigned condition based on homeless support service; this was a small pilot study with very few events and hence we judged clustering to have very little impact on our overall result. If larger cluster-randomized trials are eligible in the future, we will assess whether study authors have adjusted for this clustering, and whether this had an impact on the overall result. When clustering appears to have had little impact on the results, we will use unadjusted quit-rate data; however when clustering does appear to have an impact on results, we will adjust for this using the intraclass correlation (ICC).

For randomized cross-over trials, we report results at the end of the first assignment period where available and where sufficiently long to meet our inclusion criteria for outcomes. All other outcomes from randomized cross-over trials are reported narratively. We offer a narrative synthesis of data from non-randomized studies, and where possible use effect direction plots as described in the *Cochrane Handbook* (Higgins 2021).

Dealing with missing data

For smoking cessation, we used a conservative approach, as is standard for the Cochrane Tobacco Addiction Group, treating participants with missing data as still smoking. We based the proportion of people affected by adverse events on the number of people available for follow-up, and not the number randomized. For other outcomes, we use complete-case data and do not attempt to impute missing values.

Assessment of heterogeneity

We assessed the clinical and methodological diversity between studies to guide our decision as to whether data should be pooled. We were also guided by the degree of statistical heterogeneity, assessed by calculating the I^2 statistic (Higgins 2003), and considering a value greater than 50% as evidence of substantial heterogeneity. We did not present pooled results where I^2 values exceeded 75%.

Assessment of reporting biases

Reporting bias can be assessed using funnel plots, where 10 or more RCTs contribute to an outcome. However, there are currently insufficient studies to support this approach.

Data synthesis

We provide a narrative summary of the included studies. Where appropriate, we have pooled data from these studies in meta-analyses. For dichotomous data, we used a fixed-effect Mantel-Haenszel model to calculate the RR with a 95% confidence interval, in accord with the standard methods of the Cochrane Tobacco Addiction Group for cessation studies.

For continuous outcomes, we pooled mean differences (or standardized mean differences for studies using different measures for the same construct), using the inverse variance approach (also with a 95% CI).

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analyses to investigate differences between studies, such as:

- Intensity of behavioral support used;
- Type of EC (cartridge; refillable; pod);
- Instructions for EC use (e.g. study provision, length of provision, whether participants had a role in product choice);
- Type of participants (e.g. experience of EC use).

However, there were too few studies to conduct such analyses. Should further studies become available in future, we will follow this approach. For safety outcomes, we present subgroups by length of follow-up for descriptive purposes.

In the absence of sufficient data for subgroup analyses on EC type, in the text we specify the type of nicotine EC when reporting pooled results for cessation.

Sensitivity analysis

We conducted sensitivity analyses to detect whether pooled results were sensitive to the removal of studies judged to be at high risk of bias.

Summary of findings and assessment of the certainty of the evidence

Following standard Cochrane methodology, we created 'Summary of findings' tables for our three main comparisons using GRADEpro GDT: nicotine EC versus non-nicotine EC; nicotine EC versus NRT; and nicotine EC versus behavioral support only/no support. We

selected these comparisons a priori as being the most clinically relevant. In the 'Summary of findings' tables, we present data on our primary outcomes (cessation, adverse events, serious adverse events) for these main comparisons. Also following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence for each outcome, and to draw conclusions about the certainty of evidence within the text of the review.

RESULTS

Description of studies

Results of the search

For this update, our bibliographic database searches identified 825 non-duplicate records (Figure 1). We screened all records and retrieved the full-text papers of 100 potentially relevant articles. After screening and checking the full-text of 100 papers, we included 26 records, representing six studies new for this update (Czoli 2019; Ikonomidis 2020; Ozga-Hess 2019; Pulvers 2020; Scheibein 2020; Yingst 2020), nine new articles linked to studies already identified, and 11 new references to ongoing studies (see Characteristics of ongoing studies). Secondary study reports, commentaries, and correspondence relating to included studies are linked to studies in the reference section. Figure 2, Figure 3 and Figure 4 present PRISMA flow charts for previous versions of this review.

Figure 1. 2021 update flow diagram

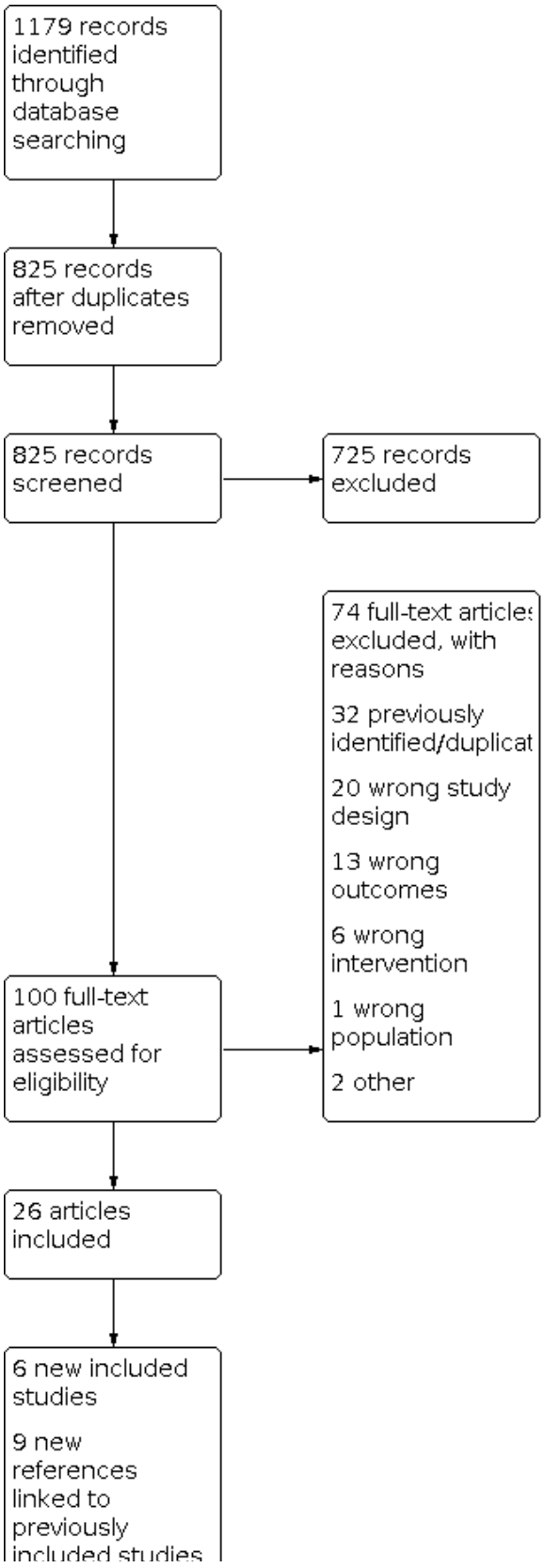


Figure 1. (Continued)

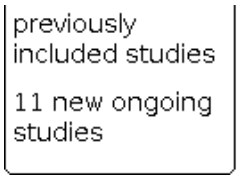


Figure 2. 2020 update flow diagram

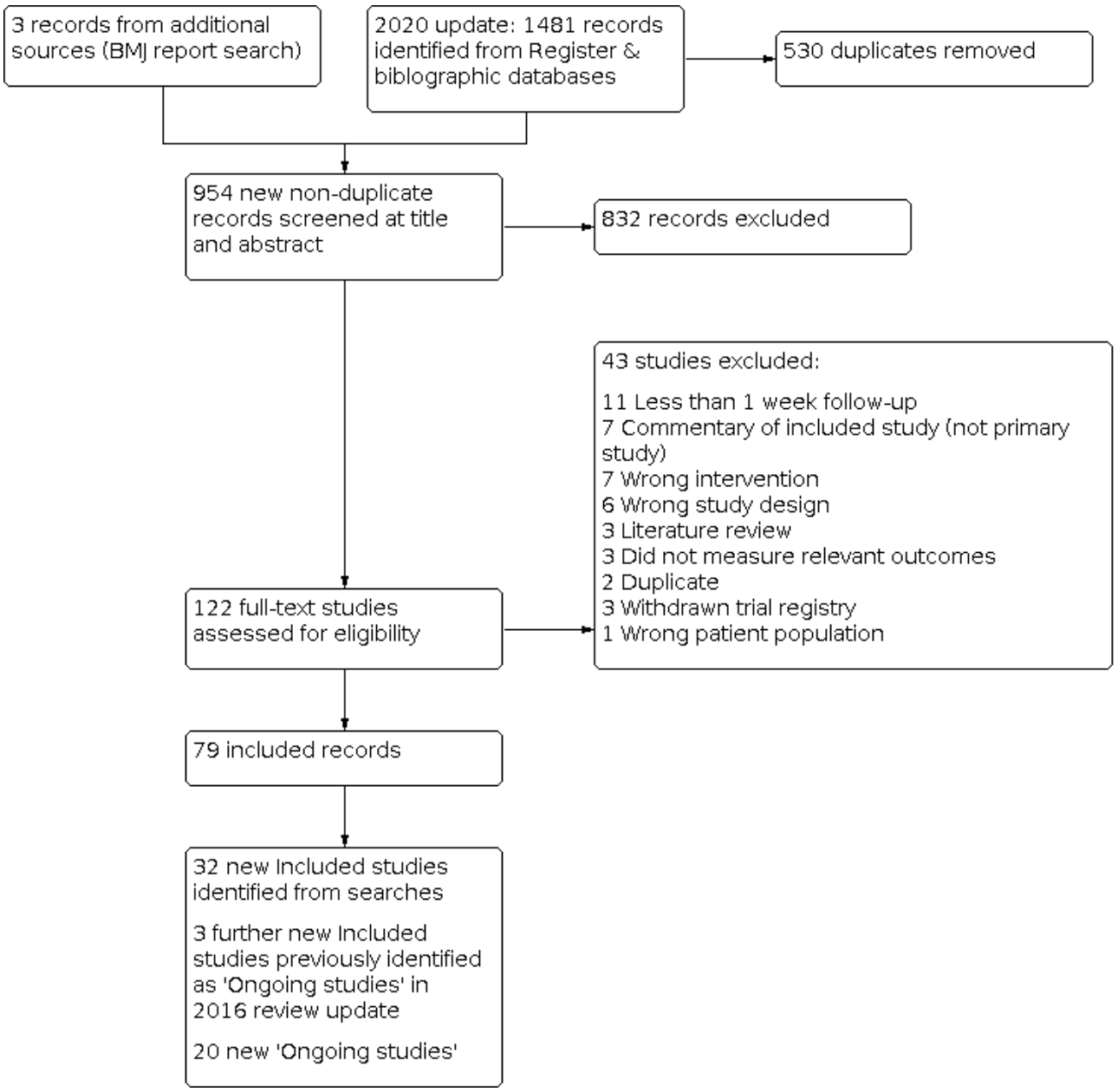


Figure 3. 2016 update flow diagram

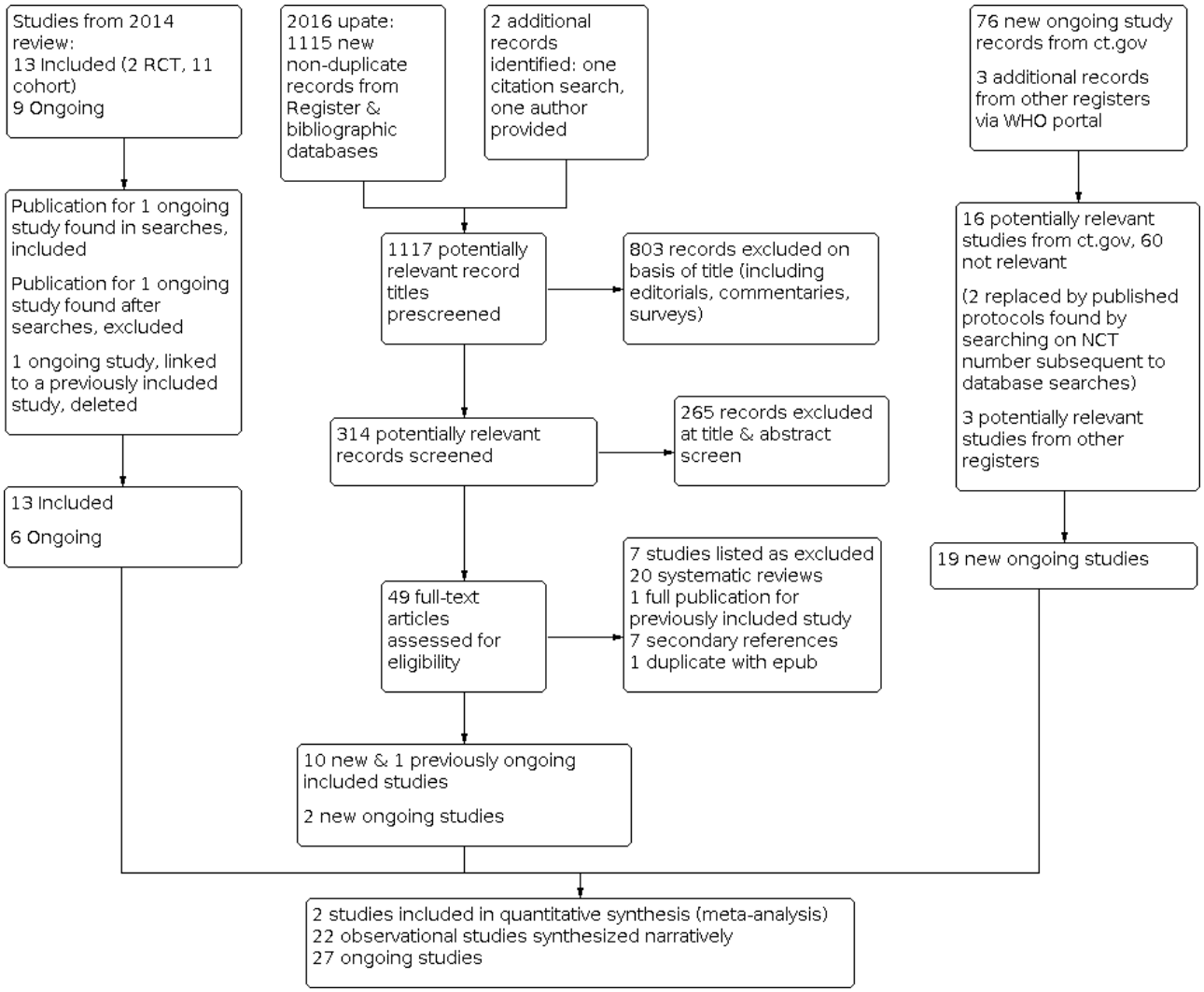
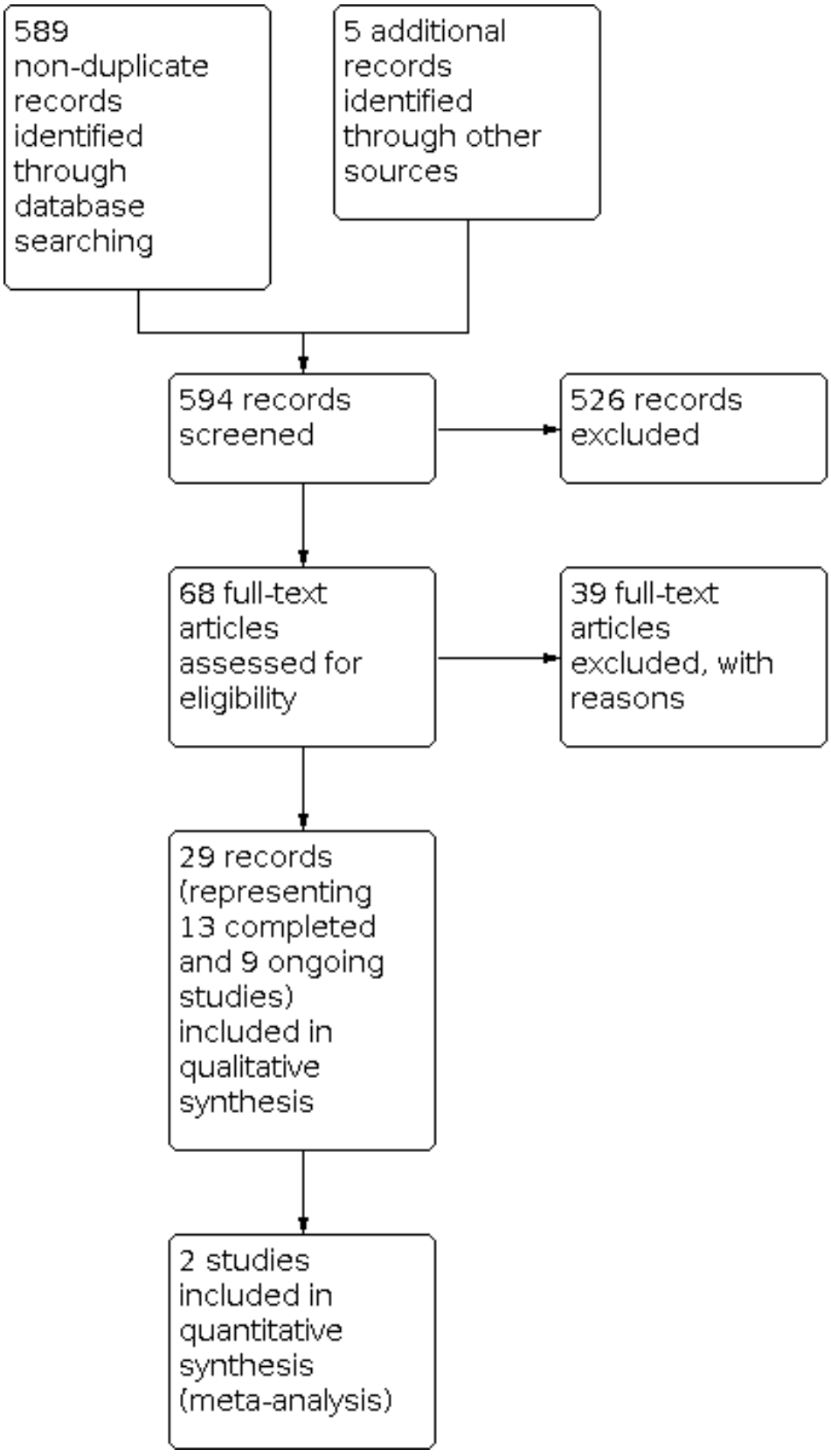


Figure 4. 2014 flow diagram



Included studies

In total, we include 56 studies, six new included studies and 50 eligible included studies identified in previous versions of the review. Key features of the included studies are summarized below. Further details on each included study can be found in the Characteristics of included studies tables.

Participants

The 56 included studies represented 12,804 participants. Twenty-four studies were conducted in the USA, nine were conducted in the UK, seven in Italy, three in Greece, two each in Australia, New Zealand, and Canada, and one each in Belgium, Ireland, Poland, the Republic of Korea, South Africa, Switzerland, and Turkey. All studies were conducted in adults who smoke. Seventeen studies exclusively recruited participants who were not motivated to quit smoking, and 29 studies exclusively recruited participants motivated to quit; motivation was not specified for the other studies. Eighteen studies recruited from specific population groups; these included six studies which recruited participants based on physical health condition (heart attack, cancer, HIV, periodontitis, awaiting surgery), three studies which recruited participants with serious mental illness, and three studies which recruited participants in treatment or having recently completed treatment for alcohol or other drug use. Two studies recruited people accessing homeless centres or using supported temporary accomodation. One study each recruited: people aged 55 or older, young adults, and black and latinx participants.

Interventions and comparators

All but one study provided nicotine EC, either alone (50 studies) or in conjunction with NRT or varenicline (five studies). One study recruited dual users at baseline, and instructed them to continue using their own EC devices (Czoli 2019). In two studies where nicotine EC was provided on its own, nicotine levels were judged to be so low as to be clinically comparable to non-nicotine EC (Lee 2019; Van Staden 2013); we include these studies in non-nicotine EC comparisons. Eight studies compared nicotine EC with non-nicotine EC, 16 studies compared nicotine EC to behavioral support only or to no support, and eight studies compared nicotine EC to NRT. One study directly compared a cig-a-like with a refillable (tank) device (Yingst 2020). Results from these studies are reported by comparison in Effects of interventions. Further details on the intervention and comparator groups (where applicable) for each study can be found in the Characteristics of included studies tables.

Where reported in the primary research publications, details on the devices tested can also be found in the Characteristics of included studies tables. Of the studies with sufficient data with which to judge, 26 used cartridge devices (only one of which had high nicotine delivery), 21 used refillable devices, three used both types, one used a pod device, and the remainder did not report device type.

Outcomes

Of the 56 included studies:

- 22 reported data on abstinence
- 39 reported data on adverse events
- 24 reported data on serious adverse events
- 36 reported data on carbon monoxide
- 9 reported data on heart rate
- 12 reported data on blood pressure
- 2 reported data on blood oxygen saturation
- 9 reported data on at least one known toxin/carcinogen
- 5 reported data on at least one measure of lung function

Study types and funding

Twenty-nine studies were RCTs, 13 of which contributed to cessation analyses. Five studies used randomized cross-over designs, and the remainder were uncontrolled cohort studies. Of the 46 studies which reported funding information, 32 had no EC industry funding or support.

Excluded studies

We list 92 studies excluded at full-text stage, along with reasons for exclusion, in the Characteristics of excluded studies table. The most common reason for exclusion was that studies were short-term, following up participants for periods of less than one week.

Risk of bias in included studies

Overall, we judged five studies (Bullen 2013; Eisenberg 2020; Hajek 2019; Lee 2018; Lee 2019) to be at low risk of bias, ten to be at unclear risk, and the remaining 41 at high risk of bias (note, this includes the non-randomized studies, which we deemed to be at high risk due to this lack of randomization).

Details of 'Risk of bias' judgments for each domain of each included study can be found in the Characteristics of included studies table. Figure 5 illustrates judgments for each included study.

Figure 5. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

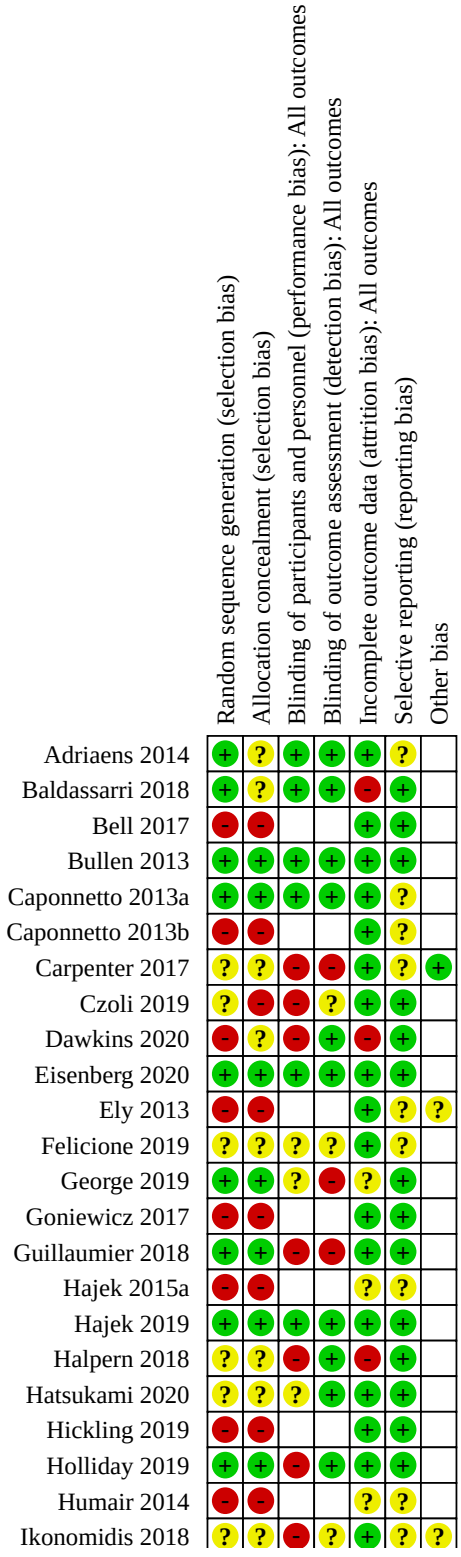
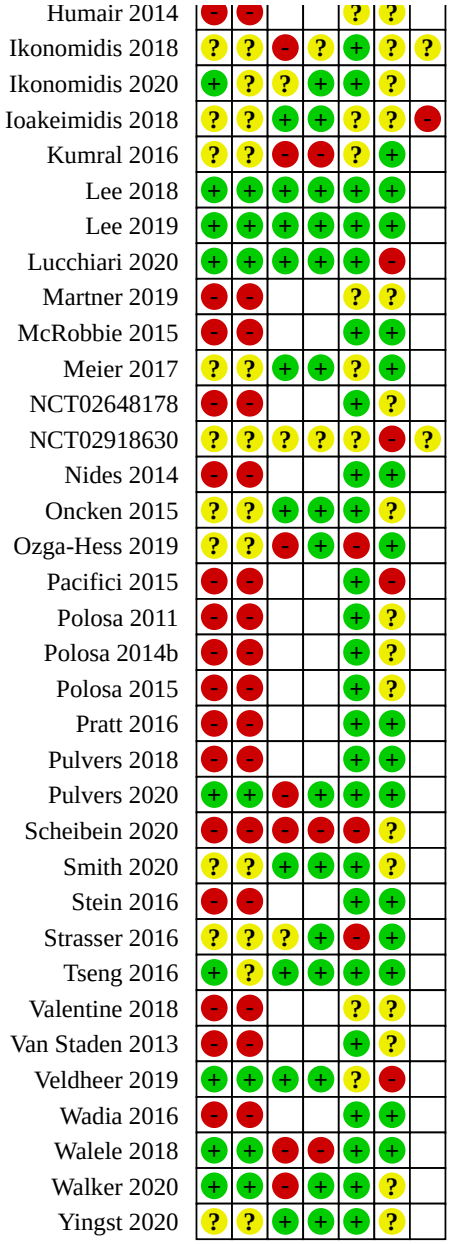


Figure 5. (Continued)



Allocation

We judged 23 studies to be at high risk of selection bias; for 22, this is because the studies were not randomized. We also rated a pilot cluster-randomized trial at high risk as randomization was not carried out as intended for pragmatic reasons (Dawkins 2020). We judged 14 studies to be at low risk of selection bias, and the remainder to be at unclear risk as there was insufficient information with which to judge.

Blinding

Of the 35 studies assessed for these domains, we judged 16 to be at low risk for both performance and detection bias. We rated 14 at high risk for performance or detection bias, or both. In these studies, blinding was not used and different levels of support were provided; this alone or in conjunction with the outcome measures being used (subjective rather than objective measures) meant we thought there was a high risk of bias being introduced. We judged the rest to be at unclear risk.

Incomplete outcome data

We judged most studies (40 out of 56) to be at low risk of attrition bias. We rated six studies with substantial loss to follow-up at high risk of attrition bias. The remainder did not provide sufficient data on which to judge, and hence we judged them to be at unclear risk.

Selective reporting

Of the 56 studies, we considered that 29 were at low risk of reporting bias, as all prespecified/expected outcomes were reported. We

rated four at high risk, as data were not presented as specified in the original protocols. We judged the rest to be at unclear risk, due to insufficient information with which to make a judgment.

Other potential sources of bias

We considered Ioakeimidis 2018 to be at high risk of other bias; data were from a conference poster and the associated abstract, and quit rates in the intervention arm differed between the two sources.

Effects of interventions

See: **Summary of findings 1** Nicotine EC compared to NRT for smoking cessation; **Summary of findings 2** Nicotine EC compared to non-nicotine EC for smoking cessation; **Summary of findings 3** Nicotine EC compared to behavioral support only/no support for smoking cessation

Data on our outcomes of interest are summarized below. Due to the volume of data available, some relevant information is hosted on a companion repository; these data are open-access and can be found at https://doi.org/10.5287/bodleian:dX4Dgp7dJ. They are referred to below as supplemental tables. Forest plots are available through 'analysis' links; for some outcomes, benefit is plotted on the right, for others on the left. This is due to direction of effect, e.g. an increase in cessation is a benefit, whereas an increase in a carcinogen is not.

Direct comparisons between nicotine EC and other pharmacotherapies

Comparisons reported here include cartridge and refillable nicotine ECs versus NRT, and cartridge nicotine ECs versus varenicline. Only randomized controlled trials contribute data.

Cessation

Pooled data from three studies (2 cartridge, 1 refillable), all of which we rated at low risk of bias, showed higher quit rates in people randomized to nicotine EC than to NRT (RR 1.69, 95% CI 1.25 to 2.27; I^2 = 0%; 1498 participants; Analysis 1.1). One study (Ioakeimidis 2018), available as a conference presentation only and considered at high risk of bias due to inconsistencies in the data reported and an unclear definition of abstinence, found lower quit rates in people allocated to nicotine EC (cartridge) compared to those allocated to varenicline (RR 0.31, 95% CI 0.11 to 0.82; 54 participants; Analysis 2.1).

Adverse events

Pooled data from two studies (both considered at low risk of bias) showed no evidence of a difference in the number of participants reporting adverse events (AEs) between nicotine EC and NRT arms (RR 0.98, 95% CI 0.80 to 1.19; I^2 = 0%; 485 participants; Analysis 1.2). Hajek 2019 did not contribute data to this analysis due to the way in which events were recorded; of their prespecified adverse reactions of interest, nausea was more frequent in the NRT group, throat/mouth irritation was more frequent in the nicotine EC group, and there was little difference in other reactions (see Supplemental Table 1 for more detail).

In Ioakeimidis 2018, reports of sleep disorders were evenly distributed between groups, and nausea was more common in the varenicline arm than in the nicotine EC arm (see Supplemental Table 1 for more detail).

Serious adverse events

Two studies comparing nicotine ECs with NRT provided data on SAEs; in one (Lee 2018) none occurred in either arm. In Hajek 2019 (n = 698), more events occurred in the nicotine EC arm than in the NRT arm, but the confidence interval was wide and included no difference as well as the possibility of more events in the NRT arm (RR 1.37, 95% CI 0.77 to 2.41; Analysis 1.3). As noted above, Bullen 2013, which compared nicotine EC, non-nicotine EC, and NRT, only reported that no serious adverse events (SAEs) occurred that were considered related to study treatment. No events occurred in Ioakeimidis 2018 (Analysis 2.2).

Carbon monoxide (CO)

Pooled data from two studies (Hatsukami 2020; Lee 2018; neither considered at high risk of bias) comparing nicotine EC with NRT found that CO levels decreased more in those randomized to nicotine EC, but the point estimate was small, confidence intervals were wide, and statistical heterogeneity was substantial (MD −0.66 ppm, 95% CI −1.94 to 0.62; I^2 = 69%; 136 participants; Analysis 1.4).

Heart rate, blood pressure, and oxygen saturation

Only Hatsukami 2020 contributed data for these outcomes. A small benefit in favor of EC was found for change in heart rate (Analysis 1.5). No difference was found for blood pressure or blood oxygen saturation, although confidence intervals were wide (Analysis 1.6; Analysis 1.7).

Toxicants

Again, only Hatsukami 2020 contributed data for these outcomes. For 3-HPMA, 2-HPMA, HMPMA, PheT, and CEMA, point estimates favored EC but confidence intervals included no difference (Analysis 1.8; Analysis 1.10; Analysis 1.11; Analysis 1.12; Analysis 1.13). Both AAMA and NNAL decreased more in NRT than in EC groups, with confidence intervals excluding no difference (Analysis 1.9; Analysis 1.14).

Lung function

Lee 2018 measured change in FEV1 and FEV1/FVC; for both outcomes, point estimates favored EC over NRT; confidence intervals excluded no difference for FEV1 (Analysis 1.15; Analysis 1.16).

Nicotine EC alone or versus control

Comparisons reported here include nicotine EC versus non-nicotine EC, and nicotine EC compared to behavioral support only or to no support. In this section, we also report results from studies in which all participants received nicotine EC (cohort studies and randomized studies which did not differ across arms in EC provision, device generation, or nicotine content).

Cessation

Randomized controlled trials

At six months or longer, quit rates were higher in nicotine EC groups than in comparator groups. Compared to EC without nicotine (placebo EC), pooled results showed nicotine EC produced higher quit rates (RR 1.70, 95% CI 1.03 to 2.81; I^2 = 0%; 3 studies of cartridge devices, 1 refillable, 1057 participants; Analysis 3.1). The effect size increased when we removed the one study at high risk of bias (Lucchiari 2020). The effect was more pronounced when comparing

nicotine EC to behavioral support only or to no support (RR 2.70, 95% CI 1.39 to 5.26; I^2 = 0%; 5 studies (3 refillable, 2 cartridge), 2561 participants; Analysis 4.1). As this involved unblinded comparisons with unequal levels of support, we judged all data contributing to this outcome to be at high risk of bias.

Pulvers 2020 (pod device) measured cessation at six months in the intervention group only, using self-report. As they did not measure cessation at six months in the comparator group we could not include these data in meta-analysis. At six months, 23 (24%) of intervention participants were exclusively using EC and 10 (10.4%) reported using neither EC nor combustible cigarettes (making a combined quit rate of 34.4% in the intervention arm at six months).

Data from other studies

Eight studies provided all participants with nicotine EC and assessed abstinence at six months or longer (Table 1; 1 refillable, 6 cartridge, 1 not specified). The highest proportion of quitters was observed in Ely 2013 (cartridge), in which all participants (n = 48) used EC and 18 used additional pharmacotherapy: 44% of participants were abstinent at six months. The lowest quit rates were seen in two studies where participants were not motivated to quit at baseline: in Caponnetto 2013b, 14% of participants were abstinent at 12 months, and in Polosa 2011 23% of participants were abstinent at six months, but this fell to 13% at 24 months (both studies used cartridge devices).

Adverse events

Randomized controlled trials

Pooled data from three studies (none at high risk of bias) showed no evidence of a difference in the number of participants experiencing adverse events when comparing nicotine EC to non-nicotine EC (RR 1.01, 95% CI 0.91 to 1.11; I^2 = 0%; 601 participants; Analysis 3.2). When comparing nicotine EC to behavioral support only or to no support, more people in the groups randomized to nicotine EC reported experiencing adverse events (RR 1.22, 95% CI 1.12 to 1.32; I^2 = 41%; 4 studies, 765 participants; Analysis 4.2). As this involved unblinded comparisons with unequal levels of support, we judged all data contributing to this outcome to be at high risk of bias.

A further seven randomized controlled trials provided adverse event or related data for this comparison, but could not be included in the meta-analysis due to the way in which data were presented (see Supplemental Table 1). In the studies comparing nicotine EC to non-nicotine EC, one found similar event rates across arms (Caponnetto 2013a), and two reported more events in the nicotine EC arms (Felicione 2019; Tseng 2016). In a further study comparing nicotine to non-nicotine EC, events were reported by type, with an increase in some seen in the nicotine group and an increase in others seen in the non-nicotine group (Lucchiari 2020). In the three studies comparing nicotine EC to behavioral support only or traditional cigarettes, Kumral 2016 found an increase in sinonasal symptoms in the group receiving nicotine EC compared to behavioral support only, and Ozga-Hess 2019 found that throat irritation, cough, and dry mouth increased in the e-cigarette group relative to the traditional cigarette group. By contrast, Pulvers 2020 found a reduction in respiratory symptoms in the e-cigarettes compared to the traditional cigarettes group.

Data from other studies

Seventeen studies provided all participants with nicotine EC and assessed adverse events at one week or longer (see Supplemental Table 1). In the seven studies which tracked event rates over time, six showed adverse events reducing over time (Bell 2017; Caponnetto 2013b; Goniewicz 2017; Polosa 2011; Polosa 2014b; Pratt 2016). Hickling 2019 showed no change. The most commonly-reported adverse events were throat/mouth irritation, headache, cough, and nausea.

Serious adverse events

Randomized controlled trials

Four studies compared nicotine EC with non-nicotine EC and reported data on SAEs; in three of these, no events occurred, so results could not contribute to the meta-analysis, although they are included in the forest plots for descriptive purposes. In the one study (Eisenberg 2020, n = 255 for this comparison) where events occurred, more were reported in the non-nicotine arm (RR 0.60, 95% CI 0.15 to 2.44; Analysis 3.3). We rated this study at low risk of bias.

Six studies compared nicotine EC with behavioral support only or no support and reported data on SAEs; in four of these, no events occurred. Pooled results from the two studies in which events occurred showed more events occurring in the nicotine EC arm, but confidence intervals were wide and encompassed clinically significant benefit and clinically significant harm (RR 1.17, 95% CI 0.33 to 4.09; I^2 = 5%; 2 studies, 1011 participants; Analysis 4.3).

Bullen 2013, which compared nicotine EC, non-nicotine EC, and NRT, only reported that no SAEs occurred that were considered to be related to study treatment. In a study in people experiencing homelessness (Dawkins 2020), SAEs were not reported, but authors report that four to seven participants in the usual-care arm and five to seven participants in the nicotine EC arm visited Accident & Emergency services at a hospital. Further detail can be seen in Supplemental Table 2.

Data from other studies

Seven studies provided all participants with nicotine EC and reported SAEs at a week or longer (Supplemental Table 2). In five of these (Bell 2017; Caponnetto 2013b; Humair 2014; Polosa 2011; Valentine 2018), authors report that no SAEs occurred. In NCT02648178 (19 participants), one death occurred (no further detail provided). Hickling 2019 (50 participants) recruited participants from mental health settings; five SAEs were recorded during the study, all of which were psychiatric hospitalizations. None were considered related to study treatment.

Carbon monoxide

Randomized controlled trials

Pooled data from two trials (neither considered at high risk of bias) comparing nicotine EC with non-nicotine EC found lower exhaled CO levels in people randomized to nicotine EC (MD −2.44 ppm, 95% CI −3.91 to −0.97; 171 participants; Analysis 3.4). Although statistical heterogeneity was substantial (I^2 = 71%), point estimates in both studies favored nicotine EC. Three further randomized studies measured CO levels in those assigned to nicotine EC and those assigned to non-nicotine EC, but did not present data in a way that could be pooled: George 2019 did not compare data by

group; Tseng 2016 reports no between-group differences; and Meier 2017 found a slightly higher CO reading in those using nicotine EC, but the clinical and statistical significance of this difference was not clear (see Supplemental Table 3 for more detail). These data are from all study participants based on group randomized, not on subsequent EC or cigarette use.

Pooled data from six studies comparing nicotine EC to behavioral support alone or no support resulted in a high I^2 value (92%); pooled results are not presented here (see Analysis 4.4 for individual study data). Heterogeneity was primarily driven by magnitude rather than direction of effect, with results generally favoring nicotine EC. Three further trials reported data which could not be included in a meta-analysis. Walele 2018 compared nicotine EC to cigarettes and found CO levels declined in the EC group and remained similar to baseline in the cigarette group. Veldheer 2019 compared nicotine EC with a cigarette substitute (non-pharmacological); change in CO was similar between groups. Czoli 2019 instructed baseline dual users to spend periods only using EC or only using traditional cigarettes; CO measured during sole EC use was lower than baseline and lower than during cigarette-only periods. Further detail can be seen in Supplemental Table 3.

Data from other studies

Eighteen studies provided all participants with nicotine EC and reported data on CO at one week or longer. In the 17 studies that presented change over time, CO declined from baseline, although in Ikonomidis 2018 CO levels were equivalent to baseline again at 24 weeks, and in Polosa 2014b a decline was observed in people who quit smoking or reduced cigarette consumption by at least half, but not in those who continued smoking at least half as many cigarettes as they had from baseline.

Heart rate

Randomized controlled trials

One RCT (Caponnetto 2013a) provided data on heart rate and compared nicotine EC with non-nicotine EC; there was a greater decrease in heart rate in the nicotine EC arm (MD −2.80, 95% CI −3.85 to −1.74; 141 participants; Analysis 3.5). This was comparable with findings from the one RCT (Hatsukami 2020) comparing nicotine EC with no pharmacotherapy, which also found a greater reduction in the EC arm (MD −2.70, 95% CI −4.25 to −1.15; 90 participants; Analysis 4.5).

A further three RCTs provided data on heart rate which could not be included in a meta-analysis. George 2019 compared nicotine to non-nicotine EC and found no difference in heart rate between arms; Walele 2018 compared a nicotine EC with a traditional cigarette and reported "no clinically significant changes", and Veldheer 2019 found decreases in both the nicotine EC and QuitSmart cigarette substitute groups, with the decrease being slightly greater in the latter group. See Supplemental Table 4 for further information.

Data from other studies

Five studies in which all participants received a nicotine EC also reported data on heart rate; changes were minimal and directions of effect were mixed (see Supplemental Table 4).

Blood pressure

Caponnetto 2013a found no difference in the change in systolic blood pressure (BP) between nicotine EC and non-nicotine EC arms (MD 0.60, 95% CI −0.99 to 2.19;1 41 participants; Analysis 3.6). Similarly, Hatsukami 2020 and Ikonomidis 2018 found no difference in the change in blood pressure when comparing nicotine EC to cigarettes. However, Pulvers 2020 found a benefit in favor of the EC arm; pooling data from these three studies resulted in high levels of statistical heterogeneity (I^2 = 82%), so pooled results are not presented (Analysis 4.6). Three further RCTs measured change in blood pressure but presented results in such a way that they could not be pooled. George 2019 compared nicotine EC and non-nicotine EC and combined data from both groups; BP declined over time. Compared to a QuitSmart cigarette substitute, Veldheer 2019 found EC led to a greater reduction in BP. Walele 2018 found "no clinically significant changes" when comparing nicotine EC to a conventional cigarette at two weeks. Further data can be found in Supplemental Table 5.

Five studies which provided nicotine EC to all participants reported change in blood pressure; results were mixed and small (Hickling 2019; Ikonomidis 2018; Oncken 2015; Van Staden 2013; Walele 2018; see Supplemental Table 5).

Oxygen saturation

Hatsukami 2020 found a small increase in blood oxygen saturation when comparing nicotine EC to cigarettes (MD 0.50%, 95% CI 0.31 to 0.69; 89 participants; Analysis 4.7). Van Staden 2013, a short-term pre-post study which measured outcomes after two weeks of EC use, found that people who smoked who switched to ECs had significant improvement in blood oxygen saturation (96.2% (SD 1.8) to 97.5% (SD 1.3); 1.3% increase, 95% CI 0.6 to 2.1; P = 0.002).

Toxicants

All randomized controlled trials measuring these outcomes compared nicotine EC with no pharmacotherapy.

Two trials measured change in **3-HPMA** (one at high risk of bias). In both, the point estimate favored the EC arm, but statistical heterogeneity was substantial (I^2 = 97%), reflecting differences in magnitude of effect. We therefore do not present a pooled result, but data from the studies can be seen in Analysis 4.8. Four further studies in which all participants were given nicotine EC measured 3-HPMA; all found reductions over time (Supplemental Table 6).

Four trials measured change in **NNAL** (three at high risk of bias; Analysis 4.9). Three of the four studies found results favoring nicotine EC, but for the fourth the point estimate went in the opposite direction; statistical heterogeneity was again high (I^2 = 95%), so pooled results are not presented. Pulvers 2018, which provided all participants with nicotine EC, found a reduction in NNAL over time, and Czoli 2019, which was a cross-over trial, found NNAL decreased when using nicotine EC compared to using traditional cigarettes (Supplemental Table 6).

One trial found reductions in **2-HPMA** and **AAMA** compared to control (Analysis 4.10; Analysis 4.14), and a further two studies in which all participants received nicotine EC found reductions in both of these measures over time (Supplemental Table 6).

One trial found reductions in **S-PMA** compared to control (Analysis 4.15); this was consistent with the one study (Goniewicz 2017) in which all participants received nicotine EC that measured S-PMA, where levels declined over time (Supplemental Table 6).

In single trials, changes favored EC for reductions in HMPMA (Analysis 4.11), PheT (Analysis 4.12), and CEMA (Analysis 4.13). Of the 19 remaining measurements in studies where all participants received an EC, 14 reduced over time and five increased (Supplemental Table 6).

Lung function

Caponnetto 2013a measured a number of lung function parameters. FeNO increased more in the nicotine EC than the non-nicotine EC group (MD 2.35, 95% CI 1.78 to 2.92; 90 participants; Analysis 3.7). No difference was found between nicotine and non-nicotine EC for FEV1, FVC, or FEV1/FVC (Analysis 3.8; Analysis 3.9; Analysis 3.10).

Compared to behavioral support only/no support, Walele 2018 found improvements in FVC favoring nicotine EC (Analysis 4.16), and no difference in FEV1 or PEF 25-75 (Analysis 4.17; Analysis 4.19). Pooled data from Walele 2018 and Pulvers 2020 showed no difference in FEF 25-75, with substantial levels of statistical heterogeneity (MD −0.06, 95% CI −0.18 to 0.06, I^2 = 72%; 2 studies, 555 participants; Analysis 4.18).

Veldheer 2019, which randomized participants to nicotine EC or the QuitSmart cigarette substitute, measured change in a number of lung function parameters: direction of effect was mixed across these, with no statistically or clinically significant between-group differences at 12 weeks (Supplemental Table 7).

Two studies which provided all participants with nicotine EC measured change in lung function over time: Hickling 2019 found an increase in peak flow, and Oncken 2015 "no significant differences" in airway function (Supplemental Table 7).

Combination therapy: nicotine EC and NRT

This section covers two comparisons: studies in which all arms received NRT and participants were randomized to nicotine EC or non-nicotine EC, and studies in which all participants received NRT and one arm was randomized to nicotine EC in addition. All studies contributing data are randomized controlled trials. No studies in this group reported data on heart rate, blood pressure, oxygen, or toxicants.

Cessation

Two trials (both at high risk of bias, both testing refillable devices) in which all participants received NRT compared nicotine EC to non-nicotine EC; pooled results favored nicotine EC (RR 1.77, 95% CI 1.07 to 2.94; I^2 = 0%; 1039 participants; Analysis 5.1). Walker 2020 also compared nicotine EC + NRT to NRT alone; the point estimate favored nicotine EC but the confidence interval was wide and included no difference (Analysis 6.1).

Adverse events

The two trials (both at high risk of bias) in which nicotine ECs were compared to non-nicotine ECs in participants receiving NRT found no evidence of a difference in the number of people experiencing AEs between arms; data from Walker 2020 can be seen in Analysis 5.2; Baldassarri 2018 reported results combined across groups but noted "no significant differences by treatment group" (Supplemental Table 1).

The two trials comparing nicotine EC + NRT to NRT alone that contributed data to this outcome were both at high risk of bias. Statistical heterogeneity was high when combining data (I^2 = 79%) and hence we do not present pooled results. In one study (Walker 2020), AEs were lower in the EC group and the confidence interval excluded no difference, while in the other study (Guillaumier 2018) AEs were higher in the EC group but the confidence interval was wide (Analysis 6.2).

Serious adverse events

Walker 2020, comparing nicotine EC with non-nicotine EC as adjuncts to NRT, had fewer SAEs in the nicotine EC group than in the non-nicotine EC group, but the confidence interval includes no difference (Analysis 5.3).

Three studies provided data on SAEs and compared nicotine EC + NRT to NRT alone. The pooled estimate favored the NRT-alone group, but again the confidence interval was wide and included no difference (RR 1.26, 95% CI 0.46 to 3.42: I^2 = 0; 682 participants; Analysis 6.3).

Carbon monoxide

Walker 2020 (which compared nicotine EC + NRT, non-nicotine EC + NRT, and NRT alone) measured change in CO levels but did not report data in a way that could be pooled. CO declined over time, with the greatest reduction seen in the nicotine EC group (see Supplemental Table 3). Baldassarri 2018, comparing nicotine and non-nicotine EC as adjuncts to NRT, found a slightly greater reduction in CO in the nicotine EC group, but the confidence interval included no clear evidence of a difference (Analysis 5.4) between groups.

Lung function

Baldassarri 2018, which compared nicotine EC to non-nicotine EC and in which both groups received NRT, found no between-group differences in FeNO, FEV1, or FVC (Analysis 5.5; Analysis 5.6; Analysis 5.7); confidence intervals were wide for all outcomes.

Comparisons based on nicotine dose

Two trials provided data comparing different doses of nicotine in EC (although other studies provided a range of doses, these were not randomly assigned). In Caponnetto 2013a, where different concentrations were available via the same device, cessation and adverse event data were not available. No serious adverse events were reported in either arm (Analysis 7.1). There were no clinical or statistically significant differences between arms for carbon monoxide, heart rate, blood pressure, or lung function measures (Analysis 7.2 to Analysis 7.8). In Yingst 2020 (cross-over, comparing different doses and different devices) exhaled CO and reported nausea were not different between devices; self-reported dizziness was low overall but slightly higher in the higher-dose arm. Further detail can be found in Supplemental Table 1 and Supplemental Table 3.

Non-nicotine EC

Although non-nicotine ECs serve as a 'control group' in our primary analysis, due to their behavioral properties they can also be considered an intervention in and of themselves. Comparisons included here are: non-nicotine EC versus NRT; non-nicotine EC versus usual care; and non-nicotine EC as an adjunct to NRT. All contributing data are from randomized controlled trials. None of these studies reported data on change in CO, heart rate, blood pressure, oxygen saturation, toxicants, or lung function.

Cessation

When comparing non-nicotine EC to behavioral support only, pooled results from two studies (n = 388) found higher quit rates in participants randomized to non-nicotine EC, but the confidence interval included the possibility of no difference (RR 1.74, 95% CI 0.76 to 3.96; I^2 = 0%; Analysis 8.1). When evaluating non-nicotine EC as an adjunct to NRT, Walker 2020 also found higher quit rates in participants randomized to non-nicotine EC, although again the confidence interval included no difference (Analysis 9.1).

Lee 2019 compared non-nicotine EC with NRT; the point estimate favored NRT but the confidence interval included no difference (Analysis 10.1).

Adverse events

Eisenberg 2020 found a higher rate of adverse events in the EC arm than in behavioral support only, with the confidence interval excluding no difference (Analysis 8.2). By contrast, Walker 2020 found fewer adverse events in participants receiving non-nicotine EC + NRT compared to NRT alone, with the confidence interval excluding no difference (Analysis 9.2). Lee 2019 also found that fewer participants receiving non-nicotine EC reported adverse events than those receiving NRT, with the confidence interval excluding no difference (Analysis 10.2).

Serious adverse events

Eisenberg 2020 found a higher rate of SAEs in the EC arm than in the behavioral support-only arm, but confidence intervals were wide and incorporated clinically significant benefit and clinically significant harm (Analysis 8.3). In Walker 2020, more SAEs occurred in the group randomized to non-nicotine EC + NRT than in the NRT-alone group, but the confidence interval included no difference as well as the potential for a clinically significant difference in favor of the intervention (Analysis 9.3). No SAEs were reported in either arm of Lee 2019 (non-nicotine EC versus NRT).

DISCUSSION

Summary of main results

This update includes a further six studies compared with the previously published version. Our three main comparisons, nicotine EC compared to NRT, nicotine EC compared to non-nicotine EC, and nicotine EC compared to behavioral support only/no support still show increased quit rates in people assigned to nicotine EC arms; this is moderate-certainty for the first two comparisons, and very low certainty for the latter (Summary of findings 1; Summary of findings 2; Summary of findings 3). In absolute terms, pooled data suggest an additional four people for every 100 would quit smoking with nicotine EC compared to non-nicotine EC or to NRT, and that an additional seven people per 100 would quit if offered a nicotine EC compared to being offered behavioral support alone or no support. Most data come from studies of cartridge devices which deliver relatively little nicotine in comparison to newer device models. However, within newer device models with better nicotine delivery, this update includes the first included study of a pod device (Pulvers 2020).

The certainty of the evidence for adverse events in nicotine EC compared to non-nicotine EC has been upgraded from low- to moderate-certainty evidence of no difference. Evidence on adverse events (AEs) and serious adverse events (SAEs) was of low to very low certainty across all other comparisons, due to a paucity of data. SAEs were rare, in both intervention and comparator arms, with many of the studies which measured SAEs reporting no such events in either study arm. For nicotine EC compared to non-nicotine EC, pooled data suggest no difference in the number of people experiencing AEs and one fewer person per 100 experiencing SAEs with nicotine EC compared to non-nicotine EC arms, but confidence intervals include no difference. Conversely, data from comparisons between nicotine EC and behavioral support alone or no support suggest an additional 13 people per 100 assigned to nicotine EC may experience AEs, with no difference in the number experiencing SAEs. As with AEs from other smoking cessation treatments (e.g. NRT, Hartmann-Boyce 2018a), these events typically related to irritation at site (e.g. dry mouth, cough) and resolved over time. Compared to NRT, one fewer person per 100 might be expected to experience an AE if assigned to nicotine EC, and two additional people per 100 might be expected to experience an SAE. These figures should be treated with caution, due to large confidence intervals encompassing no clinically significant difference. The small amount of contributing data, and the variation in 'control group' risk across comparisons, reflect different methods of collecting data and different lengths of follow-up. No studies in any of the different comparison conditions detected serious harms considered to be related to EC use.

Beyond AEs and SAEs, we consider data on a range of safety- and health-related outcomes, including carbon monoxide and other toxins, lung function, blood pressure, pulse, and oxygen levels. Data on all of these outcome measures are limited; for most outcomes within most comparisons, only one study currently contributes data. Pooled data from two studies in which all participants received nicotine replacement therapy showed that nicotine EC led to higher quit rates than non-nicotine EC, but we judged both studies to be at high risk of bias, meaning the effect remains uncertain.

Overall completeness and applicability of evidence

This field of research and EC devices themselves continue to evolve rapidly. This is the first update conducted as part of our 'living systematic review' approach, with which we will proceed for at least the next 12 months, meaning we can continue to rapidly incorporate new evidence (see Appendix 1). This is important, as all of our analyses currently suffer from imprecision.

This update captures data from the past year, up to February 2021. Subsequent monthly searches will keep this review current. Although studies predominantly came from the USA and UK, overall this review covers data from 14 countries; geographical range in studies may be particularly important in this area, due to the marked differences in EC regulation between countries; for example, studies conducted in countries that limit nicotine

dose in EC or allow only certain EC devices to be tested may observe less pronounced effects on quitting. This review includes studies in some 'harder to reach' populations, including people not motivated to quit smoking, people with substance misuse disorders, and people experiencing homelessness. Quit rates in these groups are traditionally lower, which may make it more difficult to detect effects of interventions. However, it could be that these groups may particularly stand to benefit from EC if they are effective, because in absolute terms conventional cessation methods are often not as effective for them.

As well as the rapid pace of research in this field, EC technology itself continues to evolve, which poses a challenge when considering the applicability of our evidence to the present. We had downgraded the certainty of our data in the 2016 update, as the devices tested in the trials were first-generation 'cig-a-like' devices which did not deliver nicotine well, meaning the studies may have yielded more conservative estimates than would be seen with newer models, as newer devices and models have tended towards improved nicotine delivery. Nicotine delivery is also relevant to the comparator NRT arms tested; use of both a shorter- and a longer-acting form of NRT shows the highest success, and it is important that where possible this be the comparator chosen for such trials (Lindson 2019).

Regarding EC device type, in the 2020 update and now in this update, we have more data from newer devices, although there will always be a time lag between current devices and the research evidence available. None of the analyses of our primary outcomes signified substantial levels of statistical heterogeneity, despite the fact that different devices were used in the included studies. However, this could be because confidence intervals were wide for individual studies, and does not rule out clinically significant differences in effects between EC types. As further data emerge, we hope to be able to formally test for differences in subgroup analyses, and ideally over time in head-to-head comparisons of different device types. Our review now includes one study of a pod device (Pulvers 2020) and one study directly comparing device types (Yingst 2020). However, neither contributes data to our cessation outcomes.

The adverse effects described in both the RCT and cohort studies continue to look similar, regardless of the brand of EC used or nicotine content, with placebo and nicotine-containing ECs showing similar numbers and types of adverse events in direct comparisons. They also reflect what is reported in survey data (Dawkins 2013b; Etter 2011), so we believe that they are broadly applicable to most EC brands.

There has been concern raised that the dual use of cigarettes and EC may expose people to greater health risks, including higher nicotine levels. However, given that people who smoke like to maintain relatively stable blood nicotine levels (Russell 1990), receiving nicotine from an alternative source (i.e. EC) is likely to reduce nicotine intake from cigarettes, which should be accompanied by a reduction in smoke and toxin intake (Fagerström 2004). In a study assessing biochemical changes exclusively in dual-users, there was a significant decrease in exhaled carbon monoxide levels and urinary 3-HMPA (McRobbie 2015). In this update, we found one new study conducted in dual-users. Similar to McRobbie 2015, Czoli 2019 found that levels of biomarkers of exposure to toxicants were significantly lower when participants exclusively used EC compared to dual use; by contrast, biomarkers of exposure increased when participants exclusively smoked as compared to dual use. These results are supported by longer-term studies in people who smoke and were provided with ECs, which found decreases in exhaled carbon monoxide among dual-users (Adriaens 2014; Pacifici 2015; Polosa 2011; Polosa 2014b).

The structure of our analyses follows standard practice of the Cochrane Tobacco Addiction Group, i.e. evaluating outcomes on an intention-to-treat basis, meaning our pooled results represent the effect of *offering an EC intervention.* This is different from evaluating the per protocol effect, or the effect only in those who use the EC to quit smoking entirely, or continue to smoke whilst also using EC. Some of our included studies have also assessed data using these groupings and we have attempted to note this in the supplemental tables. Although pragmatic and hopefully of use to those designing and delivering interventions, we acknowledge that our intention-to-treat approach limits the ability to use the data presented here to draw conclusions about biomarkers in subgroups of participants based on subsequent EC use/smoking profiles.

Certainty of the evidence

We consider the certainty of the evidence below as it relates to primary outcomes for our three main comparisons: nicotine EC versus NRT; nicotine EC versus non-nicotine EC; nicotine EC versus behavioral support only/no support (Summary of findings 1; Summary of findings 2; Summary of findings 3). The certainty of evidence for all other comparisons and outcomes should be considered very low due to a paucity of data.

Our 'Summary of findings' tables and assessments of certainty are based on the evidence from randomized controlled trials (RCTs). The cohort studies that we include were all deemed to have high risks of bias, which is inherent in the study design. Data presented from these studies need to be interpreted with caution. However, data from cohort studies were reassuringly consistent with data from RCTs.

Risk of bias did not impact on the certainty of evidence for comparisons between nicotine and non-nicotine EC, or between nicotine EC and NRT. For the latter, we judged all three studies to be at low risk of bias overall. For the former, removing the one study at high risk of bias increased the effect estimate for our efficacy outcome. Risk of bias decreased our certainty in the effect estimates for our nicotine EC versus behavioral support only/no support comparison, as due to the nature of the comparison, blinding was not possible and differential levels of support could lead to bias. All but one of our main comparisons were downgraded for imprecision, due to wide confidence intervals and few events. Other than risk of bias and imprecision, we identified no other issues which decreased the certainty of the primary outcomes for our main comparisons. In the previous version of this review we had downgraded cessation outcomes for indirectness, due to the included studies testing devices that were no longer available due to poor nicotine delivery (we therefore judged it plausible that our analyses could be underestimating the effect of devices available at the time the review was published). In this version, we no longer downgrade on this basis, as this update includes a wider range of EC models, including more recent devices, and heterogeneity in outcomes remains low.

Cessation

All three comparisons found effect estimates favoring nicotine EC for smoking cessation. For nicotine EC versus non-nicotine EC and for nicotine EC versus NRT, we judged the evidence to be of moderate certainty, meaning we think the true effect is likely to be close to the estimate of effect. For nicotine EC versus behavioral support only/no support, we judged the evidence to be of very low certainty, meaning we have very little confidence in the effect estimate. Another way to look at this, however, is to consider that nicotine EC versus non-nicotine EC comparisons isolate the effect of nicotine as provided by an EC, and nicotine EC versus NRT comparisons isolate the effect of the sensorimotor elements provided by an EC. Given that both of these comparisons find a benefit of nicotine EC for smoking cessation, it might logically follow that the comparison between nicotine EC and behavioral support only/no support would find a benefit in favor of nicotine EC, since this comparison would capture both pharmacological and sensorimotor mechanisms of effect. This increases our confidence in the effect of nicotine EC when compared to behavioral support alone or to no support.

Adverse and serious adverse events

In this update, we have upgraded the certainty of evidence for adverse events in the nicotine EC versus non-nicotine EC comparison; the addition of new data has led to narrower confidence intervals, and as a result we have upgraded the evidence from low to moderate certainty of no difference. For our other comparisons and adverse effect outcomes, effect estimates of adverse events and serious adverse events were judged to be of low or very low certainty, with the main problem being imprecision. This means the true effect may be substantially different from the estimate of the effect. None of the analyses signaled serious harm, nor did complementary data from cohort studies, but unlike our cessation analyses, many of the confidence intervals encompassed the possibility of both clinically significant harm and clinically significant benefit. This uncertainty should reduce as more studies become available.

Potential biases in the review process

We consider the review process we used to be robust. For outcome assessment, we followed the standard methods used for Cochrane Tobacco Addiction Review Group cessation reviews. Our search strategy included the Cochrane Tobacco Addiction Group Specialized Register and we were able to capture a number of ongoing studies. However, there may be unpublished data that our searches did not uncover. We also considered participants lost to follow-up as continuing to smoke, which is standard practice in this field. There are concerns that frequently updating meta-analyses can lead to issues with multiple testing; we followed Cochrane guidance in conducting this living systematic review and hence do not adjust for multiple testing (Brooker 2019).

Three of our review authors are authors of included studies. These authors were not involved in the decisions about inclusion of their studies, or in data extraction or 'Risk of bias' assessment for these studies.

Agreements and disagreements with other studies or reviews

This Cochrane Review aligns with but updates the conclusions of the 2018 U.S. National Academies of Science, Engineering, and Medicine's Consensus Study Report, *Public Health Consequences of E-cigarettes* (NASEM 2018), which reviewed literature published through August 2017 to address the question, "Do e-cigarettes help smokers quit smoking combustible tobacco cigarettes?". Focusing on RCTs and existing systematic reviews, it used a prespecified Level of Evidence framework to develop conclusions. The report's overall conclusion was that there was "limited evidence that e-cigarettes may be effective aids to promote smoking cessation." Based on the RCTs available, it concluded that there was "moderate evidence" that e-cigarettes containing nicotine were more effective for cessation than e-cigarettes without nicotine, but "insufficient evidence" about the effectiveness of e-cigarettes compared to no treatment or to FDA-approved smoking cessation treatments. Our review contradicts this latter point, as we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT; this is primarily due to a large RCT published after NASEM 2018. A 2021 review from Public Health England, which cites the 2020 version of this Cochrane Review, concludes that, compared to their 2018 review, there is now stronger evidence that nicotine vaping products are effective for smoking cessation (McNeill 2021).

Findings are also broadly consistent with those from other reviews published in the past year, with some exceptions. Amato 2020 did not evaluate effectiveness and focused only on safety; consistent with our review, they found very low- to moderate-certainty evidence on a range of possible adverse effects, with the most frequently reported being cough, dry mouth, shortness of breath, irritation of the mouth and throat, and headache. Akiyama 2021 reviewed biomarker findings from clinical studies and concluded that the use of EC could lead to a significant reduction in exposure to harmful substances compared to traditional cigarettes; this is again consistent with findings from our review. Martinez-Morata 2021 reviewed blood pressure findings and concluded that EC may result in short-term elevations, but that more data are needed; our review also lacks sufficient data to draw any conclusions about blood pressure at one week or longer.

Zhang 2021 conducted a rapid review; while their pooled analysis also suggested that EC increased quit rates compared to NRT or non-nicotine EC, they judged the evidence to be of low certainty according to GRADE. As with us, they downgraded by one level due to inconsistency, but unlike us they also downgraded by one level for statistical heterogeneity. Zhang 2021 combined studies with NRT comparators and those with non-nicotine EC comparators in the same analysis and found moderate statistical heterogeneity; we evaluated these two comparisons separately and did not find evidence of statistical heterogeneity. Patnode 2021 reviewed evidence on tobacco cessation interventions for the US Preventive Services Task Force (USPFTS 2021). They state that none of their included EC trials suggested higher rates of serious adverse events; this is in line with our analyses. However, they report that findings across EC trials were inconsistent for effectiveness, with some finding statistically significant evidence of benefit and some finding no statistically significant difference. They did not conduct statistical meta-analyses and include five trials, all of which are included in our cessation meta-analyses. None of our cessation meta-analyses, which include these trials, detected levels

of heterogeneity beyond what would be expected from chance alone. Wang 2021 reviewed data both from observational studies and from randomized controlled trials; in the trials, e-cigarettes were associated with increased smoking cessation (as with our review). In observational studies, ECs were not associated with increased smoking cessation. As discussed in Methods, although we included non-randomized studies in which an EC intervention is provided in this review, we do not include observational studies in which no EC intervention is provided, due to known issues with confounding.

Reviews of ECs for policymaking are often broader in scope than our review, which focuses exclusively on their role in supporting smoking cessation in people who smoke. Outside of smoking cessation, there remain unanswered questions about the impact of EC availability and use on young people; we hope to evaluate this in a separate review.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence suggesting nicotine EC can aid in smoking cessation is consistent across several comparisons. There was moderate-certainty evidence, limited by imprecision, that EC with nicotine increased quit rates at six months or longer compared to non-nicotine EC and compared to NRT. There was very low-certainty evidence (limited by risk of bias as well as imprecision) that EC with nicotine increased quit rates compared to behavioral support alone or to no support.

The effect of nicotine EC when added to NRT was unclear.

None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use. The most commonly-reported adverse effects were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate with continued use. In some studies, reduced toxin concentrations and biomarkers of harm were observed in people who smoked and switched to vaping, consistent with reductions seen in smoking cessation.

Implications for research

Further randomized controlled trials of nicotine EC are needed, following up participants at six months or longer. Studies with active comparators (i.e. comparing nicotine EC to frontline smoking cessation pharmacotherapies) are likely to be of particular use to decision-makers. All studies (including uncontrolled intervention cohort studies) should aim to assess the safety profile of electronic cigarettes for as long as possible (the current review only includes data up to two years), and ideally be powered to detect differences in safety outcomes, including adverse events and serious adverse events. Evidence from one well-conducted RCT suggests that people who quit smoking using EC may continue to use EC longer than they might use other stop-smoking pharmacotherapies, making assessments of their long-term safety profile particularly important. Safety results should be presented in both absolute and relative risk terms (in comparison to the risks of continuing to smoke tobacco).

Studies should offer recent devices to participants, to be most representative of what will be on the market at the time results are released. Data on pod-type EC are particularly lacking, though we now include one trial. Protocols and statistical analysis plans should be registered in advance and openly available.

Further RCTs need to be adequately powered. Further trials of pod devices would be of particular value, as would RCTs providing EC in a way that would be used in real-world settings (e.g. taking into account individual preferences for strengths and flavors of e-liquids and even EC devices, and also allowing for changes in preferences over time).

Further reviews, using best available methods, need to be conducted to evaluate the possible relationships between EC use and availability and youth uptake of EC and conventional cigarettes.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adriaens 2014

Study characteristics	
Methods	Design: 3-armed RCT; with all participants then assigned to nicotine EC (treated as cohort in this review) Recruitment: Advertisement on university website, flyers on university campuses, emails to personnel and advertisement in local newspaper Setting: Community and laboratory, Belgium Study start date/end date: Not stated
Participants	Total N: 48 provided data Randomized to: EC1 16; EC2 17; control 17 Inclusion criteria: • Smoker for at least 3 years, • Smoking at least 10 cpd, not intending to quit in the near future but willing to try a less unhealthy alternative Exclusion criteria: • Diabetes; • Severe allergies; • Asthma or other respiratory diseases; psychiatric problems; • Dependence on chemicals other than nicotine; • Pregnancy; • Breastfeeding; • Hypertension; • CV disease; • Currently using any kind of smoking cessation therapy; prior use of EC 56% women, mean age 44, mean cpd 19, mean FTCD 5.79, all unwilling to quit with no baseline EC use
Interventions	**EC: Refillable**

Adriaens 2014 *(Continued)*

	Intervention: 2 intervention groups (EC1 and EC2) provided with EC and instructed to use EC or smoke ad libitum (EC1 group provided with Joyetech eGO-C, EC2 group provided with Kanger T2-CC) and provided guidance on EC use. For both types, provided 30 mL bottles of tobacco-flavored e-liquid (Dekang "Turkish Blend"), containing 18 mg/mL of nicotine. 4 bottles at baseline replenished at 4 weeks, keep any remaining after 8 weeks **Control:** 6 bottles for 2 months at week 8 (half offered EC1, half offered EC2); no guidance on use
Outcomes	3 lab sessions over 2 months (weeks 1, 4 and 8), plus online questionnaires, further follow-up at 3 and 6 m after last lab session Cessation: measured but definition not provided, validated with eCO 5 ppm or less Adverse events and biomarkers: eCO, salivary cotinine measured during lab sessions. Also collected craving and withdrawal symptoms via lab sessions, "benefits and complaints", mood, EC usage
Study funding	"No external funding for this study was obtained. Electronic cigarettes and e-liquids were purchased at E-cig4U (`t Rond 10, 4285 DE Woudrichem, The Netherlands; http://www.e-cig4u.nl/) with balances of previous research funds obtained by Frank Baeyens."
Author declarations	The authors declare no conflict of interest
Notes	Randomization was for short-term outcomes only Additional data provided from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization was performed by using a randomization tool available on the website www.randomizer.org
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinded but as this review only includes data on objective measurements and not cessation judged unlikely to affect outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	36 out of 48 completed follow-up (11/16 in EC1 group, 12/17 in EC2 group, 13/17 in control group)
Selective reporting (reporting bias)	Unclear risk	Outcome reporting somewhat non-traditional; for example, collecting complaints but not explicitly adverse events, and incidence of AEs not reported. Unable to find prospectively-registered protocol

Baldassarri 2018

Study characteristics

Baldassarri 2018 *(Continued)*

Methods	Design: Randomized parallel-assignment double-blind trial Recruitment: outpatient pulmonary and primary care clinics, Tobacco Treatment Service, referrals from medical providers Setting: Hospital outpatient and primary care clinics, USA Study start date: October 2014; Study end date: June 2014
Participants	Total N: 40 N per arm: Non-Nicotine: 20; Nicotine EC: 20 Inclusion criteria: • Age 18 years or older • Smoking 1 or more cpd • Willing to quit smoking Exclusion criteria: • Unstable psychiatric or medical conditions requiring hospitalization within the past 4 months; • Acute coronary syndromes or stroke within the past 30 days; • History of allergic reactions to adhesives; • Women who were pregnant, nursing, or not practicing effective contraception; • Current use of an EC for the purpose of stopping tobacco cigarette smoking Women: 52.5%; Mean age: 53 Mean cpd: 17 Mean FTND: 5.9; motivated to quit E cigarette use at baseline: Not reported
Interventions	**EC: Refillable** Both groups received standard care (8 weeks nicotine patch and counseling) and were randomized to **nicotine EC** or **non-nicotine EC**. EC: eGO style EC (650 mAh battery, EVOD clearomizer, 3.7 V, 1.8 Ω single bottom coil), provided with e-liquid purchased from an online vape shop (0 mg/ml or 24 mg/ml nicotine strength, 70/30 propylene glycol/vegetable glycerin, tobacco flavor); Instructed to use it as needed as a substitute for tobacco to try to satisfy cravings to smoke. If the patch alone proved adequate to prevent withdrawal and smoking cravings, the participant was advised not to use the EC. Additional EC devices, replacement coils, and liquid were provided as needed for the first 8 weeks of the study
Outcomes	Questionnaires and CO measurements taken at baseline, treatment visits at week 2, 4, 6, 8 and follow-up at week 24 Cessation: 7-day point prevalence abstinence, eCO ≤ 6 ppm Adverse events and biomarkers: Side effects were measured although it is unclear whether a questionnaire with prespecified symptoms was used Spirometry and FeNO at baseline and 6-month follow-up Other outcomes: Change in reported number of cpd at weeks 8 and 24; Change in per cent predicted FEV1 and FVC from baseline to week 24, and EC use patterns
Study funding	"Funding for this study was provided by the Yale School of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine and the National Heart, Lung, and Blood Institute grant T32HL007778. NHLBI had no role in the study design, collection, analysis, or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication."

Baldassarri 2018 *(Continued)*

Author declarations	"Dr. Toll received a grant from Pfizer for medicine only for a research study, and he receives funding as an expert witness in litigation filed against the tobacco industry. Dr. Chupp received grants from NIH, Genetech, Glaxo Smith Kline, Astra Zeneca/Medimmune and Boston Scientific. He received consulting/speaking fees from Genetech, Astra Zeneca/Medimmune, Mannkind, and Boston Scientific. There are no other conflicts of interest for the remaining authors."
Notes	New for 2020 update. Study listed as ongoing study NCT02498145 in 2016 review update Additional data provided from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomized using a random number generator with 1:1 blocked randomization (block size n= 8)."
Allocation concealment (selection bias)	Unclear risk	Both groups received standard care (nicotine patch and counseling) and were randomized to: nicotine EC or non-nicotine EC (no further detail given)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment assignment was blinded to both the investigators and participants"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	CO biochemically validated
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "The study had a modest loss to follow-up (20%) at week 24." Number lost to follow-up in each group is not reported in the paper Week 24 retention rate: Nicotine EC group: 19/20 (95%); Non-nicotine EC group: 13/20 (65%); > 20% difference between groups
Selective reporting (reporting bias)	Low risk	Outcomes reported align with those listed in the clinicaltrials.gov record. (registered 2015; prior to study completion in 2016)

Bell 2017

Study characteristics

Methods	Design: Pragmatic, uncontrolled, mixed-methods trial Recruitment: Targeted settings for people with HIV Setting: Community, Brisbane, Australia Study start date: 21 February 2017; Study end date: 26 October 2017
Participants	Total N: 30 Inclusion criteria: • Diagnosis of HIV • Aged 18 years, or over • Smoke ≥ 5 cpd at the time of enrolment into the trial

Bell 2017 *(Continued)*

	• Have been smoking for at least 12 months • Willing to attempt to quit tobacco smoking after study enrolment Exclusion criteria: • Participating in a smoking-cessation programmed • Pregnant or breastfeeding or planning to be during trial period • Experienced chest pain, or another cardiovascular event or procedure in the last month • Being treated with oxygen therapy Inclusion based on specific population characteristic: People living with HIV 29 participants identified as male, and 1 participant did not identify as male or female; Mean age: 42; Mean cpd: 18 EC use at baseline: 46.7% (n = 14) Never tried; 50% (n = 15) Tried, never used for an extended period; 3.3% (n = 1) Used on a regularly (weekly) basis Willing to attempt to quit
Interventions	**EC: Refillable** Single-arm study. Print materials to help quit smoking. Provided booklet with instructions on how to use, store and handle EC; copies of device user manuals. Given Innokin Endura T18® vaporiser kit, Innokin Endura T22® vaporiser kit, 4 spare coils, 1 wall charger, 10 x 10-mL bottles of Nicophar® 12 mg nicotine e-liquid. Supplies to last 12 weeks
Outcomes	Weeks 1, 4, 8, 12, 24; Self-report and semistructured interviews Cessation: 7 days point prevalence at weeks 4, 8, 12 and 24. Continuous abstinence at weeks 12 and 24. No biochemical validation Adverse events Other outcomes: Acceptability and use of trial products; Number of quit attempts
Study funding	"This work was supported by the HIV Foundation Queensland. The funder will play no role in the analysis and interpretation of results. All trial products were purchased and the suppliers have no involvement in the conduct of the trial or the interpretation or reporting of the results."
Author declarations	"No other authors declare conflicts of interest. Mark Boyd has received research grant funding (paid to the institution) from AbbVie, Gilead and Merck and received honoraria for participation in HIV Advisory Boards and for the preparation and delivery of educational materials from AbbVie, Boehringer-Ingelheim, Bristol Myers Squibb, Gilead, Janssen-Cilag, Merck and ViiV Healthcare."
Notes	Additional data provided from authors. New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled study
Allocation concealment (selection bias)	High risk	Uncontrolled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: “At Week 24, 26 of the 30 participants who enrolled in the study were followed up.” (confirmed by authors)

Bell 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	Study not published at time of data extraction, but study protocol published

Bullen 2013

Study characteristics	
Methods	Design: 3 parallel groups RCT Recruitment: People who smoke recruited from the community, via newspaper advertisements Setting: Research Unit, New Zealand Study start date: 6 September 2011; Study end date: 5 July 2013
Participants	Total N: 657. 289 nicotine EC (NEC), 295 patch, 73 non-nicotine EC (PEC) Inclusion criteria: • 18 years of age or older; • Smoked 10 or more cpd over past year; • Wanted to stop smoking Exclusion criteria: • Pregnant and breastfeeding • Using cessation medicines or using other support to quit • Heart attack, • Stroke, • Severe angina in the last 2 weeks, • Poorly-controlled medical disorder, • Allergies, • Other chemical dependence 62% women, mean age 42, ⅓ NZ Maori, smoking 18 cpd, mean FTND score 5.5 Motivated to quit E cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** Randomized to NEC, PATCH or PEC use for 13 weeks (from 1 week prior to TQD) • **NEC:** Elusion brand 16 mg cartridges; sent product via courier • **PATCH:** 21 mg/24-hour patch; sent voucher to exchange for NRT at pharmacy (dispensing costs covered) • **PEC:** As per EC, but 0 mg cartridges All participants referred to Quitline and received an invitation to access phone- or text-based support. This was accessed by < 10%
Outcomes	Sustained (≤ 5 cigarettes allowed) validated (exhaled breath CO < 10 ppm) abstinence at 6 months ≥ 50% self-reported reduction in baseline cigarettes at 6 months Participants reporting any adverse events Proportion of AEs that were serious

Bullen 2013 *(Continued)*

	Proportion of unrelated AEs
Study funding	Health Research Council of New Zealand
Author declarations	"We declare that we have received no support from any companies for the submitted work and have no non-financial interests that might be relevant to the submitted work. ML, via his company Health New Zealand, previously did research funded by Ruyan (an e-cigarette manufacturer). CB and HM have done research on Ruyan e-cigarettes funded by Health New Zealand, independently of Ruyan. HM has received honoraria for speaking at research symposia, has received benefits in kind and travel support from, and has provided consultancy to, the manufacturers of smoking cessation drugs. NW has provided consultancy to the manufacturers of smoking cessation drugs, received honoraria for speaking at a research meeting and received benefits in kind and travel support from a manufacturer of smoking cessation drugs. JW has provided consultancy to the manufacturers of smoking cessation medications."
Notes	Accessed support: NEC: 115/289; PATCH: 106/295; PEC: 26/73

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized block randomization
Allocation concealment (selection bias)	Low risk	Computerized via study statistician
Blinding of participants and personnel (performance bias) All outcomes	Low risk	NEC and PEC were blind to treatment condition in relation to one another. No blinding for NEC/PEC vs PATCH conditions, but as NEC and PATCH were both active treatments performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU 22% (all considered to be smoking). Patch group had a higher LTFU and withdrawal than EC (loss to follow-up 17% NEC, 27% patches, 22% PEC). However, minimal difference in per-protocol and ITT analyses
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Caponnetto 2013a

Study characteristics

Methods	Design: 3-arm double-blind randomized controlled trial: EC with 7.2 mg nicotine for 12 weeks; same for 6 weeks followed by 5.2 mg for 6 weeks: EC with no nicotine for 12 weeks Recruitment: Newspaper advertisements Setting: Outpatient clinic, Italy Study start date: April 2010; Study end date:April 2012
Participants	Total N: 300

Caponnetto 2013a *(Continued)*

	Inclusion criteria: • Smoked at least 10 cpd for past 5 years; • Age 18 - 70 • In good health • Not currently or intending to quit smoking in the next 30 days Exclusion criteria: • Symptomatic cardiovascular or respiratory disease • Regular psychotropic medicine use • Current or past history of alcohol abuse • Use of smokeless tobacco or NRT • Pregnant or breastfeeding 36% women, mean age 44 (SD 12.5), mean cpd 20 (IQR: 15 - 25) Not currently or intending to quit smoking in the next 30 days E cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** EC presented as a healthier alternative to tobacco smoke and could be freely used, ad libitum (up to 4 cartridges a day) for 12 weeks, as a tobacco substitute EC used: 'Categoria' (model 401) with disposable cartridges • **Grp A**: 12 weeks of 7.2 mg capsules ('Original') • **Grp B**: 6 weeks 7.2 mg ('Original'), then 6 weeks 5.4 mg ('Categoria') • **Grp C**: 12 weeks of 0 mg ('Original') Baseline visit and up to 7 follow-up visits to receive more cartridges, hand-in diaries, measure CO and vital signs
Outcomes	Abstinence at 12 months (complete self-reported abstinence from tobacco smoking since previous visit at 6 months, confirmed with CO < 7 ppm at 12 months) ≥ 50% reduction in baseline cigarettes at 12 months Recorded AEs thought to be related to tobacco smoking and EC at baseline and at each study visit (7 follow-up visits over 12 weeks, plus at 24 and 52 weeks)
Study funding	"This research was supported by a grant-in-aid from Lega Italiana AntiFumo. The study sponsor had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication. RP and PC are currently funded by the University of Catania, Italy. The e-cigarette supplier had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication."
Author declarations	"RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl, the distributor of the CategoriaTM e-Cigarette. The other authors have no relevant conflict of interest to declare in relation to this work."
Notes	Additional data provided from authors
Risk of bias	

Bias	Authors' judgement	Support for judgement

Caponnetto 2013a *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated, block size 15 (5:5:5 ratio)
Allocation concealment (selection bias)	Low risk	Randomization carried out by pharmacy, who did not have direct contact with the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Quote: "Blinding was ensured by the identical external appearance of the cartridges. The hospital pharmacy was in charge of randomization and packaging of the cigarettes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	211 (70.3%) and 183 (61%) attended 6- and 12-month follow-up (at 12 m, 35% lost in 7.2 group; 37% lost in 5.4 group; 45% lost in no-nicotine group)
Selective reporting (reporting bias)	Unclear risk	Unclear if original intention was to combine groups A+B or not. In sample size calculation they compared A+B with C, but results are not always reported in this way

Caponnetto 2013b

Study characteristics	
Methods	Design: Prospective cohort Recruitment and setting: Inpatients at a psychiatric institution in Italy Study start date/end date: Not specified
Participants	Total N: 14 Inclusion criteria: • Smoked ≥ 20 cpd for at least the past 10 years • Diagnosis of schizophrenia Exclusion criteria: • Alcohol and illicit drug use • Recent myocardial infarction • Angina pectoris • High blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both) • Diabetes mellitus • Severe allergies • Poorly-controlled asthma or other airway diseases • Inclusion based on specific population characteristic: Diagnosis of schizophrenia 57% women, mean age 44.6 (SD 12.5), mean pack years smoked 28.8 (SD 12.9) Motivated to quit: Not specified E cigarette use at baseline: Not specified

Caponnetto 2013b *(Continued)*

Interventions	**EC: Cig-a-like** Seen at baseline, given EC ('Categoria' brand) with an initial 4-week supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges a day. EC cartridges supplied at months 1, 2, and 3 No instruction on cessation or reduction was provided.
Outcomes	Follow-up at 1, 2, 3, 6 and 12 months where cigarette consumption, CO, AEs and positive and negative symptoms of schizophrenia were measured Sustained reduction of ≥ 50% for at least 30 days at 12 months 30-day point prevalence CO-validated abstinence at 12 months Adverse events
Study funding	"We wish to thank Arbi Group Srl (Milano, Italy) for the free supplies of “Categoria” e-cigarette kits and nicotine cartridges as well as their support. We would also like to thank LIAF (Lega Italiana AntiFumo) for the collaboration."
Author declarations	"Pasquale Caponnetto, Roberta Auditore, Cristina Russo and Giorgio Carlo Cappello declare no conflict of interest. Riccardo Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has served as a consultant for Pfizer and Arbi Group Srl (Milano, Italy), the distributor of the CategoriaTM e-cigarette."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort; no randomization
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/14 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Carpenter 2017

Study characteristics

Methods	Design: Randomized parallel-assignment open-label trial Recruitment: Recruitment from local urban community in southeastern USA, using various media outlets Setting: Community, southeastern USA Study start date: November 2014; Study end date: May 2016

Carpenter 2017 *(Continued)*

Participants	Total N: 68 N per arm: Control group: 22; ENDS group: 46 (split into 2 non-randomized groups: BluCig 16 mg: 25; BluCig 24 mg: 21) Inclusion criteria: • Age 18+ • Current smoker of ≥ 5 cpd for ≥ 1 year • No recent history of cardiovascular distress, COPD, cancer (any non-dermatologic), or uncontrolled diabetes mellitus • Neither pregnant nor breastfeeding (verified) • Absence of any major current psychiatric impairment, including current alcohol/drug abuse/dependence • Current, active use of email • At least some concern for health effects of smoking (> none at all on a Likert scale) • Not used any ENDS product in the past 6 months • Never purchased an ENDS product Exclusion criteria: • Use of non-cigarette tobacco products (e.g. cigarillos) in the last 30 days • Current use of any smoking cessation medications • Current enrolment in a smoking cessation treatment study Women: 59.7%; Mean age: 42.2; Mean cpd: 15.3; Heaviness of smoking (0 - 6): 2.9 EC use: Control: 9%; ENDS 16 mg group: 4%; ENDS 24mg group: 33% Motivation to quit smoking in next month (0 – 10): Control: 4.0; ENDS 16 mg: 5.0; ENDS 24 mg: 4.4
Interventions	**EC: Cig-a-like** **Intervention**: At study start, choice of tobacco or menthol flavor Blu Starter Pack EC, with 16 mg/mL nicotine. Midway through study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlusþ, with 24 mg/mL nicotine. 3-week sampling period, given up to 7 cartridges at each of 3 weekly visits. Instructions on usage "kept minimal to preserve naturalistic intent." The study team suggested that ENDS could be used "as you wish, to cut down or quit smoking, help manage smoking restrictions, or both." **Control**: own brand of cigarettes
Outcomes	Weeks 2, 3, 4, 8, 12 and 16 Carbon monoxide, NNAL Other outcomes: cessation (< 6 months), product evaluation, EMA
Study funding	"Support was provided by NIH R21 DA037407 (to M.J. Carpenter), P01 CA200512 (to K.M. Cummings, M.J. Carpenter, and M.L. Goniewicz), UL1 TR001450, and P30 CA138313. M.L. Goniewicz's laboratory is supported via P30 CA016056. B.W. Heckman is supported via K12 DA031794 and K23 DA041616. T.L. Wagener's effort is partially supported by the Oklahoma Tobacco Research Center, which is funded by the Oklahoma Tobacco Settlement Endowment Trust."
Author declarations	"M.L. Goniewicz is a consultant/advisory board member for Johnson & Johnson. K.M. Cummings reports receiving a commercial research grant from and is a consultant/advisory board member for Pfizer Inc., and has provided expert witness testimony for various plaintiffs in lawsuits involving cigarette manufacturers. No potential conflicts of interest were disclosed by the other authors."

Carpenter 2017 *(Continued)*

Notes	New for 2020 update. Listed as ongoing study NCT02357173 in 2016 review update. Additional data provided from authors In all, 25 participants (54%) received the Blu Starter Pack (16 mg), and 21 participants (46%) received BluPlusþ (24 mg); no switches were made within participants. Note: this is not included in our analysis of higher v lower as assignment to nicotine dose was not done at random; 24 mg and 16 mg merged in our main analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomization to group was stratified by motivation to quit in the next 30 days (0–6 vs. 7–10 on a VAS scale) but proportioned 2:1 (ENDS:control) to increase precision estimates for e-cigarette uptake and usage."
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and includes non-active control
Blinding of outcome assessment (detection bias) All outcomes	High risk	CO biochemically verified but abstinence not used as outcome in this review, so rated based on adverse event reporting. Self-report, no blinding of participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Retention rate: Week 4: Control:19/22 (86%); ENDS 16 mg: 23/25 (92%); ENDS 24 mg: 20/21 (95%) Week 16: Control: 16/22 (73%); ENDS 16 mg: 19/25 (76%); ENDS 24 mg: 15/21 (71%)
Selective reporting (reporting bias)	Unclear risk	Not specified
Other bias	Low risk	Midway through the study, the manufacturer of Blu altered the product and discontinued availability of the device, replaced with BluPlusþ, with 24 mg/mL nicotine, again offered in both tobacco and menthol flavorings, and with improved battery duration (4-watt battery for both devices). In all, 25 participants (54%) received the Blu Starter Pack (16 mg), and 21 participants (46%) received BluPlusþ (24 mg); no switches were made within participants. The change in product (IRB approved) allowed us the unexpected opportunity to assess what impact, if any, the change in product design had on study outcomes. Note that the manufacturer, style of device, and packaging did not change, nor did our messaging to participants. The only difference was the strength of product. Thus, trial outcomes are reported across 3 groups: control versus 16 mg versus 24 mg ENDS. We have not rated this as high risk of bias as our analyses do not compare on nicotine strength and both nicotine arms are combined in our main analysis

Czoli 2019

Study characteristics

Czoli 2019 *(Continued)*

Methods	Design: Nonblinded within-participants cross-over Recruitment: advertisements placed in newspapers, online, and in local vape shops, and received CAD 295 for participating in the study Setting: Kitchener–Waterloo and Toronto, Ontario, Canada Study start date: September 2015. Study end date: NR
Participants	Total N: 48 29.2% female; mean age 35.9 (SD 11.7); mean cpd NR; dual EC users at baseline; not motivated to quit Inclusion criteria: • > 18 • Dual user s of tobacco cigarettes and e-cigarettes. Dual users were identified as current daily tobacco cigarette smokers (had smoked ≥ 100 cigarettes in their lifetime, and smoked ≥ 5 cigarettes/day) and current daily e-cigarette users (had used an e-cigarette at least once a day for each of the past 7 days) Exclusion criteria: • Serious intentions to quit smoking in the next 6 months • use of other tobacco products in the past 7 days • use of nicotine replacement therapy in the past 7 days • use of any smoking cessation medications in the past 7 days • participation in individual or group counseling programs for smoking cessation in the past 7 days • experience of serious cardiac health issues • experience of a heart attack or stroke within the last 3 months • experience of cancer within the last year • experience of asthma, chronic obstructive pulmonary disease, a seizure disorder, or any life-threatening medical conditions with a prognosis of less than a year • a history of psychosis, schizophrenia, bipolar disorder, or suicidal thoughts
Interventions	**EC: own choice (mainly tank)** 3 consecutive 7-day periods in which the use of tobacco cigarettes and e-cigarettes was experimentally manipulated 4 study conditions: Dual use (e-cigarette and tobacco cigarette); Tobacco cigarette; E-cigarette; No product use Virtually all dual users reported using tank systems (92%) and e-cigarettes with nicotine (94%) To control for order effects, participants were randomly assigned to 1 of 2 condition orders, A or B Following the baseline condition of dual use: Group A participants switched to E-cigarette use, then to Tobacco cigarette use, and finally to No product use Group B participants switched to Tobacco cigarette use, then to E-cigarette use, and finally to No product use
Outcomes	Baseline (visit 1) and after each of the 7-day periods (visit 2 (week 1), visit 3 (week 2), visit 4 (week 3)) Carbon monoxide Urinary concentration of cotinine

Czoli 2019 *(Continued)*

	Urinary concentrations of 1-hydroxypyrene (1-HOP) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)
Study funding	This research was supported by an Ontario Ministry of Health and LongTerm Care Health System Research Fund grant (#06697 awarded to DH). Additional support was provided by the Canadian Institutes of Health Research (CIHR), the Vanier Canada Graduate Scholarship (CDC), a CIHR and Public Health Agency of Canada, Applied Public Health Chair (DH), and an Ontario Institute for Cancer Research Investigator Award (GTF)
Author declarations	MLG reports grants from and served as an advisory board member to pharmaceutical companies that manufacture smoking cessation drugs. DH has provided paid expert testimony in tobacco litigation on behalf of governments and class-action plaintiffs on issues related to tobacco product science and regulation. The other authors have no competing interests to declare
Notes	New for 2021 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details of randomization method given
Allocation concealment (selection bias)	High risk	No blinding
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All followed up
Selective reporting (reporting bias)	Low risk	No evidence of selective reporting

Dawkins 2020

Study characteristics

Methods	Design: Prospective cohort 4-center pragmatic cluster feasibility trial Recruitment: At homeless centers Setting: 4 homeless centers in the UK Study start date: 1 October 2018; Study end date: 31 March 2020
Participants	Total N: 80 N per arm: EC 48; UC 32

Dawkins 2020 *(Continued)*

	Inclusion criteria: • Adults who smoke (18 and over) accessing homeless support services on a regular basis and also known to staff • Self-reported daily smokers only with smoking status also confirmed by support staff • Smoking status was also biochemically verified by exhaled CO breath Exclusion criteria: • Non-smokers, or those reporting using another smoking cessation aid at the current time • Anyone below the age 18 years, reporting pregnancy, or unable to consent, e.g. currently intoxicated or unable to speak English • All those not well known to centre staff were ineligible Inclusion based on specific population characteristic: people accessing homeless centers 35% women; mean age 42.7; mean cpd 20; mean FTND: FTCD 5.51 Motivated to quit: "varied considerably; large majority expressed a desire to quit smoking in the near future" E-cigarette use at baseline: Not specified
Interventions	**EC: Refillable** **Usual care**: Written information on quitting smoking (adapted from NHS Choices); signposting to the local stop-smoking service (SSS) by center staff **Intervention**: as usual care, plus refillable EC provided once with e-liquid provided 1 x wk for 4 weeks, Aspire PockeX (tank style), choice of 3 flavors (fruit, menthol, tobacco) and 2 nicotine strengths (12 mg/mL or 18 mg/mL). Written info for EC use and support from center staff, who met once a week to provide e-liquid and troubleshoot EC use
Outcomes	Weeks: 4, 12, 24; Clinic visits and self-report Cessation: CO-validated sustained at 24 weeks Adverse events and biomarkers: Self-reported negative effects in EC arm only – each participant asked to rate on scale so cannot meta-analyse; exhaled CO; unintended consequences Other outcomes measured: Qualitative process evaluation; costs; self-reported positive and negative affects; recruitment rates; retention; EC/other tobacco/nicotine product use at study end; HRQoL; healthcare service utilization; other drug use/dependence; unintended consequences
Study funding	This study is funded by the National Institute for Health Research Public Health (project reference: 17/44/29)
Author declarations	SC, AF, JL, CB, AT, DR, IU, LB, SP have no competing interests. PH has received research grant from and provided consultancy to Pfizer. LD has provided consultancy for the pharmaceutical industry relating to the development of smoking cessation products
Notes	New for 2021 update. Authors provided information prior to peer review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Intention was to randomize but were unable to due to practical constraints

Dawkins 2020 *(Continued)*

		Quote: "Thus the actual allocation of centres to each arm was a pragmatic decision based on centre readiness and staff/researcher availability though we balance potential confounders and differences in environment by ensuring each cluster (EC and UC) contained one day centre and one residential unit."
Allocation concealment (selection bias)	Unclear risk	Quote: "Participants joined after cluster randomisation… Allocation was concealed to participants until after the baseline assessment." Comment: But unclear if allocation was concealed for those recruiting, and allocation would have been known to new participants
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and different levels of support between arms, so performance bias cannot be ruled out
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Cessation (primary outcome) biochemically-validated
Incomplete outcome data (attrition bias) All outcomes	High risk	13/48 (27.1%) lost to follow-up in the intervention arm and 20/32 (62.5%) lost to follow-up in the control arm at 24 weeks
Selective reporting (reporting bias)	Low risk	All anticipated outcomes reported

Eisenberg 2020

Study characteristics	
Methods	Design: 3-arm RCT Recruitment: Community Setting: Canada Study start date: November 2016. Study end date: September 2019.
Participants	Total N: 376; Nicotine e-cigarettes = 128; Non-nicotine e-cigarettes = 127; Counselling (control) = 121 47% female; mean age 52.66; mean cpd 21; mean FTND 6 (SD 2). Motivated to quit - Yes Inclusion criteria: • Active smoker, 10 or more cigarettes per day, on average, for the past year • Age of 18 years or older • Motivated to quit according to the Motivation To Stop Scale (MTSS) (level 5 or higher) • Able to understand and to provide informed consent in English or French • Likely to be available for follow-up (1 year) Exclusion criteria: • Medical condition with a prognosis < 1 year • Current or recent cancer (less than 1 year in remission) • Pregnant or lactating women

Eisenberg 2020 *(Continued)*

- Current or recent use (in the past 30 days) of any pharmacotherapy or behavioral therapy for smoking cessation (e.g. nicotine replacement
- Therapies, bupropion, varenicline, or counseling)
- Any e-cigarette use (nicotine or non-nicotine) in the past 60 days, or ever use of any e-cigarette for more than 7 days consecutively
- History of psychosis, schizophrenia, or bipolar disorder
- Less than 1 month following a myocardial infarction, life-threatening arrhythmia, severe or worsening angina pectoris, or cerebral vascular accident
- Use of any illegal drugs in the past year (excluding marijuana)
- Planned use of tobacco products other than conventional cigarettes (e.g. cigarillos, cigars, snuff, shisha, etc.) or marijuana during the study period

Interventions	**EC: Cig-a-like** **Nicotine e-cigarettes plus counseling:** 12 weeks of e-cigarettes. Rechargeable base with prefilled, disposable, tobacco-flavored liquid cartridges (15 or 0 mg nicotine/mL), which were produced specifically for use in clinical studies (purchased from NJOY Inc, Scottsdale, Arizona). 21 cartridges at baseline with additional cartridges supplied as needed. Nicotine and nonnicotine e-cigarettes were identical in appearance. Instructed to be used as desired. No schedule for e-cigarette tapering, but participants were aware that they would return their e-cigarettes after 12 weeks Participants received individual smoking cessation and relapse prevention counseling (minimum 30 minutes at baseline, 10 minutes during telephone follow-ups, and 15 - 20 minutes at clinic visits). Individualized quit plans **Non-nicotine e-cigarettes plus counseling:** As above with 0 mg nicotine/mL in liquid cartridge **Counseling (control):** Participants received individual smoking cessation and relapse prevention counseling (minimum 30 minutes at baseline, 10 minutes during telephone follow-ups, and 15 - 20 minutes at clinic visits). Individualized quit plans
Outcomes	Follow-up was conducted by telephone at weeks 1, 2, 8, and 18, and at clinic visits at weeks 4, 12, 24, and 52 Self-reported smoking (7-day recall), adherence, and adverse events (AEs) were assessed during follow-up contacts Biochemically-validated 7-day point prevalence smoking abstinence at 4, 12 and 24 weeks, defined as self-reported abstinence in the past 7 days with exhaled carbon monoxide < 11 ppm At baseline: cpd; FTND; Glover-Nilsson Smoking Behavioral Questionnaire (to assess behavioral dependence on smoking); and Beck Depression Inventory II (BDI-II; to assess depressive symptoms)
Study funding	This trial was funded by the Canadian Institutes of Health Research (CIHR; funding reference No. 133727 and 155969). Both nicotine e-cigarettes and nonnicotine e-cigarettes were purchased from NJOY Inc (Scottsdale, Arizona)
Author declarations	Dr Eisenberg reported receiving educational grants from Pfizer Inc for providing continuing medical education in cardiology. Dr Wilderman reported receiving financial compensation from Pfizer Inc for his involvement in a smoking cessation study using varenicline. Dr Filion reported receiving salary support from the Fonds de Recherche du Quebec, a William Dawson Scholar award from McGill University, and personal fees from Institut National D'excellence en Santé et Services Sociaux. No other disclosures were reported

Eisenberg 2020 *(Continued)*

Notes	New cessation and adverse event data for 2021 update. Previously listed as NCT02417467 (included with SAE data only)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomized via an online central randomization system. The system used a computer-generated randomization list containing permuted blocks of 6 and 9, stratified by center
Allocation concealment (selection bias)	Low risk	Participants, investigators, and study personnel were blinded to nicotine content in the e-cigarette groups
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants, investigators, and study personnel were blinded to nicotine content in the e-cigarette groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, and study personnel were blinded to nicotine content in the e-cigarette groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low numbers lost to follow-up, treated as ITT
Selective reporting (reporting bias)	Low risk	Due to a prolonged and unforeseen delay in e-cigarette manufacturing, enrolment was paused on 27 September 2019, and then terminated on 14 November 2019. Given reduced power, the timing of the primary endpoint was changed from 52 weeks to 12 weeks on 04 December 2019. No 12-month follow-up but this was for manufacturing reasons and was reported

Ely 2013

Study characteristics

Methods	Design: Prospective cohort Recruitment: Letter sent to family practice patients who currently smoked Setting: Single family practice, Colorado USA Study start date: 14 April 2013; Study end date: Not specified
Participants	Letters sent to 640 patients, 48 chose to participate and 44 completed the program, 4 were lost to follow-up Inclusion criteria: • Want to quit or switch from tobacco cigarettes to ECs Exclusion criteria: • None reported Of the 44 participants, 66% women, all non-Hispanic/white, aged 20 - 75 (30% were age 51 - 60), 57% had a high school education or less

Ely 2013 *(Continued)*

	Motivated to quit: Want to quit or switch from tobacco cigarettes to ECs E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** The 6-month smoking cessation program was based on The '5 A's' model and transtheoretical model. Options for treatment were discussed with each participant at the start of the program. All used an EC, with 16 using bupropion and 2 using varenicline as well Participants were provided with written information on “blu cig” and “smoke tip” ECs, about cost, availability, nicotine dosage options
Outcomes	Phone follow-ups at 2 weeks, 1 month, 3 months, and 6 months At completion of program (using ITT) Abstinence from smoking and EC use Abstinence from smoking but not EC use ≥ 50% reduction of baseline cigarette consumption (still using ECs)
Study funding	Not specified
Author declarations	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/48 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	No definition of abstinence provided Not clear if 'completed program' was at 6 months.

Felicione 2019

Study characteristics

Methods	Design: Double-blind RCT Recruitment: People who smoke were recruited from an outpatient opioid-maintenance clinic in West Virginia, USA

Felicione 2019 *(Continued)*

	Setting: Outpatient opioid-maintenance clinic in West Virginia, USA Study start date/Study end date: Not reported
Participants	Total N: 25; N per arm: Placebo (non-nicotine): 11; Active (18 mg/ml nicotine): 14 Inclusion criteria: • ≥18 years of age • Report smoking ≥10 cpd for ≥ one year • Report a current interest in quitting smoking Exclusion criteria: • Reported regular use of any nicotine/tobacco product other than cigarettes, including EC, or were already engaged in attempts to quit smoking Inclusion based on specific population characteristic: People who smoke who were currently receiving a buprenorphine/naloxone combination in sublingual form, and had maintained sobriety from opioids and all other illicit substances for at least 90 consecutive days as verified via urinalysis 73.0% women; mean age 32.5; mean cpd 22; mean FTND 5.8 Motivated to quit: Quit ladder Score (range 1 - 10): 5.6 average
Interventions	**EC: Refillable** Compared **nicotine** (18 mg/ml) to **non-nicotine EC**. Second-generation EC consisted of the eGo-T battery (900mAh, 3.3 V constant output) (Joyetech; Irvine, CA) and the Kanger mini Protank-II, 1.5 ml Pyrex glass tank with a drip tip and atomizer head coils (KangerTech; China), choice between tobacco (n = 15) and menthol (n = 10) flavored liquid (2-week supply). Participants were then trained in EC device operation, including assembly, liquid filling, manual battery operation, and cleaning/storage. Practised puffing on EC in the presence of a team member, and asked questions if needed. Participants instructed to use their ECIG ad libitum every day for 2 weeks
Outcomes	Baseline (day 1), 14 days, 28 days for clinic measures. Data also collected via text-messages over 2-week intervention period Withdrawal/side effects: Every evening during the 2-week intervention period, participants rated a variety of effects possibly experienced as a result of nicotine/tobacco withdrawal and/or use of the ECIG: nausea, dizziness, throat irritation/soreness, cough, dry mouth, headache, shortness of breath, irritability/frustration/anger, craving/urge to smoke, and other. Each item was rated on a continuous scale that ranged from 0 (not at all) to 100 (extremely) Expired air CO Other outcomes: Self-reported cigarette and EC use; readiness to quit at day 1, 14 and 28
Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement

Felicione 2019 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "Using a mixed factorial, simple randomization, double-blind study design, participants were assigned to one of two ECIG conditions…" (No further details given)
Allocation concealment (selection bias)	Unclear risk	No details on allocation given.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "double-blind study design", no further detail given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "double-blind study design", no further details given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "…80.6% completed the two-week intervention (n=14 active; n=11 placebo), and 70.9% also completed the follow-up session (n=13 active; n=9 placebo)." Active follow-up completion rate: 13/14 = 93%; Placebo follow-up completion rate: 9/11= 82% N.B. 6 participants were disqualified post-randomization: Quote: "Of those individuals who were screened for the study, 93.9% were enrolled (n = 18 active; n = 13 placebo); two individuals who were ineligible provided an expired air CO level < 10 ppm. Six of the enrolled participants (n = 4 active and n = 2 placebo; n = 5 tobacco flavor and n = 1 menthol flavor) were disqualified for responding to 7 or fewer days of text messages."
Selective reporting (reporting bias)	Unclear risk	All measures listed were reported: Self-reported cigarette use, text message-based cigarette use, e-cig use, expired air CO, readiness to quit ladder, withdrawal/side effect; No study protocol or clinical trial record available to confirm all intended outcome measures were reported

George 2019

Study characteristics	
Methods	Design: Prospective, randomized controlled trial with a parallel, nonrandomized preference cohort Recruitment: Participants were recruited from local advertisements, smoking cessation databases, and visits to local businesses, as well as via the Scottish Primary Care Research Network Setting: Single tertiary research centre, UK Study start date: August 2016; Study end date: July 2018
Participants	Total N: 114 in "final evaluable dataset" (145 recruited into the trial) N per arm: Tobacco cigarettes (TC): 40; EC nicotine (16 mg): 37; EC-Nicotine-free: 37 Inclusion criteria: • People who smoke ≥ 18 years of age who had smoked ≥ 15 cigarettes/day for at least 2 years

George 2019 *(Continued)*

- were free from established CV disease, diabetes, and chronic kidney disease; and were not on medication for those conditions
- Willing to stop tobacco cigarettes for period of study if required
- Willing not to use electronic cigarettes if required
- Able to give informed consent

Exclusion criteria:

- Pregnant or lactating
- Women of childbearing potential who do not abstain from sex or use effective contraception
- On current prescribed medication for cardiovascular disease
- History of cardiovascular disease (excluding hypertension), diabetes, active malignance or chronic renal disease
- Nut allergy
- Participation in another clinical trial (other than observational trials and registries) with an investigational product and/or intervention within 30 days before visit 1

65.4% women; mean age 46.9; mean cpd 18.7

Motivated to quit: TC group: No; EC nicotine (16 mg): Yes; EC-Nicotine-free: Yes.

Interventions	**EC: Cig-a-like** **EC nicotine** (16 mg) arm: EC containing 16 mg nicotine (Vapourlites Starter Kit with XR5 16 mg nicotine cartomizer; Vapourlites, Peterlee, United Kingdom) **EC-Nicotine-free** arm: Nicotine-free EC plus nicotine flavoring (Vapourlites Starter Kit with 0 mg nicotine cartomizer) **(non-randomized) TC arm:** continued their usual daily smoking habits and did not use EC for the 4-week period of the trial
Outcomes	Week 4 Adverse events and biomarkers: BP, heart rate, adverse events Other outcomes measured: Endothelial function, oxidized low-density lipoprotein, high-sensitivity C-reactive protein, tissue plasminogen activator, and platelet activation inhibitor-1
Study funding	"The VESUVIUS (Vascular Effects of Regular Cigarettes Versus Electronic Cigarette Use) trial was funded by the British Heart Foundation (grant PG/15/64/31681); and supported by Immunoassay Biomarker Core Laboratory, University of Dundee, the Tayside Medical Sciences Centre, and the NHS Tayside Smoking Cessation Service. The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication."
Author declarations	"Dr. Donnan has received research grants from AbbVie, Shire, and Gilead Sciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose."
Notes	New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Consented participants who were willing to quit smoking were randomized to one of the EC arms in a 1:1 fashion using a centrally controlled web-based good clinical practices– compliant randomization system to either: 1) EC containing 16 mg nicotine; or 2) nicotine-free EC plus nicotine flavoring because it was considered by the institutional ethics committee as ethically unacceptable to randomize those who were willing to quit smoking into a smoking arm.

George 2019 *(Continued)*

		Those unwilling to consider quitting smoking continued in the parallel preference TC cohort
Allocation concealment (selection bias)	Low risk	Central randomization
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded and AE/SAE data are self-report only. For other outcomes, low risk as objectively measured: Quote: "Patients fasted overnight and measurements were conducted at baseline and 1 month according to the International Brachial Artery Reactivity Task Force guidelines (19) by a single operator (M.H.) blinded to study allocation at a single site." "Pulse wave velocity and augmentation index were measured at baseline and 1 month by a single operator (M.H.) blinded to study allocation."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number randomized not provided per group. Quote: "A total of 145 patients were recruited into the trial (Figure 1). A final number of 114 patients (40 TC, 37 EC-nicotine, 37 EC-nicotine-free) completed both visits."
Selective reporting (reporting bias)	Low risk	Clinical trial record lists: Change in FMD; Change in oxidized LDL; Change in PAI-1; Change in hs-CRP; Change in Pulse Wave Velocity; Change in tPA; Change in Augmentation Index@75bpm All reported in the paper

Goniewicz 2017

Study characteristics	
Methods	Design: Longitudinal within-subjects observational Recruitment: Advertisements in the media, the internet, posted advertisements in clinics and offices, and by word of mouth Setting: University, Poland Study start date: March 2011; Study end date: June 2011
Participants	Total N: 22 started out and 2 dropped out in the first week due to an adverse event (nausea) and inability to commit to clinic visits. This resulted in analytic sample of 20 Inclusion criteria: • 18 or older, current daily cigarette smokers (> 5 cpd within the last 12 months) • May have had interest in quitting smoking, in good health (at the clinic screening visit) • Able to communicate in Polish • Able to use an e-cigarette safely Exclusion criteria:

Goniewicz 2017 *(Continued)*

	• Diagnosed as having asthma, COPD, hypertension, inhaled allergies, chronic heart disease, or cancer • were taking a cardiac medication • were pregnant 60% women; mean age 31; mean cpd 16; mean FTND 3.9 Motivated to quit: At the time of screening, 95% of participants (n = 19) reported planning to quit smoking, with 80% (n = 16) reporting that they have made at least 1 quit attempt prior to involvement in the study E cigarette use at baseline: Not reported
Interventions	**EC: Cig-a-like** Pen-style M201 e-cigarettes for 2 weeks, with an automatically-operated battery with an output power of 4.6 Volts (280 mAh) and the heating element resistance of 3.6 – 3.8 Ohms. At baseline, provided with EC (M201 Mild, Poland) with 20 tobacco-flavored cartridges a week containing 11.0 ± 1.5 mg of nicotine in a mixture of propylene glycol and vegetable glycerin (50:50). Encouraged to substitute their regular cigarettes with the e-cigarette for 2 weeks and refrain from smoking
Outcomes	Day 7, Day 14 Adverse events and biomarkers: • Biomarkers were metabolites of 13 major carcinogens and toxicants in cigarette smoke: 1 tobacco-specific nitrosamine (NNK), eight volatile organic compounds (1.3-butadiene, crotonaldehyde, acrolein, benzene, acrylamide, acrylonitrile, ethylene oxide, and propylene oxide), and 4 polycyclic aromatic hydrocarbons (naphthalene, fluorene, phenanthrene, and pyrene) • Questionnaire on 'health': At each visit, participants were asked, "In the last week, have you experienced any of the following symptoms?", while providing a response of "never," "rarely," or "often" to the following list of health effects: daytime cough, difficulty concentrating, difficulty breathing during sleep, difficulty sleeping, dizziness, headache, irritability, nausea, nighttime cough, chest pain, phlegm, shortness of breath, tightness in chest, visual disturbances, and wheezing. Responses of "rarely" or "often" were combined to indicate presence of an adverse health effect • Expired CO Other outcomes measured: • 7 nicotine metabolites (3-Hydroxycotinine, Cotinine, Cotinine N-Oxide, Nicotine N-Oxide, Norcotinine, Nornicotine, Nicotine) • Revised Minnesota Nicotine Withdrawal Scale (MNWS-R) administered to measure 'withdrawal symptoms' (0 - 5 rating scale)
Study funding	"This work was supported by the Ministry of Science and Higher Education of Poland (grant number N N404 025638). Instrumentation and analytical chemistry at UCSF was supported by the National Institutes of Health, P30 DA012393 and S10 RR026437. The study sponsor had no involvement in the study design, collection, analysis, and interpretation of data, the writing of the manuscript or the decision to submit the manuscript for publication."
Author declarations	"MLG was a faculty member of the Medical University of Silesia, Poland during the study. He received a research grant from Pfizer, a pharmaceutical company that markets smoking cessation medications. MLG and NLB have been consultants to pharmaceutical companies that market smoking cessation medications. NLB has been an expert witness in litigation against tobacco companies. The other authors declare no potential conflicts of interest."
Notes	New for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement

Goniewicz 2017 *(Continued)*

Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts – 1 for nausea, 1 could not complete clinic visits. Analysis based on 20 completers
Selective reporting (reporting bias)	Low risk	All outcomes reported

Guillaumier 2018

Study characteristics	
Methods	Design: Pragmatic, open-label, single-centre, 2-arm randomized controlled trial Recruitment: Withdrawal service in Melbourne, Australia Setting: Substance use disorder treatment setting, and following discharge, community setting, Melbourne, Australia Study start date: 1 August 2017; Study end date: April 2019.
Participants	Total N: 100 N per arm: EC intervention = 50; NRT Control = 50 Inclusion criteria: • Aged 18 years or over • Tobacco smoker on entering the residential service • Have the capacity to consent and able to understand the participant materials and follow the study instructions and procedures (e.g. sufficient English language ability) Exclusion criteria: • Have used an END containing nicotine in the past month; • Currently pregnant or breast-feeding (measured by self-report); • Currently enrolled in another study; • Scheduled to be transferred to a long-term rehabilitation unit following discharge from the residential withdrawal unit. Inclusion based on specific population characteristic: Participants were discharged from a smoke-free alcohol or other drugs (AOD) residential withdrawal service 32% women; mean age 40.9; mean cpd 21 Motivated to quit: Median (SD) = 7.3 (2.4) of 1 to 10 scale with 10 "highly motivated"
Interventions	**EC**: Refillable. Up to an hours training session, information pack. Innokin Endura T22 starter kit and refill liquid (Nicophar). 4-week supply of liquid nicotine, with further supplies of liquid nicotine mailed twice at 4-week intervals. Dosing schedule of e-liquid dependent nicotine dependence score: high-nicotine-dependence category assigned initial 4-week e-liquid supply (total 8 × 10 ml bottles) consisting of: 2 × 10 ml bottles of 18 mg e-liquid and 6 × 10 ml bottles of 12 mg e-liquid. The second and third batches = 8 ×

Guillaumier 2018 *(Continued)*

	10 ml bottles of 12 mg e-liquid only. Participants scoring in the moderate- and low-dependence categories: three 4-week supplies of 8 × 10 ml bottles of 12 mg e-liquid. Participants given 1-week supply of nicotine patches for use while getting used to the EC. **NRT control**: Information pack, 12 weeks NRT on the same schedule as for ENDs. 4-week supply of patches plus a nicotine spray and inhaler, followed by refills including patches plus inhaler, gum and lozenges. Both groups received proactive referral to quitline counseling (call-back service), which provides calls at pre-discharge and on days 1, 3, 7, 14 and 28 post-discharge, with an emphasis on relapse prevention. Counsellors trained on the use of ENDs.
Outcomes	Week 6, 12; self-report. Adverse events collected Other outcomes measured: • Acceptability and feasibility of interventions • Treatment adherence • Cigarettes smoked per day - Heaviness of Smoking Index • Frequency of cravings • Minnesota Nicotine Withdrawal Scale (MNWS) • 10-item Kessler Psychological Distress Scale (Kessler-10) • Quitting self-efficacy, motivation to quit and the Heaviness of Smoking Index were assessed at baseline
Study funding	"The study is supported by a VicHealth Innovation Research Grant (2016–0096). AG is supported by a post-doctoral fellowship from the Heart Foundation. ALB is supported by an Australian National Health and Medical Research Council (NHMRC) senior research fellowship and a Faculty of Health and Medicine, University of Newcastle Gladys M Brawn senior research fellowship. BB is supported by an Australian NHMRC career development fellowship (GNT1063206) and a Faculty of Health and Medicine, University of Newcastle Gladys M Brawn career development fellowship." "This study was supported by a VicHealth Innovation Research Grant (2016-0096)."
Author declarations	"The authors declare that they have no competing interests." "None to declare."
Notes	New for 2020 update; additional data originally provided by authors and subsequently published

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Upon completing the baseline survey, participants were randomised 1:1 to an intervention via a computer-sequenced 4–6 block randomisation embedded in the tablet device software.”
Allocation concealment (selection bias)	Low risk	Quote: “At the end of the baseline survey, participants will be randomised 1:1 to an intervention via a computer-sequenced 4–6 block randomisation embedded in the iPad.”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: “Participants were informed of their intervention group by the RA and provided with a training session of up to one hour.” “Due to the nature of the intervention, neither participants nor staff can be blinded to allocation. However, the data safety monitoring committee and the statistician responsible for the data analysis will be blinded.”

Guillaumier 2018 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	No biochemical validation, self-report data
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "At 6 and 12-weeks, 63 participants (63%) and 50 participants (50%) were followed up, respectively. While slightly higher retention rates were evidence in the VNP group at 6-weeks (68% vs 58% in NRT group; p=0.300); there were no differences between groups at 12-weeks (25 recontacted in both arms; i.e., 50%)."
Selective reporting (reporting bias)	Low risk	Unpublished findings provided by authors report on all outcomes mentioned in the protocol

Hajek 2015a

Study characteristics	
Methods	Design: Prospective cohort, intervention provided Recruitment: People who smoke attending stop-smoking service Study start date: March 2014; Study end date: March 2015 Setting: Stop-smoking service, London, UK
Participants	Total N: 100 (69 of whom accepted offer of EC) Inclusion criteria: • All people who smoked joining stop-smoking service 38% women (those who accepted) 55% women (those who declined), mean age 41, mean cpd 14, all motivated to quit. EC use at baseline not specified but some who declined EC offer had used EC in the past Motivated to quit: Yes E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like and refillable** EC: offered to all people who smoke joining service; offered choice of 'cig-a-like' (Gamucci, 1.6% or 2.2% nicotine per ml) product or tank model (EVOD, 1.8%; later replaced with Aspire product due to leakage issues). 69% of those offered received an EC on TQD Medication: Offered stop-smoking medications including NRT and varenicline as in standard protocol. Of EC users 33% opted to also use NRT, 29% varenicline, 38% nothing Support: weekly, as in standard protocol
Outcomes	Adverse events collected throughout, method for collection unclear Also collected: 4-week biochemically-validated abstinence, participant feedback, cost
Study funding	"The pilot study was sponsored by City of London Corporation."
Author declarations	"Peter Hajek received research funds from and provided consultancy to manufacturers of smoking cessation medications. The remaining authors have no conflicts of interest to declare."

Hajek 2015a *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	26% lost in EC group, dropout rate in EC decliners not reported. Reasons for dropout not stated
Selective reporting (reporting bias)	Unclear risk	Unclear which outcomes authors set out to collect, no protocol available

Hajek 2019

Study characteristics

Methods	Design: Multicentre pragmatic randomized controlled trial to examine the efficacy of e-cigarettes compared with nicotine replacement therapy Recruitment: participants attending UK stop-smoking service and via social media Setting: U.K. National Health Service stop-smoking services Study start date: 1 April 2015; Study end date: 31 March 2018
Participants	Total N: 886 N per arm: EC: 439; NRT: 447 Inclusion criteria: • Adults who smoke (aged 18 or over) with no strong preference to use or not to use nicotine replacement or e-cigarettes, and were currently not using either type of product • Able to read/write/understand English Exclusion criteria: • Pregnant or breastfeeding • Strong preference to use or not use NRT or EC, currently not using either type of product 48% women; median age 41; median cpd 15 ; mean FTND 4.6; 41.5% reported past use of ECs Motivated to quit: Not reported
Interventions	**EC: Refillable** **NRT:** Informed of range of NRT products and selected preferred product, encouraged to use combination. Participants free to switch products. Supplies provided for up to 3 months **EC:** Starter pack (1 Kit, Aspire UK) provided along with 30 ml bottle of Tobacco Royale flavor e-liquid, concentration 18 mg/ml. Participants showed how to use and asked to purchase future e-liquid online or from local vape shops and to buy different EC device if the 1 provided did not meet their needs.

Hajek 2019 *(Continued)*

	Enouraged to experiment with e-liquids of different strengths and flavors. If unable to obtain own supply, provided with further 10-ml bottle (not proactively offered). Oral and written info on how to operate EC Both arms received multi-session behavioral support as per UK stop-smoking service practice (one-to-one sessions weekly with local clinicians, exhaled CO monitored for at least 4 weeks post-TQD); signed behavioral contract not to use other therapy for at least 4 weeks
Outcomes	Weeks 4, 26 and 52 Cessation: Sustained and biochemically-validated CO < 8 ppm Adverse events and biomarkers: “adverse reactions”: presence or absence of nausea, sleep disturbance and throat and mouth irritation, and respiratory symptoms (presence or absence of shortness of breath, wheezing, coughing and phlegm), death Other outcomes measured: • Use and ratings of trial products • Rating of withdrawal symptoms (weeks 1 - 6) • Reduction of cigarette consumption • Cost effectiveness
Study funding	“Supported by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (project number, 12/167/135) and by a grant (A16893) from the Cancer Research UK Prevention Trials Unit.”
Author declarations	From ICJME disclosure forms: “Miss Natalie Bisal has nothing to disclose. Dr. Dawkins reports personal fees from Johnson & Johnson, outside the submitted work; Dr. Goniewicz reports personal fees from Johnson and Johnson, outside the submitted work; Dr. Hajek reports grants and personal fees from Pfizer, outside the submitted work; Ms. Li reports grants from NCCHTA, during the conduct of the study; Dr. McRobbie reports grants from NIHR HTA program, during the conduct of the study; personal fees from Pfizer, personal fees from Johnson & Johnson, outside the submitted work; Dr. Myers Smith has nothing to disclose. Dr. Parrott has nothing to disclose. Dr. Pesola has nothing to disclose. Mrs Anna Phillips-Waller has nothing to disclose. Dr. Przulj reports grants from Pfizer, outside the submitted work; Dr. Ross has nothing to disclose. Dr. Sasieni has nothing to disclose. Ms. Wu has nothing to disclose."
Notes	New for 2020 update, listed as ongoing study ISRCTN60477608 in 2016 review update Note higher use of allocated product at 12 m in intervention group compared to control group: “Among participants with 1-year abstinence, 80% (63 of 79) were using e-cigarettes at 52 weeks in the e-cigarette group and 9% (4 of 44) were using nicotine replacement in the nicotine-replacement group.”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomization took place on the quit date to limit differential dropout. Randomization sequences (1:1 ratio in permuted blocks of 20, stratified according to trial site) were generated with the use of a pseudorandom number generator in Stata software and were embedded into an application that only revealed the next treatment assignment once a participant had been entered into the database.”
Allocation concealment (selection bias)	Low risk	Refer to 'Random sequence generation'.

Hajek 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded, but as both arms contained active interventions performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	At 12 months: EC Arm: 356/439 NRT Arm: 342/447
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Halpern 2018

Study characteristics	
Methods	Design: Randomized clinical trial Recruitment: Eligible participants were employees and their spouses at 54 companies that used Vitality wellness programs Setting: Online resources via workplace setting (54 companies), USA Study start date: First phase of recruitment October 2014, second phase November 2015 (to meet recruitment target); Study end date: 20 April 2017
Participants	Total N: 6006 N per arm: Usual care: 813; Free e-cigarettes: 1199; Free cessation aids: 1588; Reward incentives plus free cessation aids: 1198; Redeemable deposit plus free cessation aids: 1208. Inclusion criteria: • At least 18 years old • Reported current smoking on a health risk assessment within the previous year • Employees and their spouses that used Vitality wellness programs Exclusion criteria: • Participants who express wanting to opt out of this program will be un-enroled and excluded 51.1% women; median age 44; median cpd 10 Ecig use at baseline: 10.7% current use; 23.1% past but not current use; 39.7% never used ECs Motivated to quit: Unselected sample (total sample): 9.2% no plan to quit; 61.6% want to quit later; 27.7% want to quit/need help
Interventions	**EC: Cig-a-like** a) **Usual care:** Standardized Vitality program aimed at promoting tobacco cessation. This program includes existing employee benefits for quitting and the use of text/email messages to encourage tobacco cessation

Halpern 2018 *(Continued)*

	b) as (a), plus **free EC**: Free NJOY e-cigarettes (including battery sticks, a USB charger, and up to 20 chambers with 1.0 to 1.5% nicotine per week in participants' chosen flavors). Use of all products was free until 6 months after the quit date c) as (b) plus access to free NRT, bupropion or varenicline d) as (c) plus incentives across 6 m for testing negative for tobacco use e) as (c) plus provide money at start and lose money from this fund if they do not test negative across 6 m
Outcomes	Months 1, 3, 6 and 12 Cessation: Sustained smoking abstinence for 6 months, biochemical validation (urine cotinine, anabasine and blood carboxyhemoglobin) Other outcomes measured: Costs
Study funding	"Supported by a grant from the Vitality Institute to the University of Pennsylvania Center for Health Incentives and Behavioral Economics."
Author declarations	"Disclosure forms provided by the authors are available with the full text of this article at NEJM.org. Check these and: Dr. Troxel reports other from VAL Health, outside the submitted work. Dr. Volpp reports grants and personal fees from CVS Health, personal fees from VAL Health, grants from Humana, grants from Merck, grants from Weight Watchers, grants from Hawaii Medical Services Association, grants from Oscar Health Insurance, outside the submitted work. All of the other authors state that they have nothing to disclose."
Notes	New for 2020 update. Study listed as ongoing study NCT02328794 in 2016 review update Only arms (a) and (b) included in our analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and different amounts of support given to each group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	High risk	At 12 months very low numbers completed biochemical validation. Submitted a sample n = CG:1, free e-cigs;4, free cessation:5, rewards: 14, deposits:16
Selective reporting (reporting bias)	Low risk	Expected outcomes reported and checked with trial registration

Hatsukami 2020

Study characteristics	
Methods	Design: randomized trial Recruitment: Media advertisements Setting: Clinic visits in community, USA Study start date: 25 November 2014; Study end date: 2 December 2018
Participants	Total N: 264 N per arm: Usual brand: 36; AD-E: 76; CS-E: 76; CS-NRT: 76. Inclusion criteria: • At least 18 years of age • Smoking at least 5 cpd for the past year with a breath CO at least 10 ppm or NicAlert test = level 6 if CO less than 10 ppm • In stable physical and mental health Exclusion criteria: • A serious quit attempt in the past 3 months • Recent (< 3 months) alcohol or drug abuse problems • Regular use of other nicotine or tobacco products (e.g. > 9 days per month to minimize confounding effects of these products on biomarker outcomes) • Planning to quit smoking in the next 3 months • Chronic conditions affecting results of biomarker analyses (e.g., liver disease) • Currently using NRT or other cessation medications • Pregnant, planning to become pregnant, or breastfeeding 49% women; mean age 45.2; mean cpd 15.2; mean FTND 3.4 E cigarette use at baseline: Not reported Motivated to quit: Initially uninterested
Interventions	**EC: Cig-a-like**, but the only cig-a-like product with high nicotine content **Usual brand** arm: Purchased their own usual brand of cigarettes; at end of clinical trial phase (week 8), offered ECs or NRT for up to 8 weeks, with a choice of product and no specific instructions for use **EC AD-E** arm: Use EC whenever you like instead of a cigarette; can smoke as many or as few cigarettes as you want **EC CS-E** arm: Complete substitution with e-cigarettes (i.e. “you will stop smoking cigarettes and use only e-cigarettes”) The primary e-cigarette product was Vuse Solo (4.8% nicotine, manufactured by RJ Reynolds, Inc). Initially a choice of Blu cigarettes (cartridge-based system, marketed previously by Lorillard) and Fin (pre-filled tanks system, manufactured by Fin Branding Group) was offered; but because Vuse attained the highest market share during the early phase of the study, switched exclusively to Vuse. Participants could choose 1 of 4 flavors: tobacco, mint, menthol, and berry. Participants were provided 7 cartridges a week with the option of returning to the clinic before their next visit to obtain additional cartridges if needed. All products provided free to the participants. All unused products and used EC cartridges were collected at each visit **CS-NRT** arm: Complete substitution with 4 mg nicotine gum or lozenge, with the participant choosing what product they would like to use (i.e. “you will stop smoking cigarettes and use only nicotine gum

Hatsukami 2020 *(Continued)*

	or lozenge"). The 4 mg was down-titrated to 2 mg if adverse side effects were experienced. Nicotine gum came in mint, cinnamon, and fruit flavors, while the nicotine lozenge was mint or cherry flavors. All these products were provided free to the participants and unused products were collected at each visit Behavioural support: **CS-E arm** and **CS-NRT arm**: received brief counseling on how to avoid smoking cigarettes
Outcomes	2-week baseline period (weeks −1 and 0); Week 1, 2, 3, 4, 6 and 8 Adverse events and biomarkers: • Urinary total nicotine equivalents (total nicotine + total cotinine + total 3′-hydroxycotinine; TNE) • Exhaled CO • Urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL, biomarker for NNK) • Urinary phenanthrene tetraol (PheT, an indicator of carcinogenic polycyclic aromatic hydrocarbons) • Urinary metabolites of VOCs (mercapturic acids)—2-cyanoethylmercapturic acid (CEMA, biomarker for acrylonitrile), 3-hydroxypropylmercapturic acid (3-HPMA, biomarker for acrolein), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA, biomarker for crotonaldehyde/methylvinyl ketone), 2-hydroxypropylmercapturic acid (2-HPMA, biomarker for propylene oxide), and N-acetyl-S-(carbamoylethyl)-L-cysteine(AAMA, biomarker for acrylamide) • A safety check for adverse events was conducted at a week-20 follow-up • Blood pressure, heart rate and oxygen saturation Other outcomes measured: • Cessation (< 6 months)
Study funding	"supported by grants U19CA157345 from the National Cancer Institute (DKH/PS), UL1 TR000062 and UL1 TR002494 from the National Center for Advancing Translational Science of the National Institutes of Health, and T32 DA007097 from the National Institute of Drug Abuse (EM). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies"
Author declarations	"RJC is a member of the FDA Tobacco Products Scientific Advisory Committee. PGS serves or has served as an expert witness in tobacco company litigation on behalf of plaintiffs"
Notes	New for 2020 update. AD-E arm not included in this review Additional data provided from authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not blinded and some interventions contained different levels of support

Hatsukami 2020 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded but all relevant outcomes for our analyses were objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There was a significant difference in dropout rates across groups following study entry (p = .041), with the highest dropout rates observed in the complete substitution groups, particularly in the NRT group…" AD-E: Week 1 = 73/76; Week 2 = 73/76; Week 4 = 69/76; Week 6 = 66/76; Week 8 = 65/76 = 85% CS-E: Week 1 =69/76; Week 2 = 67/76; Week 4 = 66/76; Week 6 = 61/76; Week 8 = 58/76 = 69.7% CS-NRT: Week 1 =72/76; Week 2 = 65/76; Week 4 = 60/76; Week 6 = 57/76; Week 8 = 53/76 = 69.7% UB: Week 1 = 35/36; Week 2 = 35/36; Week 4 = 33/36; Week 6 = 33/36; Week 8 = 32/36 = 88.8%
Selective reporting (reporting bias)	Low risk	Table in supplementary section describes that heart rate, blood pressure and oxygen levels were measured, but findings not reported in paper; however, provided by authors upon request

Hickling 2019

Study characteristics	
Methods	Design: Single-group assignment – pre-test post-test pilot study Recruitment: Participants were referred from community mental health teams within the South London and Maudsley NHS Foundation Trust. Setting: Healthcare setting, UK. Study start date: 24 September 2014; Study end date: 2 May 2017
Participants	Total N: 50 Inclusion criteria: • Aged 18–70 years; • Daily smoker (unwilling to quit soon); • Exhaled CO level of more than five parts per million; • An established clinical diagnosis of schizophreniform, schizophrenia, schizoaffective disorder or bipolar disorder, or attending an early detection service in a high-risk state Exclusion criteria: • The use of e-cigarettes on more than two occasions in the past 30 days; • Intention to quit smoking in the next 30 days; • Medication use that may reduce smoking (including, bupropion, nicotine replacement therapies, acamprosate, varenicline, baclofen, clonidine, naltrexone, buprenorphine, nortriptyline, disulfiram and anti-seizure medications) • Hospitalisation/change in dose of psychotropic medication(s) in the last 30 days; • Unstable physical health in the past 3 months; • A previous serious stomach ulcer and/or phaeochromocytoma

Hickling 2019 *(Continued)*

	• Severe heartburn, stroke, unstable kidney/liver disease, an uncontrolled overactive thyroid gland in the past 3 months; • Individuals who meet the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for illicit/alcohol drug dependency; • Medical contraindications to nicotine; • Asthma • Suicidal ideation/suicide attempt in the past month • Pregnancy Inclusion based on specific population characteristic: People who smoke tobacco with a psychotic disorder (established clinical diagnosis of schizophreniform, schizophrenia, schizoaffective disorder or bipolar disorder, or attending an early detection service in a high-risk state) 24% women; mean age 38.96; mean cpd 17.94; mean FTND not reported Motivated to quit: “unwilling to quit soon” E-cigarette use at baseline: Must not have used e-cigarettes on more than 2 occasions in the past 30 days
Interventions	**EC: Cig-a-like** Participants provided with free tobacco-flavored NJOY traditional bold disposable e-cigarette (4.5% nicotine) in an "amount equivalent to 150% of their daily tobacco use (as recommended by the manufacturer)" for 6 weeks. Participants were instructed in the use EC; not required to stop smoking tobacco, but were encouraged to replace it with EC as much as possible. Followed up at 4 weeks and encouraged to continue EC use, informed about EC types and where these could be purchased
Outcomes	Weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 24 Self-reported and biochemical validation Cessation: Tobacco use, as measured by the Time Line Follow Back. Tobacco cigarette use was also indexed weekly by measuring exhaled CO levels with a Smokerlyzer ED50 CO meter (Bedfont Instruments, UK) Adverse events and biomarkers: • Side effects associated with e-cigarette use – reported weekly • Respiratory symptoms: lung capacity (measured by Wright’s Mini Peak-flow Meter (Clement Clarke International Ltd., UK) at baseline, weeks 6, 10 and 24; Peak flow was obtained 3 times at each assessment • Heart rate and blood pressure • Occurrence of (serious) adverse events was assessed on a weekly basis In a subsample of participants (N = 8), 3-hydroxypropylmercapturic acid (3-HPMA, a measure of the toxicant acrolein) and formic acid were measured at baseline and week 6. These participants were chosen as their tobacco intake had decreased by more than 50% in this period. The measurement of 3-HPMA and formic acid was also performed by validated LC-MS/MS assays Other outcomes measured: • Urinary cotinine • Weight • Motivation to Stop Scale (MTSS) • Smoking Consequences Questionnaire-Adult (SCQ-A) • Positive and Negative Syndrome Scale (PANSS) • Calgary Depression Scale for Schizophrenia (CDSS)

Hickling 2019 *(Continued)*

Study funding	"This work was funded by the Maudsley Charity (grant number 715); and supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London."
Author declarations	"R.P-I. has received honoraria and speaker support from Lundbeck. L.D. has provided consultancy for the pharmaceutical industry (Johnson & Johnson 2015, 2017) and acted as an expert witness for an e-cigarette patent infringement case (Porzio, Bromberg & Newman Attorneys at Law, 2015). Between 2011 and 2013, she conducted research for several independent electronic cigarette companies (Totally Wicked, SKYCIGS and E-Lites) for which the University of East London received funds. The e-cigarette companies involved had no input into the design, conduct or write up of these projects and she has not received any funds from e-cigarette companies in the last 4 years. She has no links with, and has not received any funds from, the tobacco industry, although two e-cigarette companies that she worked with in 2013 were subsequently acquired by the tobacco industry (SKYCIGs and E-Lites). L.H., T.R., K-V.S., J.M., A.M. and P.M. have no conflicts of interest."
Notes	Study listed as ongoing study NCT02212041 in the 2016 review update Additional data provided from authors

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled study
Allocation concealment (selection bias)	High risk	Uncontrolled study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Follow-up: Week 6: 46/50; Week 10: 42/50; Week 24: 40/50
Selective reporting (reporting bias)	Low risk	Report all outcomes listed on http://clinical trials.gov except NNAL. Authors confirmed that they had intended to test for NNAL but had major issues with the assays

Holliday 2019

Study characteristics

Methods	Design: Pilot RCT Recruitment: Recruited via the Newcastle Dental Hospital and by primary care practitioners working in the north-east England region Setting: Dental clinical research facility (DCRF), located in the Newcastle Dental Hospital, Newcastle upon Tyne, UK. Study start date: 20 September 2016; Study end date: 31 July 2018
Participants	Total N: 80 N per arm: Intervention group: 40; Control group: 40 Inclusion criteria: • Aged over 18 years old; smoker (≥10 cigarettes/day)

Holliday 2019 *(Continued)*

	• Willing and able to come to the DCRF for the required study visits • Having a minimum of 16 natural teeth (excluding third molars) • Being diagnosed with periodontitis Exclusion criteria: • Having used an e-cigarette for more than 2 days in the last 30 days • Infectious or systemic diseases that may be unduly affected by participation in this study • Haemodynamically unstable • Patients taking the medication adenosine (due to drug interaction risk) • Lack of capacity to be able to consent to the research project or inability to follow study instructions, or both • Participation in a dental research study within the previous 20 days • Pregnant by medical history, or nursing • Received any non-surgical periodontal therapy other than a routine scale and polish in the last 6 months • Currently undergoing or requiring extensive dental, orthodontic or implant treatment, or treatment for peri-implantitis Inclusion based on specific population characteristic: Periodontitis 52.5% women; mean age 44.36; mean cpd 17.4; mean FTND 5 Motivated to quit: Not selected on motivation and not reported E-cigarette use at baseline: Not currently using an e-cigarette, or not having used 1 for more than 2 days in the last 30 days
Interventions	**EC: Refillable** All participants given standard stop-smoking advice (10 - 15 minutes in duration) and offer of referral to stop-smoking services **Intervention**: given EC starter kit (Vype eTank clearomizer) and brief training on its use by a dentist. Provided with an approximately 2-week supply of e-liquid (20 ml) with a choice of flavor (Blended Tobacco, Crisp Mint, Dark Cherry and Vpure (flavorless)) and nicotine strength (0 mg/ml, 6 mg/ml, 12 mg/ml, 18 mg/ml) and information on where to buy more. EC intervention delivered directly following the standard stop-smoking advice and was expected to be 10 - 15 minutes in duration **Control group**: no further intervention
Outcomes	Months 1 and 6; Self-report and biochemical validation of smoking status Cessation: Rates of continuous eCO-verified smoking abstinence at 6 months were calculated following the Russell Standard (RS6) Adverse events and biomarkers: expired air CO, adverse events monitored at each study visit Other outcomes measured: • Feasibility outcomes • Oral health outcomes • Smoking behavior outcomes comprised: self-reported tobacco and e-cigarette use, eCO, e-salivary cotinine (SC), salivary anabasine (SA), FTND and Mood and Physical Symptoms Scale (MPS)
Study funding	"Richard Holliday is funded by a National Institute for Health Research Doctoral Research Fellowship (DRF-2015-08-077). This paper presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care."

Holliday 2019 *(Continued)*

Author declarations	"The authors declare that they have no competing interests."
Notes	New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using a secure password-protected web-based system
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation allocation schedule will be generated by a statistician with no other involvement in the study to achieve concealment of allocation."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nature of study precluded blinding; different levels of support across intervention arms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition < 50%
Selective reporting (reporting bias)	Low risk	All prespecified outcomes are reported

Humair 2014

Study characteristics

Methods	Design: Prospective cohort Recruitment: People attending an outpatient clinic Setting: University hospital outpatient clinic, Switzerland Study start date/end date: Not specified
Participants	Total N: 17 Inclusion criteria: • Wish to reduce tobacco use or had failed to stop smoking using varenicline, bupropion or NRT in past Inclusion based on specific population characteristic: No Mean 23 cpd, 82% had a psychiatric illness Motivated to quit: Yes E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like**

Humair 2014 *(Continued)*

	Offered an EC with nicotine 59% also reported using NRT or varenicline in addition to EC
Outcomes	Smoking cessation and reduction by at least 30% at 12 months (self-report) Adverse events No significant side effects
Study funding	Not specified
Author declarations	Not specified
Notes	Abstract only, hence little detail available Not clear if EC was provided by clinic or if participants had to buy their own

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Ikonomidis 2018

Study characteristics

Methods	Design: (acute phase) Randomized cross-over assignment (outcomes measured within hours of the intervention and hence do not meet the criteria of 1 week or more); chronic phase: non-randomized, single-group assignment Recruitment: Hospital smoking cessation unit Setting: Hospital smoking-cessation unit, Greece Study start date: 31 January 2017; Study end date: Estimated completion date: December 2021
Participants	Total N: 90 Inclusion criteria: • Active conventional cigarette smoker • Adults 18 to 60 years Exclusion criteria: • Health condition adversely affected by smoking, history or presence of cardiovascular disease

Ikonomidis 2018 *(Continued)*

	Inclusion based on specific population characteristic: No 54% women; mean age 50.2; mean cpd 23.4; mean FTND: Not reported Motivated to quit: Yes – recruited from smoking cessation unit E-cigarette use at baseline: Not reported
Interventions	**EC: not clear** E cigarette details: In the chronic phase, all 70 participants were instructed to replace their conventional cigarettes (con-cig) with an e-cig containing nicotine (12 mg/dL (e-cig fluid with nicotine concentration of 12 mg/mL (propylene glycol 74.3%, glycerin 20%, flavoring 4.5%, nicotine 1.2%))) for 1 month
Outcomes	1 month; Self-report and objective measures Cessation: Self-report cessation at 1 month. CO measured at 1 month. Cessation data not used as < 6 months Adverse events and biomarkers: • Exhaled CO concentration • Heart rate; blood pressure Other outcomes measured: • Oxidative stress as assessed by malondialdehyde (MDA) plasma concentrations • Aortic stiffness as assessed by pulse wave velocity (PWV) and augmentation index (AIX75)
Study funding	This study was supported by a grant from the Hellenic Cardiology Society and Hellenic Society of Lipidiology and Atherosclerosis.
Author declarations	None
Notes	New for 2020 update. Acute phase of trial not relevant for the review as very short-term outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and differential levels of support given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Objective measures used for all outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	70 participants and 20 controls recruited – no dropout
Selective reporting (reporting bias)	Unclear risk	NCT record states that chronic endothelial integrity, platelet aggregation and high-shear stress-dependent platelet function would be assessed but is not re-

Ikonomidis 2018 *(Continued)*

		ported in this research letter – however study estimated completion date is December 2021, so perhaps data not ready for publication or limited capacity in the research letter – not the primary publication
Other bias	Unclear risk	Few details – written as commentary. Trial registration suggests this is an ongoing study

Ikonomidis 2020

Study characteristics	
Methods	RCT Recruitment: Smoking cessation clinic of second cardiology department of National and Kapodistrian University of Athens, Attikon General Hospital Setting: Hospital smoking-cessation unit, Greece Study start date: NS
Participants	N = 40; Arm 1 E-cigarette n = 20; Arm 2 conventional tobacco cigarette n = 20 80% female; mean age 44.8 (SD 11.3); mean cpd: 25.8 (C-cig 25.5 SD 9.3. E-cig: 26.2 SD 9.1) Inclusion criteria: • smokers without cardiovascular disease, who used to smoke 25.8 ± 9.2 conventional cigarettes per day of their choice Exclusion criteria: • abnormal renal function • hepatic failure (bilirubin > 2 mg/dl) • active malignancy • people treated with drugs that affect platelet function • history of coronary artery disease or peripheral artery disease • history of cardiomyopathy • age < 21 years old • people with thrombocytopenia (PLTs < 100 × 109 /L) • anemia (HCT < 28%) • alcohol or drug abuse • pregnancy • risk factors for cardiovascular disease
Interventions	**EC: Refillable** E-cig: second-generation e-cig device and popular in Greek Market e-liquid (NOBACCO eGo Epsilon BDC 1100, eGo battery, 1100 mAh, operating at 3.9 V - propylene glycol 74.3%, glycerin 20%, flavoring 4.5%, nicotine 1.2%/12 mg/ml)
Outcomes	Baseline, 4 months: Exhaled CO concentration; blood pressure Also, cpd; Ppatelet function by Platelet Function Analyzer PFA-100 and Light Transmission Aggregometry; Pulse wave velocity; Plasma malondialdehyde levels as oxidative stress index
Study funding	"There was no funding for this study"

Ikonomidis 2020 *(Continued)*

Author declarations	"The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper."
Notes	New for 2021 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers as reproduced from the online randomization software www.graphpad.com/quickcalcs/index
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not possible
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only CO outcomes used here, which are objectively measured
Incomplete outcome data (attrition bias) All outcomes	Low risk	All followed up (confirmed via contact with authors)
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial record available to confirm whether all prespecified criteria were reported

Ioakeimidis 2018

Study characteristics

Methods	Design: Randomized controlled trial Recruitment: Not specified Setting: Hospital, Greece. Study start date/Study end date: Not specified
Participants	Total N: 54 N per arm: Arm 1: 27; Arm 2: 27 Inclusion criteria: • ≥10 cpd • Motivation to quit • Hospitalized with acute coronary syndrome (ACS) • 18 or older Exclusion criteria: • Prior EC use

Ioakeimidis 2018 *(Continued)*

	• History of neuropsychiatric disorders • Prior varenicline use or use of SC pharmacotherapy at time of ACS • Cardiogencic shock or renal impairment • Hepatic impairment prior to ACS • Excessive alcohol use or current use of marijuana or non-cigarette tobacco products Inclusion based on specific population characteristic: People who have experienced acute coronary syndrome 65% women; mean age 52; mean cpd 21; mean FTND 5.6 Motivated to quit: Yes E-cigarette use at baseline: No prior EC use
Interventions	**EC:** information on whether cig-a-like or refillable not provided Both arms given "low intensity counselling" **Intervention 1:** 12-week use of EC 12 mg/ml nicotine **Intervention 2:** 12-week varenicline
Outcomes	Weeks: 4, 12, 24 Cessation: 7-day PP at 24 weeks, self-report Adverse events and biomarkers: Unclear how these were reported. Abstract says no SAEs, poster implies this may have just been CV or neuropsychiatric SAEs. Abstract says nothing about AEs but nausea and sleeping disorders given in table in poster. Implies (S)AEs collected during treatment period only Other outcomes measured: Not specified
Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update. Abstract and poster only; limited data available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not specified but equal amounts of contact and support between arms so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-report only but equal amounts of contact between arms, no reason to suspect differential misreport
Incomplete outcome data (attrition bias)	Unclear risk	Not specified

Ioakeimidis 2018 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Abstract/poster only so not able to judge
Other bias	High risk	Abstract and poster only. Two different figures presented for quit rate in EC arm (no difference in those presented in varenicline arm) between abstract and poster. Poster percentage aligns with figure, so using that (16.5%) as opposed to abstract figure (32.5%). Contacted authors but no reply. Calculated n quit based on percentages but unclear what denominators were; EC calculates back to whole number for EC but not for varenicline

Kumral 2016

Study characteristics	
Methods	Design: Prospective randomized clinical trial Recruitment: All patients admitted to a smoking cessation clinic at the Department of Otorhinolaryngology-Head and Neck Surgery, Okmeydanı Training and Research hospital Setting: Smoking cessation clinic, Turkey Study start date: March 2013; Study end date: November 2013
Participants	Total N: 98 but analysis excludes 16 from intervention and 10 from control who did not stop smoking; thus 72 analyzed N per arm: EC: 58 (42 ana lysed); Non-EC 40 (30 ana lysed) Inclusion criteria: • Smoked at least one pack of cigarettes a day for at least 5 years. Exclusion criteria: • History of allergic rhinitis, chronic sinusitis, vasomotor rhinitis, asthma, malignancy, or surgery in upper respiratory tract; • Age under 18; • Use of psychoactive drugs Inclusion based on specific population characteristic: No 44% women; mean age 36; mean cpd and mean FTND not specified Motivated to quit: “All patients were willing to quit smoking” E-cigarette use at baseline: Not specified
Interventions	**EC: Unclear** **EC arm**: “used EC to quit smoking” – allowed to select brand and flavor, used “medium density” liquid (11 - 12 mg/ml) (no further detail given) **Non-EC arm**: Received cognitive behavioral therapy (no further detail given)
Outcomes	3 Months

Kumral 2016 *(Continued)*

	Sino-nasal outcome test (SNOT-22) via self-administered questionnaire, to evaluate changes in subjective symptoms. Saccharin transit test to evaluate nasal mucociliary clearance (MCC) function which authors state is "an important defence mechanism"
Study funding	Not specified
Author declarations	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients participating in the study were randomly divided into two groups; EC smokers (group 1) and non-EC smokers (group 2)." No further detail provided
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were not blinded. The trial is described as single-blinded and outcome assessors were blinded. No placebo used
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported outcome data, participants not blinded and unequal amounts of support between arms
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout rate not clear. Only ana lysed people who quit
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Lee 2018

Study characteristics

Methods	Randomized parallel-assignment double-blind pilot trial Setting: San Francisco Veterans Affairs Medical Center (SFVAMC), USA Recruitment: veterans awaiting surgery Recruitment: In VA hospital presenting for surgery Study start date: August 2015; Study end date: May 2016
Participants	Total N: 50 N per arm: NRT: 30; END: 20 Inclusion criteria:

Lee 2018 *(Continued)*

	• Presented to the anesthesia preoperative clinic for elective surgery 3 or more days before surgery • Currently smoked more than 2 cigarettes per day, having smoked at least once in the last 7 days Exclusion criteria: • Exclusively used other forms of tobacco or marijuana only • Pregnant or breastfeeding • Unstable cardiac condition • Currently using smoking cessation pharmacotherapy • Were already enrolled in a smoking cessation trial • Currently used e-cigarettes on a daily basis Inclusion based on specific population characteristic: Patients awaiting elective surgery 10% women; mean age 54; mean cpd 14; mean FTND 3.3 Motivated to quit: Not specified E-cigarette use at baseline: Not specified but excluded daily users
Interventions	**EC: Cig-a-like** Both groups receive: i) referral to the California Smokers' Helpline, ii) brief advice lasting less than 2 minutes, iii) a brochure from the ASA about quitting smoking before surgery **EC arm**: 6-week supply of NJOY e-cigarettes (disposable, first generation). Instructed to use Bold (4.5%) ad lib for 3 weeks, then Gold (2.4%) ad lib for 2 weeks and then study (0%) ad lib for final week. Number of ECs issued corresponded to baseline cpd, assuming 1 EC = 10 cigarettes. Asked to refrain from the use of all study products at the end of 6 weeks **NRT arm**: 5-week Nicoderm CQ patches, 1 week placebo patches. Dose based on cpd at baseline: ≥ 10 cpd, 21 mg/day for 3 weeks, 14 mg/day for 1 week, 7 mg/day for 1 week, 0 mg/day for 1 week. < 10 cpd at baseline: 14 mg/day for 3 weeks, 7 mg/day for 2 weeks, 0 mg/day for 1 week
Outcomes	30 Days (phone), 8 Weeks (in person), 6 Months (phone) Cessation: 7-day PP at 30 days (not validated), 8 weeks (CO-validated), 6 months (not validated). Smoking cessation for at least 48 hours on day of surgery (CO-validated) Adverse events and biomarkers: • Adverse events, side effects, and surgical complications by self-report at 30 days, 8 weeks • At 8 weeks exhaled CO, FEV1 and FVC Other outcomes measured: • Attitudes and usage • Salivary cotinine • Smoking reduction
Study funding	"This work was funded by internal UCSF Department of Anesthesia and Perioperative Care funds (San Francisco, California, United States of America) and the UCSF Resource Allocation Program grant, administered by the Helen Diller Family Comprehensive Cancer Center developmental funds from the National Cancer Institute Cancer Center Support Grant (P30 CA 82103-16). E-cigarettes were purchased from NJOY using these funds. NJOY had no involvement in the design, execution, or analysis of the study. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript."
Author declarations	"The authors declare there are no competing interests"
Notes	3 NRT participants used EC, 2 EC participants used nicotine patch

Lee 2018 *(Continued)*

	Study listed as ongoing study NCT02482233 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was computer-generated, with randomly permuted block sizes of 3 or 6, in a 2:1 ratio using the ralloc program"
Allocation concealment (selection bias)	Low risk	Quote: "Allocation was concealed by consecutively numbered, sealed, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded but both interventions active with equal amounts of support so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-report only at 6 months and participants not blinded to condition, but similar level of support given to both groups so differential misreport judged unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 NRT and 1 ENDs loss to follow-up at 6 months
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Lee 2019

Study characteristics

Methods	Design: Randomized controlled trial Recruitment: Recruited from motor company. Setting: Motor company, medical office in Korea Study start date: 5 January 2012; Study end date: 31 August 2012
Participants	Total N: 150 N per arm: EC: 75; NRT: 75 Inclusion criteria: • Male • At least 10 cpd in previous year • Smoked for at least 3 years • Motivate to stop smoking entirely or reduce consumption Exclusion criteria: • Past history of serious clinical disease • Attempted to stop smoking in past 12 months by using NRTs Inclusion based on specific population characteristic: No

Lee 2019 *(Continued)*

	0% women; mean age 42.3; mean cpd: Not reported, 1.01 packs per day; mean FTND 4.05 Motivated to quit: Yes, or to reduce E-cigarette use at baseline: Not specified
Interventions	**EC: Refillable** Both arms received 50 mins education session on smoking cessation and use of smoking cessation aids in medical office (no further detail given). Asked to return to medical office every 4 weeks (to 24 weeks?) for "evaluation and counseling by an independent health practitioner" **Arm 1:** 50-min education sessions on smoking cessation and the use of smoking-cessation aids, instructed to visit the medical office each month for evaluation and counseling by a health practitioner who was unaffiliated with the study. Participants supplied with eGo-CTM EC (nicotine 0.01 mg/mL) from Ovale in 12-wk supply **Arm 2:** As (1) but instead of EC given 2 mg nicotine gum in 12-wk supply
Outcomes	12, 24 weeks (in person) Cessation: continuous abstinence from 9 - 24 weeks, exhaled CO < 10 ppm, negative urine cotinine Adverse events and biomarkers: Yes but just note 'adverse events' Other outcomes measured: 7-day PPA, cigarette reduction
Study funding	"none"
Author declarations	"none declared"
Notes	Study listed as ongoing study KCT0001277 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated randomization sequence with a block size of 2"
Allocation concealment (selection bias)	Low risk	Quote: "The enrolment and assignment of all subjects were performed by a clinical research coordinator not involved in the study"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded but both interventions active with equal amounts of support, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants not blinded but results biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	61/75 NRT and 71/75 EC FU at 24 weeks
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported

Lucchiari 2020

Study characteristics	
Methods	Design: Randomized parallel-assignment double-blind trial Recruitment: Participants enrolled in lung cancer-screening program Setting: Early lung cancer detection program (Cosmos II) at European Institute of Oncology, Italy Study start date: September 2014; Study end date: January 2016
Participants	Total N: 210 N per arm: 70 participants per arm Inclusion criteria: • Participants are involved in the COSMOS II study • Participants are 55 years or more and have smoked at least 10 cigarettes a day for the past 10 years • Participants wish to reduce tobacco smoking (motivational score higher than 10) who are not treated at a smoking centre • Signed informed consent Exclusion criteria: • Symptomatic cardiovascular disease • Symptomatic severe respiratory disease • Regular psychotropic medication use • Current or past history of alcohol abuse • Use of smokeless tobacco or NRT • Participation in another antismoking program in the current year Inclusion based on specific population characteristic: 55 years of age or older 37% women; mean age 62.8; mean cpd 19.38; mean FTND 4.37 Motivated to quit: yes E-cigarette use at baseline: Excluded people who smoke who had ever regularly used e-cigarettes for more than 1 week alone or in combination with tobacco cigarettes
Interventions	**EC: Cig-a-like** Both arms received “low intensity counseling” – phone at week 1, 4, 8 and 12, approx. 10 mins each **Nicotine EC arm**: e-cigarette kit and 12 10-mL liquid cartridges (8 mg/mL nicotine concentration). During the first week, participants could use the e-cigarette ad libitum. At the end of the first week, asked to use only EC for the next 11 weeks **Nicotine-free EC (placebo) arm**: Nicotine-free EC – same as above but with nicotine-free EC
Outcomes	Months 3, 6 and 12 (but only 3- and 6-month data available) Cessation: Continuous abstinence for previous month, CO ≤ 7 ppm Adverse events and biomarkers: FOR EC ARMS ONLY: • Exhaled CO • Leicester Cough Questionnaire (LCQ) • Respiratory symptoms (self-report) • Side effects using checklist

Lucchiari 2020 *(Continued)*

	Other outcomes measured: • Motivational questionnaire • HADS • EC use
Study funding	This study was supported by a grant from Fondazione Umberto Veronesi (FUV)
Author declarations	The authors declare no conflicts of interest
Notes	Listed as ongoing study Lucchiari 2016 (NCT02422914) in 2016 review; new for 2020 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list using a permuted block design (40 blocks of 6 subjects randomly assigned to 1 of the 3 treatment arms) had been previously prepared by independent personnel."
Allocation concealment (selection bias)	Low risk	Double-blind, active and placebo e-cigarettes labeled by independent personnel, researcher and participants blind
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double blind" for nicotine vs no nicotine EC but limited info given; however, as similar levels of support across arms performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Approx. 73% followed up in each group at 6 months, very little difference between groups
Selective reporting (reporting bias)	High risk	Paper states data also collected at 12 m but this is not presented and unclear why. Paper states CO collected but data not presented

Martner 2019

Study characteristics

Methods	Design: A nonconcurrent multiple baseline across participants design. Three phases were included: Baseline, EC, and EC + CM. Half the participants received the EC phase following baseline; the other half received EC + CM following baseline Recruitment: Community Setting: Set-up meetings occurred at the University of Florida Behavioral Health and Technology Research Clinic, USA Study start date/Study end date: Not specified.
Participants	Total N: 12 Inclusion criteria:

Martner 2019 *(Continued)*

- 18 - 65 years old
- Smoked ≥ 2 years
- Smoked ≥ 8 cpd on average
- Smoked in the past 24 hours
- Expressed a desire to quit smoking (yes/no)
- Had reliable access to the internet and a computer or smartphone
- Breath CO ≥ 10 ppm at set-up

Exclusion criteria:

- Current or previous medical condition that would pose an increased risk to participation
- Use of benzodiazepines, cocaine, or opiates in the previous 6 months
- Smoke marijuana more than twice a month
- Exposed to elevated CO levels (e.g. spouse smokes in house)
- Pregnant or expected to become pregnant in the next 6 months

58.3% women; mean age 37.5; mean cpd 16.25; mean FTND 5

Motivated to quit: Expressed a desire to quit smoking.

E-cigarette use at baseline: 3 participants never tried an EC prior to the study; 2 owned an EC but quit using it more than a month prior to the study; remaining 7 had tried an EC more than a year prior to the study but never owned one

Interventions	**EC: Refillable** All participants provided with smokio electronic cigarettes (second-generation ECs) and V2 e-liquid with a concentration of 24 mg/ml (2.4%) of nicotine. Researchers provided participants with a copy of the National Cancer Institute's brochure *Clearing the Air* (http://smokefree. gov). Then researchers and participants read through a manual that described the study procedures, and showed participants how to use the software to measure CO and how to use the EC Participants initially received EC without contingency for a period of 14 days following the quit attempt. If participants failed to reduce CO levels during this phase, they received contingency management in addition to EC
Outcomes	4 weeks Adverse events and biomarkers: Adverse events collected in 4-day smoking behavior questionnaires; eCO Other outcomes measured: acceptability and use of EC; overall experience of study
Study funding	"The study was supported in part by crowd-sourced funding enabled by Experiment.com. Preparation of this paper was supported in part by Grant P30DA029926."
Author declarations	"The authors declare no conflicts of interest."
Notes	N of 1 (within-participants randomized design, not between groups). New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized

Martner 2019 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details provided.
Selective reporting (reporting bias)	Unclear risk	AEs measured in behavioral change questionnaire but not reported

McRobbie 2015

Study characteristics	
Methods	Design: Prospective cohort Recruitment: advertisements in free London newspapers Setting: Smokers' clinic, East London, UK Study start date: February 2013; Study end date: September 2013
Participants	Total N: 40 Inclusion criteria: • People who smoke daily who want to quit • Aged 18 and older Exclusion criteria: • Pregnant and breastfeeding women • Current serious medical illness • EC use for more than 1 week in the past 45% women, mean age 47 (SD 12), mean cpd 19 (SD 10), mean FTND 5.2 (SD 2.8), 65% in full-time employment Motivated to quit: Yes E-cigarette use at baseline: Excluded those who had used EC for more than 1 week in the past
Interventions	**EC: Cig-a-like** Participants attended baseline session 1 week prior to their TQD. On the TQD, participants were provided with an EC (Green Smoke, 1st generation device, 2.4% nicotine cartridges). 2 cartridges a day were supplied initially, with the supply adjusted to actual use later. Attended 4 weekly follow-up sessions and received standard behavioral support
Outcomes	Cigarette consumption and CO readings collected at each session. Urine sample for cotinine and 3-HPMA analysis collected at baseline and 4 weeks post-TQD Change in urinary 3-HPMA (ng/mg creatinine) at 4 weeks Change in urinary cotinine (ng/mg creatinine) at 4 weeks Change in CO at 4 weeks
Study funding	"This study was funded by a grant given to P. Hajek, H. McRobbie, and M.L.Goniewicz from the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact."

McRobbie 2015 *(Continued)*

Author declarations	"H. McRobbie is Clincal Director at The Dragon Institute; reports receiving commercial research grant from Pfizer; and has received speakers bureau honoraria from Johnson&Johnson and Pfizer. M.L. Goniewicz reports receiving commercial research grant from Pfizer. P. Hajek has received speakers bureau honoraria from and is a consultant/advisory board member for the manufacturers of stop-smoking medications. No potential conflicts of interest were disclosed by the other authors."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/40 participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported

Meier 2017

Study characteristics

Methods	Design: Randomized cross-over trial (e-cig vs placebo) Recruitment: via local media outlets Setting: Community, USA Study start date/Study end date: Not specified.
Participants	Total N: 24 Inclusion criteria: • ≥ 18, • People who smoke daily (≥ 10 cpd) • Not interested in quitting in next 30 days • English-speaking • Interested in using EC Exclusion criteria: • Using cessation meds • Use of ECs in last 6 m • Exhaled CO < 6 ppm, • History of CV trauma or uncontrolled hypertension • Pregnant Inclusion based on specific population characteristic: No

Meier 2017 *(Continued)*

	25% women; mean age 48.5; mean cpd 16.3; FTND not reported Motivated to quit: No (eligibility criteria was to not want to quit in next 30 days) E-cigarette use at baseline: 8/24 (33%) had previously tried an EC, avg 9.4 months since last use, avg length of use 3.6 days
Interventions	**EC: Cig-a-like** Smoked "as usual" for 1 week followed by 2 weeks of either placebo or active 1st generation EC BluCig starter kit with up to 7 cartridges (prefilled, with either active 16 mg or 0 mg nicotine solution) Participants were instructed "this e-cig may or may not contain nicotine; we ask that you try it at least once, but use it however you like; smoke regular cigarettes as you wish." Shown how to charge the device and sampled the product during the visit. Provided a handout on how to use the product (e.g., switching cartridges) and general information about ECs
Outcomes	1 week in each condition, in person Adverse events and biomarkers: • Adverse events, not clear how collected • Exhaled CO Other outcomes measured: • Vaping • Regular smoking • Perceived reward from ECs • Intentions/confidence to quit • Cotinine • Withdrawal symptoms
Study funding	"..supported by grants P01 CA138389, P30 CA138313 (Hollings Cancer Center Support Grant) from the National Cancer Institute of the National Institutes of Health and UL1 TR000062 from the National Center for Advancing Translational Science of the National Institutes of Health. BWH was supported by K12DA031794"
Author declarations	"KMC has received grant funding from the Pfizer, Inc., to study the impact of a hospital-based tobacco cessation intervention. He also receives funding as an expert witness in litigation filed against the tobacco industry. We have no other declarations of interests to declare"
Notes	New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Participants were randomized to receive either an active or placebo EC first", no further information provided.
Allocation concealment (selection bias)	Unclear risk	Refer to 'Random sequence generation'.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Participants and research staff conducting sessions were blinded to dose. All cartridges were pre-loaded by the manufacturer. Labeling was removed by a research team member not involved in participant contact to mask placebo versus active ECs. We restricted flavor options to regular tobacco flavor or menthol to most closely match usual cigarette brand flavor profile and reduce unwanted variance in product"

Meier 2017 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Participants and research staff conducting sessions were blinded to dose. All cartridges were pre-loaded by the manufacturer. Labeling was removed by a research team member not involved in participant contact to mask placebo versus active ECs. We restricted flavor options to regular tobacco flavor or menthol to most closely match usual cigarette brand flavor profile and reduce unwanted variance in product"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

NCT02648178

Study characteristics	
Methods	Setting: Medical centre, USA Recruitment: People with cancer Design: Non-randomized single-group assignment trial Recruitment: Clinical settings, including outpatient clinics and the infusion suite Study start date: June 2016; Study end date: May 2018
Participants	Total N: 19 Inclusion criteria: • Histological or cytological diagnosis of aerodigestive tract cancers or bladder cancer within the past 5 years (more than 1 tobacco-related malignancy is allowed) • AJCC stages I - IV • Daily smoking (at least 10 cigarettes per day for 10 years) and breath $CO^2 \geq 8$ ppm • Does not wish to quit smoking now (anyone wishing to quit smoking will be referred for smoking cessation counseling through the WRJ VAMC or DHMC program) • May be receiving anti-cancer agents • Age 18 or older • Fluent in English • Patient must be capable and willing to provide informed written consent for study participation • Able to participate in study visits Exclusion criteria: • Cancer surgery planned in the next 9 weeks • Treatment with radiation planned for the next 9 weeks • Actively trying to quit smoking, or planning to in the next 30 days. (If a patient reports that they plan to quit smoking in the next 30 days, we will call them after the 30 days to see if they are still trying to quit) • Any use of e-cigarettes in the past 30 days • Pregnant or trying to get pregnant Inclusion based on specific population characteristic: Patients with stage I - IV aerodigestive tract cancers or bladder cancer who smoke daily

NCT02648178 *(Continued)*

	42.1% women; mean age: not reported -categories 18 - 65 years: N = 9, > 65 years: N = 10; cpd and FTND: not reported. Motivated to quit: No (inclusion criterion) E-cigarette use at baseline: Not specified but EC use within 30 days is an exclusion criterion
Interventions	**EC: Cig-a-like and refillable** Instructed on use of EC, and given a supply that is "approximately equivalent to their current nicotine intake". Given Halo Triton EC (leak-proof refillable tank system) or Halo G6 leak proof prefilled cartomizers. Began participants with 18 mg/ml and moved nicotine content up or down based on participant preference. Choice of flavors, provided for 9 weeks
Outcomes	Weeks 3, 6, 9, 12. Self-report at clinic visits Adverse events and biomarkers: • Averse events assessed with a checklist for commonly-occurring side effects from e-cigarettes and nicotine products • Exhaled carbon dioxide • Expired carbon monoxide • Urine propylene glycol • Urine 4- (methylnitrosamino)-1-(-3pyridyl)-1butanol (NNAL) 40 and 1- hydroxy naphthalene (1-HOP) Other outcomes measured: • Timeline Follow-Back Questionnaire (TLFB) • EC appeal assessed with attitudinal ratings, on a 5-point Likert-type scale • e-cigarette ease of use, satisfaction, and enjoyment, and willingness to continue to purchase e-cigarettes in the future • Change in daily cigarette smoking given 10 or more E-cig sessions • Average number of E-cigs used per day • The co-ordinators will conduct and audiorecord a 10 - 15-minute qualitative interview at 9 weeks soliciting perceptions about e-cigarettes to be transcribed and analyzed for common themes that could be useful in developing the larger intervention • urine nicotine and cotinine
Study funding	Not reported – data extracted from clinical trial registry record
Author declarations	Not reported – data extracted from clinical trial registry record
Notes	Study listed as ongoing study in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized, single-group assignment
Allocation concealment (selection bias)	High risk	Not randomized, single-group assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	19 enrolled; 10 participants followed up at 12 weeks

NCT02648178 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	The following measures were not reported: exhaled carbon dioxide; urine propylene glycol; urine nicotine, cotinine, NNAL and 1- hydroxy naphthalene (1-HOP), and Timeline Follow-Back Questionnaire (TLFB). Data at 6, 12 months also not reported

NCT02918630

Study characteristics	
Methods	Design: RCT Recruitment: Clinics Setting: SMI clinics, USA Study start date: October 2016; Study end date: August 2017
Participants	Total N: 7 N per arm: NRT: 4; EC+NRT 3 Inclusion criteria: • Be diagnosed with schizophrenia (or other SMI, not clear) • Be in stable medical condition (DSM-V) • Report smoking ≥ 10 tobacco cigarettes/day • Present a breath CO ≥ 10 ppm • Report wanting to reduce their cigarette smoking • Be fluent in English • Have a stable living situation Exclusion criteria: • Be currently pregnant or breastfeeding • Report wanting to quit smoking in the immediate future • Test positive for illicit drugs except THC • Have any illness, medical condition, or use of medications, which in the opinion of the study physicians would preclude safe or successful completion of the study, or both Inclusion based on specific population characteristic: Yes - SMI (schizophrenia and schizoaffective disorder, bipolar disorder, or PTSD) 43% women; mean age 48.3; mean cpd: NR; mean FTND: NR Motivated to quit: Wanted to quit or reduce their cigarette smoking but did not want to quit in the immediate future (this was an exclusion criterion) NB – trial registry states wanted to reduce and protocol states wanted to quit or reduce as inclusion criteria E-cigarette use at baseline: Not specified
Interventions	**EC: Refillable** Both arms received a nicotine patch 21 mg for 4 weeks **EC + NRT**: 4 weeks: 1) a 3.3 V, 1000 mAh battery; and 2) a 1.5 Ohm, dual-coil cartomizer (SmokTech; Shenzhen, China). Nicotine concentrations 36 mg/ml. Verbal and written instructions on how to use and maintain the e-cigarettes at Week 1 visit

NCT02918630 *(Continued)*

	NRT arm: NRT only
Outcomes	5 weeks Cessation: n/a but "change in smoking" Adverse events and biomarkers: Breath CO, COPD-related symptoms, EC side effects (e-cig side effects questionnaire), AEs, SAEs Other outcomes measured: Urinary cotinine, cpd, tobacco dependence, craving, withdrawal symptoms, desire to quit, confidence to quit, EC dependence, EC use, satisfaction with EC, nicotine dependence, schizophrenia symptoms (brief psychiatric rating scale), cognitive domains associated with schizophrenia (MATRICS consensus cognitive battery), changes in positive symptoms of schizophrenia (scale for the assessment of positive symptoms), changes in negative schizophrenia symptoms (scale for the assessment of negative symptoms), suicide ideation (Columbia Suicide Severity Rating Scale)
Study funding	Not reported
Author declarations	Not reported
Notes	New for 2020 update. Information from http://clinical trials gov registry and unpublished protocol; discrepancies between the two in terms of trial methods. Feasibility for future NIH grant application. Intended to recruit 20 participants but only 7 started and completed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"double-blind" but "open-label" elsewhere, no further info given
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	High risk	Schizophrenia and COPD outcomes not reported.
Other bias	Unclear risk	Some discrepancies between clinicaltrials record and protocol linked to from record, including when NRT started and inclusion criteria (just schizophrenia or all SMI). Target sample size was 20 but only 7 people recruited

Nides 2014

Study characteristics	
Methods	Design: Open-label non-comparative study Recruitment: Study site database and community advertisements Setting: Clinical Trials Unit, USA Study start date: April 2013; Study end date: 10 July 2013
Participants	Total N: 29 Inclusion criteria: • Age 18 - 65 years • Good health • BMI 18 - 35 • Smoking 10+ cpd • CO > 10 ppm Exclusion criteria: • Pregnancy or breastfeeding • Other drug dependency • Use of any psychiatric or opioid medications • EC within the previous 14 days • Use of NRT in last 30 days • Want to reduce or quit smoking within the next 30 days Exclusion criterion: EC within the previous 14 days; use of NRT in last 30 days 44% women; mean age 43; mean cpd 20.1; mean FTND 4.5 Motivated to quit: no E-cigarette use at baseline
Interventions	**EC: Cig-a-like** Participants attended 3 clinic visits at 1-week intervals Visit 1: Baseline Visit 2: Provided with 1st generation type - 'NJOY® King Bold' (NJOY, Inc. Scottsdale, AZ), with 26 mg nicotine. Used ad libitum for 20 minutes in the clinic, then ad libitum use over the next week. Recorded use of regular cigarettes and puffs on EC Visit 3: Participants abstained from all sources of nicotine for 12 hours prior to visit
Outcomes	Adverse events
Study funding	Funding for this study was provided by NJOY, Inc., Scottsdale, AZ
Author declarations	Dr Nides has received compensation from NJOY, Inc. and GlaxoSmithKline. Dr Leischow has received compensation from GlaxoSmithKline, Pfizer, and Cypress Bioscience. Mr Simmons and Ms Bhatter have no conflict of interest to report
Notes	
Risk of bias	

Nides 2014 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out between visits 1 and 2
Selective reporting (reporting bias)	Low risk	Planned comparisons reported

Oncken 2015

Study characteristics	
Methods	Design: Randomized cross-over study Recruitment: Newspaper advertisements, radio announcements, and from local general medicine practices Setting: Lab-based study, Connecticut, USA Study start date: October 2012; Study end date: June 2015
Participants	Total N: 27 Inclusion criteria: • non-treatment-seeking people who smoke who were willing to try EC for 2 weeks and abstain from conventional cigarette smoking • 18 – 55 years of age who smoked at least 10 cpd Exclusion criteria: • Pregnant • Previous myocardial infarction or stroke • Uncontrolled hypertension (blood pressure (BP) > 160/100) • Insulin-dependent diabetes • COPD or current asthma • Known allergy to propylene glycol 45% women; mean age 42; 70% white; 15% Hispanic, 15% black; mean cpd 16; 45% had tried EC at baseline, 50% smoked menthol cigarettes Motivated to quit: No E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** Prescribed Joye eGo-C (www.joyetech.com) and e-Juice (18 mg/mL nicotine) procured from American eLiquid (www.americanliquid.com) Cross-over study between menthol-flavored and non-menthol

Oncken 2015 *(Continued)*

	tobacco-flavored EC. Requested not to smoke their regular cigarettes during study period, but most (60%) reported intermittently smoking cigarettes during study
Outcomes	Follow-up at 1 wk and 2 weeks BP, heart rate, body plethysmography, static lung volumes and airways resistance (Raw) and specific conductance (sGaw) – taken at lab visits after abstaining from EC for at least 2 hrs, then taken again after inhaling EC and repeated 5 mins later Adverse events also reported but method for measuring not stated Also measured nicotine concentrations, rates of cigarette and EC use
Study funding	This project was supported by Academic Enhancement funds from the Department of Medicine at the University of Connecticut Health Center (to CO) and the Clinical Research Center at the University of Connecticut Health Center
Author declarations	CO is currently receiving study medication (nicotine inhaler and placebo) from Pfizer pharmaceuticals for an NIH funded of nicotine inhaler for smoking cessation during pregnancy
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not stated; Quote: "Subjects were then randomly assigned to use the menthol or plain e-cigarette cartridge for one week, switching to the other cartridge for the second week"
Allocation concealment (selection bias)	Unclear risk	No detail given
Blinding of participants and personnel (performance bias) All outcomes	Low risk	No detail given on blinding but equal levels of support between arms, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Some subjective outcomes but equal levels of support between arms so differential misreport judged unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	20/27 followed up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Ozga-Hess 2019

Study characteristics

Methods	Design: RCT

Ozga-Hess 2019 *(Continued)*

	Recruitment: Cigarette smokers were recruited from the community via fliers, online postings, and word of mouth Setting: Morgantown, West Virginia, USA Study start date: Not reported. Study end date: Not reported
Participants	Total N: 60; E-cigarette plus own brand = 30. Own brand cigarette (control) = 30 38.3% female; mean age completers 35.1 (SD 11) (N = 34) non-completers 36.8 (SD 12.9) (N = 26); mean cpd completers 16.7 (SD 4.9), non-completers 19.6 (SD 6.1); mean FTND completers 5.3 (SD 1.8), non-completers 5.9 (SD 1.9) Inclusion criteria: • 18 to 60 years of age; smoking ≥ 10 cigarettes per day for ≥ 1 year • exhaled air carbon monoxide (CO) level of ≥ 10 ppm (Micro+™ basic monitor; CoVita; Haddonfield, NJ) • Contemplation or Preparation Stage of Change (indicating interest in a quit attempt within the next 1 - 6 months) Exclusion criteria: • reported chronic health or psychiatric conditions • past month use of marijuana ≥ 5 days • past month use of any other illicit drugs, or regular use of ECIGs or other tobacco products (i.e. ≥ 1 day per week) • individuals in the Precontemplation (no interest in quitting) or Action (actively trying to quit) Stage of Change • currently breast- feeding or tested positive for pregnancy via urinalysis
Interventions	**EC: Refillable** **E-cigarette** (18 mg/ml) plus own brand cigarette. Kanger mini Protank-II, which is a 1.5 ml Pyrex glass tank with a drip tip and atomizer head coils (KangerTech; China), and a 3.3 V constant output, 900 mAh, eGo-T battery (Joyetech; Irvine, CA). The liquid (The Vapor Room, Sky Vapors LLC, Frostburg, MD) was labeled as 70% propylene glycol and 30% vegetable glycerin, with a nicotine concentration requested of 18 mg/ml. Participants could choose tobacco, menthol or wild berry flavor and could switch between sessions. Ad libitum use for 4 weeks **Own brand cigarette** ad libitum use for 4 weeks
Outcomes	Daily for salivary cotinine samples. Daily self-monitoring device to log e-cigarette and cigarette use. Collected used cigarette filters Weekly CO breath test Attended the laboratory weekly for assessments (Days 8, 15, 22, and 29). Then completed a follow-up visit 1-month post-intervention self-reported withdrawal symptoms Reported experience of specific symptoms rated using a visual analog scale with a range from 0 (not at all) to 100 (extremely). e.g. craving, irritability, dry mouth, throat irritation, and cough
Study funding	Financial support provided to MDB and GAD by WVU Senate Grant for Research, and to GAD, MDB, and NAT by Cooperative Agreement Number 1-U48-DP-005004 from the Centers for Disease Control and Prevention (CDC) to the West Virginia Prevention Research Center. Support provided to NJF and JEOH by the National Institute of General Medical Sciences (NIGMS T32 GM081741). Additional support provided by WV Tobacco Cessation QuitLine

Ozga-Hess 2019 *(Continued)*

Author declarations	Author SGF has consulted for various pharmaceutical companies on matters relating to smoking cessation. All other authors declare that they have no conflicts of interest
Notes	New for 2021 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Using a simple randomized design" Comment: not adequately explained
Allocation concealment (selection bias)	Unclear risk	Not adequately described in the paper
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and investigators were not blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	High risk	40% retention, but no difference between groups
Selective reporting (reporting bias)	Low risk	All outcomes reported

Pacifici 2015

Study characteristics

Methods	Design: Uncontrolled pre-post pilot study Recruitment: Word of mouth Setting: Hospital-based smoking cessation clinic, Italy Study start date/end date: Not specified
Participants	Total N: 34 Inclusion criteria: • Adults who smoke, unwilling to quit smoking tobacco cigarettes and who have never tried a quit-smoking protocol or have refused any smoking cessation treatment, or both Exclusion criteria: • None stated Inclusion based on specific population characteristic: No 47.1% women, mean age 40.6, mean cpd 21.5

Pacifici 2015 *(Continued)*

	no EC use at baseline, not motivated to quit
Interventions	**EC: Refillable** Participants were given commercially-available EC (AVATAR device, Battery 550 mAh/3.9 V, W: 7.8, cartomizer with 2, 2 ohm resistance, tank capacity 1.5 mL, temperature of the aerosol: 55/65 degrees), 2 different chargers for each EC and PUFFIT e-liquids with nicotine content matching the individual nicotine daily intake and tobacco and/or other flavors freely chosen by each participant W1: nicotine-free e-liquid W2&3: Own EC with personal nicotine dosage, encouraged to use as substitute for traditional cigarettes W4: Encouraged to forego all traditional cigarettes Throughout: assistance at any time of day from centre staff with any EC-related problem, plus follow-up group sessions and smartphone messaging application Behavioural support: Multi-component medically-assisted training program with monitoring of nicotine intake as a biomarker of correct EC use, including Information about general working principles, safety and risks of EC, together with medically-assisted face-to-face training on how to correctly use the device to absorb nicotine vapor
Outcomes	Follow-up at 1, 4 and 8 m Cessation (measure not defined) Adverse events Exhaled CO, COT, 3-HCOT concentration cpd
Study funding	The authors thank Renata Solimini, Adele Minutillo, Emilia Marchei and Maria Concetta Rotolo for their technical assistance. This work was supported by the Department of Therapeutic Research and Medicines Evaluation Istituto Superiore di Sanità, Roma, Italy
Author declarations	The authors declare no conflict of interest
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants followed up
Selective reporting (reporting bias)	High risk	AEs measured but not reported

Polosa 2011

Study characteristics	
Methods	Design: Prospective cohort Recruitment: Advertisments in local hospital in Catania, Italy Setting: not specified Study start date: February 2010; Study end date: June 2010
Participants	Total N: 40, hospital staff Inclusion criteria: • Healthy people who smoke • 18 - 60 years old • smoking ≥ 15 cpd for at least the past 10 years, and not wanting to quit smoking at any time in the next 30 days Exclusion criteria: • History of alcohol and illicit drug use • Psychiatric illness • Recent myocardial infarction • Angina pectoris • High blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both) • Diabetes mellitus • Severe allergies • Poorly-controlled asthma or other airways diseases 35% women, mean age 42.9 (SD 8.8), median cpd 25 (IQR 20 - 30), median FTND 6.0 (IQR 6 - 8) Motivated to quit: No E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** Seen at baseline, given EC ('Categoria' brand) with an initial 4-week supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges per day. EC cartridges supplied at months 1, 2, and 3 No instruction on cessation or reduction was provided
Outcomes	Follow-up at 1, 2, 3, 6, 18 and 24 months where cigarette consumption, CO, and AEs were measured, incl. 30-day PP CO-validated abstinence at 6 months and CO-validated abstinence at 18 and 24 months (not otherwise defined) Adverse events
Study funding	"We wish to thank Arbi Group Srl (Milano, Italy) for the free supplies of 'Categoria' e-Cigarette kits and nicotine cartridges as well as their support. We would also like to thank the study participants for all their time and effort and LIAF (Lega Italiana AntiFumo) for the collaboration"
Author declarations	"None of the authors have any competing interests to declare, but RP has received lecture fees from Pfizer and, from Feb 2011, he has been serving as a consultant for Arbi Group Srl.Arbi Group Srl (Milano, Italy), the manufacturer of the e-Cigarette supplied the product, and unrestricted technical and customer support. They were not involved in the study design, running of the study or analysis and presentation of the data"

Polosa 2011 *(Continued)*

Notes	Smoking cessation services provided to those who spontaneously asked for assistance with quitting. These participants were excluded from the study protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/40 were lost to follow-up, but used ITT analysis
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Polosa 2014b

Study characteristics

Methods	Design: Prospective cohort study Recruitment: Volunteers, leaflets, cessation service kiosk in hospital Setting: Smoking cessation clinic, Italy Study start date: January 2013; Study end date: November 2013
Participants	Total N: 50 Inclusion criteria: • Healthy people who smoke • 18 – 60 years old • Smoking ≥ 15 conventional cpd for at least 10 years • Unwilling to quit Exclusion criteria: • none stated 40% women, mean age 41, mean cpd 25, mean FTND 6.0 No EC use at baseline, not motivated to quit
Interventions	**EC: Refillable** 2nd generation devices (personal vaporisers - PVs): EGO/CE4 model, filled with tobacco aroma e-Liquid containing 9 mg/ml nicotine; instructed to use the study products ad libitum (up to a maximum of 5 ml/day; i.e. half vial) Behavioural support:

Polosa 2014b *(Continued)*

	Participants were instructed how to charge, fill, activate and use the EC. Key troubleshooting was addressed and phone numbers were supplied for assistance. “No emphasis on encouragement, motivation and reward for the smoking cessation-related efforts were provided during the study.”
Outcomes	4, 8, 12 and 24 weeks 30-day PP verified by CO ≤ 10 ppm Adverse events Cpd, exhaled CO, reduction rates, product usage, and opinions of the EC products
Study funding	"The authors wish to thank FlavourArt (Oleggio, NO, Italy; www.flavourart.it). Authors wish to thank LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti Smoking League) for supporting this research"
Author declarations	"RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl, an Italian distributor of e-Cigarettes. RP is currently scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti Smoking League). PC, MM, JBM, and CR have no relevant competing interest to declare in relation to this work"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	76% followed up, ITT analysis used, no significant differences in baseline characteristics between completers and those lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Polosa 2015

Study characteristics

Methods	Design: Prospective cohort Recruitment: Professional retail staff in participating vape shops Setting: 7 vape shops in Catania province, Italy Study start date/end date: Not specified
Participants	Total N: 71 Inclusion criteria:

Polosa 2015 *(Continued)*

	• Adults who smoke (≥ 18) • making first purchase at participating vape shop (definition of smoker not stated) Exclusion criteria: • none stated 38% women, mean age 41.7, mean cpd 24.9, mean FTND 5 No EC use at baseline
Interventions	**EC: Refillable** Instructed how to charge, fill, activate and use EC; key troubleshooting advice provided; phone number available for technical support "Encouraged to use these products in anticipation of reducing the number of cig/day smoked"
Outcomes	6 and 12 m follow-up 30-day PPA via self-report Details of product purchase Sustained 50% and 80% reduction in cpd from baseline
Study funding	Authors wish to thank the local participating Vape Shops and LIAF, Lega Italiana Anti Fumo (Italian acronym for the Italian Anti-Smoking League) for supporting this research
Author declarations	Riccardo Polosa has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl, an Italian distributor of e-Cigarettes. Riccardo Polosa is currently scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League). Jacques Le-Houezec is a consultant for Johnson & Johnson France, a manufacturer of nicotine replacement therapy, and was reimbursed for travel and accommodation to present at a conference in Shenzhen (China) organized by the e-cig manufacturer association (CECMOL). Pasquale Caponnetto and Fabio Cibella have no relevant conflict of interest to declare in relation to this work
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not controlled
Allocation concealment (selection bias)	High risk	Not controlled
Incomplete outcome data (attrition bias) All outcomes	Low risk	69% follow-up at 12 m. Participants lost to follow-up considered as continuing smokers
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Pratt 2016

Study characteristics	
Methods	Design: Observational study – uncontrolled experimental study Recruitment: community mental health centre through self-referral and clinician referrals Setting: community mental health centre (USA) Study start date: October 2013; Study end date: June 2014
Participants	Total N: 19 (21 originally recruited, however 2 participants did not return for any weekly visits so 19 analyzed) Inclusion criteria: • Age ≥ 18 • Primary DSM-IV axis I diagnosis, based on chart review and confirmation by the community mental health centre team psychiatrist, of schizophrenia, schizoaffective disorder, or bipolar disorder • SMI defined by at least moderate impairment in multiple domains of life functioning due to mental illness • Smoking at least 10 cigarettes per day • History of failed treatment-facilitated quit attempts • Voluntary informed consent for participation Exclusion criteria: • Current use of e-cigarettes • Medical instability • Primary diagnosis of dementia or significant cognitive impairment defined as a Mini Mental Status Examination (MMSE) score < 24 Inclusion based on specific population characteristic: Psychiatrically stable, in-treatment, people who smoke with a schizophrenia spectrum disorder or bipolar disorder 68% women; mean age 42; mean cpd: Only cigarettes per week reported: 192 (SD = 159.3). This would be an average of 27 cpd; mean FTND 5.5 Motivated to quit: “None of the participants was actively engaged in a quit attempt during the study” E-cigarette use at baseline: E-cig use was an exclusion criterion
Interventions	**EC: Cig-a-like** E-cigarette details: (NJOY brand) based on each participant's level of use of combustible tobacco. Each e-cigarette cartridge was approximately equivalent to 2 packs of combustible cigarettes. Trained research interviewers instructed participants on the proper use of e-cigarettes
Outcomes	Week 1, 2, 3, 4 Adverse events and biomarkers: • Breath CO level • Possible side effects Other outcomes measured: • Use of tobacco products • Fagerström nicotine dependence scores • Appeal of EC • Level of enjoyment of EC • Satisfaction with EC compared with usual combustible tobacco

Pratt 2016 *(Continued)*

	• Willingness to purchase EC
Study funding	"Financial support to purchase the e-cigarettes and pay small stipends to the participants in this unfunded pilot study came from Dr. Mary Brunette's discretionary reserve account."
Author declarations	"All authors declare that they have no conflicts of interest"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 dropouts (9.5%) failed to return to clinic. Analysis based on 19 participants
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Pulvers 2018

Study characteristics

Methods	Design: Observational uncontrolled experimental study Recruitment: Community Setting: Visits took place in University labs, USA Study start date: January 2015; Study end date: April 2015
Participants	Total N: 40 Inclusion criteria: • Being 18 years of age or older • Cigarette smoking on at least 4 days of the past 30 days for at least 1 year • Never using EC regularly (less than 25 lifetime uses) • Not having used EC on more than 3 of the past 30 days • Being willing to switch from smoking regular cigarettes to ECs • Fluency in English • Having regular access to a telephone and transportation to attend appointments • Being willing to abstain from using marijuana during the study Exclusion criteria: • Any use of other tobacco products (OTPs) including smokeless tobacco, cigarillos, pipes, cigars, hand-rolled cigarettes, and hookah in the past 30 days • Being currently in a smoking cessation program or another clinical trial

Pulvers 2018 *(Continued)*

- Past 30 day use of nicotine replacement therapy or medication which aids smoking cessation including bupropion, clonidine, nortriptyline, or varenicline
- Having uncontrolled asthma, severe allergies, or diabetes mellitus
- Currently taking prescription medication for emotional distress, depression, or other psychological problems
- Current dependence on a substance other than nicotine
- Presence of any cardiovascular or pulmonary illnesses in the past 6 months
- For women, pregnancy or plans to become pregnant in the next 6 months

Inclusion based on specific population characteristic: No

27% women; mean age 30.08; mean cpd 8.76; FTND not reported

Motivated to quit: over half either did not intend to quit at all or did not intend to quit in the next 6 months 22/40 (55%)

E-cigarette use at baseline: Inclusion criteria included the following:

- Never using EC regularly (less than 25 lifetime uses)
- Not having used EC on more than 3 of the past 30 days

Interventions	**EC: Refillable** 2nd generation EC starter kit with 2 e-Go C batteries (3.7 volts/650 MaH), a USB connection cord, an AC adapter, and a carrying case, and a supply of Saturn V4i atomizers (2.4 ohms) filled with liquid in their preferred flavor (28 atomizers total; 2/day). Provided 24 mg/mL dosage vegetable glycerin liquid in a tester sample to all participants. Those who reported the 24 mg was too strong were provided 12 mg/mL dosage liquid. The first session included brief education, training, action planning for making a complete switch to EC. A referral to the California Smokers' Helpline was made at the final visit (week 4).

Outcomes	3 lab visits (baseline, week 2, and week 4) and 2 phone visits (week 1 and week 3). Biological samples were taken at all 3 in-person visits (baseline, week 2, and week 4). However, due to budgetary restrictions, only the baseline and week 4 biological data were analyzed
	
	Adverse events and biomarkers:
	
	• Biochemical measures only: Breath samples were taken with a Micro + (Bedfont, Haddonfield, NJ) to measure CO
	• Urine samples taken to test for change in tobacco toxicant exposure by following measures:
	  * concentrations of NNAL measured by liquid chromatography–tandem mass spectrometry (LC–MS/MS)
	  * metabolites of a panel of potentially toxic VOCs, including benzene (PMA), ethylene oxide (HEMA), N-nitrosodimethylamine (MMA), acrylonitrile (CNEMA), acrolein(3-HPMA), propylene oxide (2-HPMA), acrylamide (AAMA), and crotonaldehyde (HPMMA) measured by LC–MS/MS,2
	
	Other outcomes measured:
	
	Cotinine, change in tobacco consumption (cpd using TLFB interview), change in frequency of EC use, change in nicotine dependence and attitudes/behavior, change in 30-day nicotine exposure

Study funding	"This study was funded by the University of Minnesota (JSA), P30 DA012393 (NLB), P50 CA180890 (NLB), and California State University San Marcos (KP)."
Author declarations	"Benowitz is a consultant to pharmaceutical companies that market smoking cessation medications and has been an expert witness in litigation against tobacco companies. The other authors have no conflicts of interest."
Notes	New for 2020 update

Pulvers 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not randomized
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	37/40 provided follow-up data
Selective reporting (reporting bias)	Low risk	All outcomes reported

Pulvers 2020

Study characteristics

Methods	Design: RCT. Unblinded. 2:1 ratio Recruitment: Participants were recruited from the San Diego, California, and Kansas City, Missouri and Kansas, metropolitan areas Setting: USA Study start date: May 2018. Study end date: May 2019
Participants	Total N = 186; Electronic-cigarettes = 125. Own brand cigarette = 61 40.3% female; mean age 43.3 (SD 12.5); mean cpd 12.1 (SD 7.2). E-cigarettes use at baseline: 0.05 (0.3%) Inclusion criteria: • > 21 years of age • Smoked cigarettes on > 25 of past 30 days • Smoked > 5 cigarettes per day on days smoked • Smoked cigarettes > 6 months • Carbon monoxide > 5 PPM at baseline • Systolic BP of < 160 mmHg and diastolic BP of < 105 mmHg at baseline • · Hispanic/Latino or African American/Black • · Fluent in English or Spanish • · Willing to switch from smoking cigarettes to ECs for 6 weeks • · Regular access to telephone • · Transportation to attend appointments (KC Only) Exclusion criteria: • Primary use of other tobacco products or equal use of cigarettes and other tobacco products • Electronic cigarette use on > 4 of the past 30 days • Currently in a smoking cessation program or another clinical trial • Use of nicotine replacement therapy or medication which aids smoking cessation in the past 30 days • Hospitalization for a psychiatric issue in the past 30 days

Pulvers 2020 *(Continued)*

	• Heart-related event in the past 30 days. Examples include heart attack, stroke, severe angina (i.e. chest pain), ischemic heart disease, and vascular disease • Uncontrolled blood pressure at baseline • Planning to move out of study centers (San Diego or Kansas City) in the next 6 weeks • Another person in the household enrolled in the study • Women: pregnant, breast-feeding, or planning to become pregnant in the next 6 months • Unstable mental status or health status
Interventions	**EC: pod** **Electronic-cigarettes**: JUUL (5% nicotine); Choice of flavors (Menthol, Mango, Cool Mint, Virginia Tobacco); Given 1 pod per pack of cigarettes; Given a 2-week supply at baseline and then a further 4-week supply at week-2 visit. At each follow-up appointment (week 1, telephone call; week 2, in-person visit; and week 4, telephone call), barriers and benefits of switching to e-cigarette were discussed and action planning for exclusive switching was revisited. Compensated on a schedule of USD 20 at baseline, USD 40 at week 2 and USD 60 at week 6 **Own brand cigarettes**: Compensated on a schedule of USD 20 at baseline, USD 40 at week 2 and USD 60 at week 6
Outcomes	Baseline, week 2 and week 6. Telephone survey at 6 months Change in past 7-day combustible cigarette use measured by 7-day timeline follow-back interview 30-day point prevalence at 6 months (EC group only) • reduction in toxicant exposure, as measured by NNAL excretion. • Cotinine • CO Lung function; Pulmonary function test of small airway disease that is most sensitive to effects of cigarette smoking; mean midexpiratory phase of forced expiratory (FEF25%-75%); respiratory symptoms as measured with the American Thoracic Society Questionnaire (scores range from 0 - 32, with higher scores indicating greater respiratory symptoms) Blood pressure Adverse events: respiratory symptoms
Study funding	Drs Pulvers and Nollen and Ms Rice were supported by grant No. 5SC3GM122628 from the National Institutes of Health (NIH). Drs Schmid and Ahluwalia were supported in part by grant No. P20GM130414, from the NIH-funded Center of Biomedical Research Excellence (COBRE). Dr Schmid was partially supported by Institutional Development Award No. U54GM115677 from the National Institute of General Medical Sciences of the NIH, which funds Advance Clinical and Translational Research (Advance-CTR)
Author declarations	Dr Schmid reported serving as a consultant for legal firms representing Eli Lilly, Boehringer-Ingelheim, and Gilead outside the submitted work. Dr Benowitz reported receiving personal fees from Pfizer and Achieve Life Sciences and serving as a consultant to pharmaceutical companies that market smoking cessation medications and as an expert witness in litigation against tobacco companies outside the submitted work. Dr Ahluwalia reported receiving personal fees from Lucy Goods outside the submitted work. No other disclosures were reported.
Notes	New for 2021 update. Additional data provided by authors

Risk of bias

Bias	Authors' judgement	Support for judgement

Pulvers 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization sequence was generated with an Excel (Microsoft) random number formula applied to each site (2:1 ratio)
Allocation concealment (selection bias)	Low risk	Allocation was placed into sealed individual envelopes labeled with participant identification numbers for each site, retrieved from a locked cabinet monitored by the project manager, and opened individually following consent of each participant
Blinding of participants and personnel (performance bias) All outcomes	High risk	Could not be blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Carbon monoxide validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	E-cig: 115/126 OB: 54/61
Selective reporting (reporting bias)	Low risk	Per protocol reporting

Scheibein 2020

Study characteristics	
Methods	Design: Non-randomized single-arm Recruitment: From supported temporary accommodation (STA) service STA project workers and support staff identified potential study participants who smoked and wished to quit Setting: Dublin Simon Community, Ireland Study start date: Recruitment February 2019 (overall trial start date March 2018). Study end date: June 2019
Participants	Total N: 23 but only report baseline for the 9 that completed the study. % female 8.7% (2/23) at baseline, (22.2% 2/9) completed and reported; mean age 43.89 (SD 7.36); mean cpd 25.22 (SD 7.77); mean FTND 7.89 (SD 1.2); mean CO 21.89 (SD 14.4 corresp) E-cigarettes use at baseline: no Motivated to quit: yes Inclusion criteria: • > 5 CO ppm (carbon monoxide) • Active smoking status • Expressed intention to quit using ENDS-device Exclusion criteria: • Self-reported pregnancy • Exhibition of florid psychotic or substance use-related symptoms which could have affected ability to consent

Scheibein 2020 *(Continued)*

Interventions	**EC: Refillable** Electronic-cigarette: Endura T22e Electronic Nicotine Delivery System and 2 10 ml bottles of fluid strengths (0, 6, 11, 18 and 20 mg/ml) and flavors ('Purple Berry', 'Ice Menthol', 'Regular Blend' and 'American Tobacco')
Outcomes	Baseline (‘week 1’), week 4, week 8, week 12: CO, adverse events Also number of cigarettes smoked; Fagerström Test Scores
Study funding	This study was completed as part of a Tobacco Harm Reduction Scholarship funded by Knowledge Action Change
Author declarations	FS was a recipient of a Tobacco Harm Reduction Scholarship provided by Knowledge Action Change. He is currently the recipient of an Enhanced Scholarship from the same organization. AM and KM acted as mentors for both the Tobacco Harm Reduction Scholarship and Enhanced Scholarship. AM is an associate of New Nicotine Alliance. KM is a recipient of a grant from the Foundation for a Smoke Free World. JW declares no interests. WR declares no interests
Notes	New for 2021 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Only 1 arm
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not randomized
Blinding of outcome assessment (detection bias) All outcomes	High risk	Self-reported adverse events
Incomplete outcome data (attrition bias) All outcomes	High risk	9/23 completed. Reason was many people moved away so not linked to unacceptability of the study. Incomplete paperwork to enable to be followed
Selective reporting (reporting bias)	Unclear risk	Protocol published afterwards

Smith 2020

Study characteristics

Smith 2020 *(Continued)*

Methods	Design: Double-blind randomized controlled trial Recruitment: Recruited from the local area via advertising on craigslist social media Setting: Laboratory and electronic diaries, USA Study start date/Study end date: Not specified.
Participants	Total N: 30 N per arm: PG/VG ratio 70/30 = NR; PG/VG ratio 50/50 = NR; PG/VG ratio 0/100 = NR Inclusion criteria: • adults age ≥ 18 who have been smoking at least 5 cigarettes daily for the past year (expired CO > 8) • usual brand is non-menthol • use of ENDS on 5 or fewer lifetime occasions • regular use of e-mail or smartphone ownership with capacity to receive SMS text and internet access (necessary for electronic diaries) Exclusion criteria: • unwilling to use ENDS as part of the trial • use of smokeless, hookah, or tobacco products other than cigarettes ≥ 10 days in the past 30 days • pregnant, trying to become pregnant, or breastfeeding • recent history of cardiovascular distress in the last 3 months (arrhythmia, heart attack, stroke, uncontrolled hypertension) • current use of cessation medications • another household member currently enrolled in the study (to prevent contamination of e-liquid assignment during sampling) 30% women; mean age 43.7; mean cpd 18.5; mean FTND 5.4 Motivated to quit: Not specified E-cigarette use at baseline: Participants had used an e-cigarette an average of 1.6 times in their life, and no one reported use in the last 30 days
Interventions	**EC: Cig-a-like** EC provided for 1 week. All aspects of the ENDS device and e-liquid were held constant between groups with the exception of PG/VG ratio: **PG/VG ratio 70/30; PG/VG ratio 50/50; PG/VG ratio 0/100.** Ego-T 1100 mAh battery and disposable cartomizers (510 Smoketech, 1.5-Ω dual coil). E-liquid was tobacco-flavored (Classic Tobacco, American E-liquid) and contained 18 mg nicotine/ml
Outcomes	1 week; 2 lab visits pre and post and participant diaries Adverse events and biomarkers: Participants provided a CO sample at each visit Other outcomes measured: cpd, ENDS puffs
Study funding	Funding for this project was provided by pilot funding from the National Cancer Institute (P01CA200512 to K.M.C.). Salary support provided by the National Institute on Drug Abuse (K12DA031794 to T.T.S., K23DA041616 to B.W.H.)
Author declarations	M.J.C. has received consulting honoraria from Pfizer. K.M.C. has received payment as a consultant to Pfizer, Inc., for service on an external advisory panel to assess ways to improve smoking cessation delivery in health care settings. He also has served as paid expert witness in litigation filed against the tobacco industry

Smith 2020 *(Continued)*

Notes	Additional data provided from authors. New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "At the conclusion of the lab visit, participants were randomized and assigned to take home one of the three e-liquids to use at home for a 1-week sampling period (10 participants/ratio)." Quote: "Participants were randomly assigned to receive one e-liquid to take home for 1 week." (no further detail given)
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "PG/VG ratio was blinded from participant and staff members who conducted experimental sessions."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of participants at follow-up not reported, but this may be due to the 1-week follow-up and it seems that all participants (excluding 1 participant who was not randomized) were followed up
Selective reporting (reporting bias)	Unclear risk	No protocol. Few details for CO measurements, just percentage change for each group, but mean CO data provided by author on request

Stein 2016

Study characteristics

Methods	Design: Non-controlled open-label experimental study Recruitment: A flyer posted at a large methadone maintenance treatment program Setting: Methadone maintenance treatment program, USA Study start date: April 2015; Study end date: Not specified
Participants	Total N: 12 Inclusion criteria: • current moderate or heavy cigarette use (10+ cpd for at least 12 months prior to enrolment) • current MMT for at least 3 months • ready to make a smoking quit attempt in the next 14 days • plan to remain on MMT for at least 12 weeks Exclusion criteria: • used e-cigarettes on more than 2 of the past 30 days • currently used medications that may reduce smoking (bupropion, varenicline, NRT)

Stein 2016 *(Continued)*

	• had unstable medical or psychiatric conditions (past-month suicidal ideation or past-year suicide attempt, hospitalization for myocardial infarction or stroke in the prior 3 months) • had regular use of marijuana (self-report or positive urine drug test) Inclusion based on specific population characteristic: People receiving MMT for opoid use disorder 50% women; mean age 45.9; mean cpd 17.8; mean FTND: Not reported Motivated to quit: yes E-cigarette use at baseline: Had not used e-cigarettes for more than 2 of the past 30 days
Interventions	**EC: Cig-a-like** 2 week supply of NJOY e-cigarettes at week 1 (quit day), consisting of 5 packs of NJOY e-cigarettes (15 in total). Participants could request an additional 5 pack (20 in total) for the following 2-week study period, if they ran out before a study visit. Participants instructed to use EC exclusively for a total of 6 weeks (end of treatment). They were referred to the state telephone QuitLine for supportive counseling at the quit-day visit (week 1)
Outcomes	Participants quit and received e-cigs at week 1. Assessments were carried out at week 3, 5, 7 and 9 Adverse events and biomarkers: • "Side effects" of e-cigarettes were recorded. Side effects were rated none, slight, mild, moderate and severe at every assessment visit. An adverse effect possibly related to e-cigarette use was defined as positive if the value at baseline was either none or slight AND the value at any of 3, 5, or 7 weeks was mild or more severe Other outcomes measured: • Reduction in the average cpd • E-cig adherence • Nicotine withdrawal
Study funding	"MDS is a recipient of National Institute on Drug Abuse Award K24 DA000512. This award funded the project described here."
Author declarations	"None declared."
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One individual dropped out after week 3 and did not return; another completed all follow-up assessments except week 7."
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Strasser 2016

Study characteristics	
Methods	Design: Randomized, factorial trial (Participants were randomized to one of the 5 brands of e-cigarettes – although only 4 brands analyzed) Recruitment: Media ads Setting: Recruitment from the community, study took place at University, USA. Study start date/Study end date: Not specified.
Participants	Total N: Analysis based on 24 (28 originally recruited, but the first 4 participants enrolled experienced malfunctioning NJOY e-cigs and withdrew – the project was removed from the market before the 5th participant was randomized) N per arm: blu: 6; Green Smoke: 6; V2: 6; White Cloud: 6 Inclusion criteria: • Age 18 to 65 and self-reported smoking at least 10 cigarettes per day. Exclusion criteria: • Use of other tobacco or nicotine-containing products, including e-cigarettes (no more than 3 previous episodes of use and not currently using) • Current diagnosis or evidence of substance abuse or dependence or major depression • Current or history of psychotic or bipolar disorder • History of suicide attempt • History of cancer or cardiovascular disease • Uncontrolled hypertension • Use of smoking cessation medications • Any current plans to try to quit smoking • Current pregnancy or lactation Inclusion based on specific population characteristic: Not applicable 29% women; mean age 43.3; mean cpd 17; mean FTND 3.7 Motivated to quit: Participants had no current plans to try to quit smoking (eligibility criterion) E-cigarette use at baseline: No more than 3 previous episodes of use and not currently using (eligibility criterion)
Interventions	**EC: Cig-a-like** All participants received nicotine EC and were instructed to use them exclusively for 9 days The 5 brands selected, including brand reported nicotine levels, were: (1) NJOY (18mg nicotine) – this brand was discontinued and not analyzed as the e-cigs provided malfunctioned; (2) V2, 18 mg nicotine; (3) Green Smoke, 18.9 - 20.7 mg nicotine; (4) blu, 20 - 24mg nicotine; and (5) White Cloud, 23 - 24 mg nicotine. Each brand advertised the delivery of the same level of nicotine (appropriate for about a pack/day smoker), provided the standard tobacco flavor (no other flavors made available), and used a disposable cigarette-like device
Outcomes	Day 10 is the only testing point of interest for us but participants were also tested at days 1 and 5 Adverse events and biomarkers: • breath CO

Strasser 2016 *(Continued)*

- direct effects of nicotine (e.g. dizzy, nauseas, headache) - visual analogue scale with a single word scored from 0 (not at all) to 100 (extremely). Total scores were summed such that higher scores indicated negative responses

Other outcomes measured:

- e-cigarette use
- direct effects of the e-cigarette (e.g. satisfying, calming, pleasant, smoke another right now) - visual analogue scale with a single word scored from 0 (not at all) to 100 (extremely). Total scores were summed such that higher scores indicated positive responses
- cotinine
- withdrawal and craving

Study funding	"National Cancer Institute (NCI) of the National Institutes of Health (NIH) and FDA Center for Tobacco Products (CTP) under Award Number P50CA179546, as well as grants from the National Cancer Institute (P50 CA143187, P30 CA16520, and P30 DA12393)"
Author declarations	"Dr Benowitz has served on scientific advisory boards for Pfizer and GlaxoSmithKline related to smoking cessation medications and has been an expert witness in litigation against tobacco companies. Dr Schnoll receives medication and placebo free of charge from Pfizer and has provided consultation to Pfizer and GlaxoSmithKline. These companies had no involvement in this study. Dr Strasser has received funding through the Pfizer GRAND program, an independent peer-reviewed grant program funded through Pfizer (2008-2011); all investigators have received funding from the United States National Institutes of Health"
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Although participants were randomized to different brands of EC, no description on how randomization was carried out
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of whether groups were blind to other conditions, but given similar levels of support between arms, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear whether any blinding took place, some outcomes were measured using objective measures and there was no difference in contact between arms
Incomplete outcome data (attrition bias) All outcomes	High risk	For blu, Green Smoke, and V2 groups, 83% of participants completed the 10-day study; only 33% of participants randomized to White Cloud completed the 10-day study; meaning loss to follow-up was considerably higher in this group
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Tseng 2016

Study characteristics

Tseng 2016 *(Continued)*

Methods	Design: 2-arm; double-blind placebo-controlled RCT Recruitment: Advertisements placed in Craigslist as well as flyers distributed on the street and placed in New York City venues with details for how to contact study staff. Setting: Community, USA Study start date: July 2014 – 2015 (month unclear); Study end date: Not specified
Participants	Total N: 99 (100 were randomized but 1 participant randomized to the control arm was found to be ineligible between randomization and baseline) N per arm: Nicotine EC: 50; Placebo EC: 49 Inclusion criteria: • age 21 – 35 (confirmed with some form of identification document) • daily smoker • smoked ≧ 10 cigarettes a day (verified by a CO level of ≥ 8 ppm) • interested in reducing cigarette consumption • able to provide consent • had a cell phone and was willing/able to receive text messages and counseling on their cell phone • willing to use an EC for 3 weeks Exclusion criteria: • Pregnant and/or breastfeeding • had a history of asthma, other airways diseases, or heart disease • were currently using smoking cessation medications (including other forms of NRT, bupropion, or varenicline), or enrolled in a smoking cessation program or another cessation trial. • Use of EC in the past 14 days or any other tobacco products (pipe, cigar, cigarillos, snuff, chewing tobacco, rolling tobacco, or hookah/shisha) in the past 30 days • having a moderate to severe drug use disorder defined as a score of at least 5 on the Drug Abuse Screening Test-10 and/or a hazardous or active alcohol use disorder defined as at least 7 for men and at least 5 for women on the Alcohol Use Disorders Identification Inclusion based on specific population characteristic: Young adults 32.3% women; mean age 28.43; mean cpd 14.33; FTND not measured but time to first cigarette was measured categorically. The mode category was 6 - 30 mins (39/99; 41.5%) Smoking behavioral dependence scale (11 items): mode category 'Moderate' (51/99; 51.5%) Motivated to quit: Readiness to quit (1 – 10 scale, 1 – 8 apply to current people who smoke): 5.57 ± 1.49 E-cigarette use at baseline: No use of e-cigs in past 14 days (eligibility criterion)
Interventions	**EC: Cig-a-like** E-cigarette details: 3 weeks of disposable 4.5% nicotine NJOY, King Bold (NJOY, Inc, Scottsdale, AZ) which resemble conventional cigarettes. NJOY also manufactured the non-nicotine placebo EC. Both nicotine and placebo ECs were tobacco-flavored. The products were purchased by the investigators and provided to the participants free of charge Other stop-smoking pharmacotherapies: None Behavioural support: Prior to receiving the ECs, participants were required to complete a 20- to 30-minute telephone counseling session with a trained tobacco cessation Counsellor. The purpose of the telephone counseling was to review current smoking patterns and offer behavioral and environmental change strategies.

Tseng 2016 *(Continued)*

	These included specific smoking reduction options, such as eliminating cigarettes at work and in the home, carrying only those cigarettes needed for that day, dropping cigarettes associated with less intense triggers first, avoiding smoking triggers, and other strategies to manage urges.18 participants were asked to reduce the number of cigarettes smoked daily by at least 50% of the total number of cigarettes smoked per day at baseline. To mimic real-life EC use, minimum EC use instruction was provided. Participants were encouraged to replace cigarettes with as much or as little use of an EC as needed in order to reduce nicotine withdrawal symptoms
Outcomes	Week 1, 3 Cessation: Not applicable Adverse events and biomarkers: adverse events and symptoms related to EC use Other outcomes measured: • self-reported reduction of at least 50% in the number of cpd • percentage reduction in number of cpd • Use of ECs • satisfaction with ECs
Study funding	"This work was supported by the National Center for Advancing Translational Sciences at the National Institutes of Health (grant number UL1TR000038)."
Author declarations	"None declared"
Notes	Study listed as ongoing study NCT02628964 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer generated"
Allocation concealment (selection bias)	Unclear risk	Quote: "…was concealed from research assistants. Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs". However, not enough information given on how allocation was concealed at the point of randomization
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Blinding of the allocation of nicotine or placebo EC was ensured by the identical appearance of the ECs"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nicotine EC ltfu: 10/50; Placebo EC ltfu: 10/49
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Valentine 2018

Study characteristics	
Methods	Design: Open-label prospective cohort study Recruitment: Recruited from within the Department of Veterans Affairs (VA) Connecticut Healthcare System by word of mouth Setting: Receiving psychiatric services from Department of Veterans Affairs healthcare system, USA Study start date/Study end date: Not specified.
Participants	Total N: 50 (sample analyzed for primary outcomes on week 1 completers – N = 43) Inclusion criteria: • Without an immediate intention to stop smoking • Smoking history of at least 5 cigarettes a day for the past year Exclusion criteria: • Current untreated medical or psychiatric or substance use disorders, or both, as determined by a review of the veteran's electronic medical record • current use of nicotine replacement or other cessation pharmacotherapies • use of e-cigarettes or smokeless tobacco products for more than 2 of the past 30 days Inclusion based on specific population characteristic: Military veteran people who smoke who had no immediate intention to stop smoking and were currently receiving psychiatric services from the Department of Veterans Affairs healthcare system. 7% women; mean age 56.9; mean cpd 16.6; mean FTND 4.9 Motivated to quit: Had no immediate intention to stop smoking E-cigarette use at baseline: E-cigarettes or smokeless tobacco products may have been used for less than 2 of the past 30 days
Interventions	**EC: Refillable** All given eVic Supreme (Joyetech), "a commercial, variable-power, tank-type device". 6.5 mL tank (Delta 23, Joyetech) and a C3 triple coil atomizer head (Joyetech) with a total resistance of 1.8 ohms. Participants could choose flavor (menthol or tobacco) and nicotine concentration (12 or 24 mg/mL). Participants taught how to use EC, with additional materials dispensed as needed. Participants were informed that they could use the study e-cigarette or regular tobacco cigarettes, or both, ad libitum during study participation
Outcomes	Week 1, 2, 3, 4, 8 (Weekly lab visits and 1 month follow-up) Adverse events and biomarkers: Alveolar (breath) CO levels (ppm) Other outcomes measured: • Number of cpd • The frequency of e-cigarette use (mean days/week) • The amount of money spent on combustible cigarettes (US dollars/week) • Fagerström Test of Nicotine Dependence • Contemplation Ladder • E-cigarette questionnaire (assessed changes in perceptions about e-cigarettes (e.g. harmfulness, benefits, cost), motivations to use (or not use) them, and the reasons for e-cigarette or combustible cigarette preferences) (measured at baseline and follow-up) • Cotinine

Valentine 2018 *(Continued)*

Study funding	"This research was supported by the New England Mental Illness Research, Education and Clinical Center and the U.S. Department of Veterans Affairs. Statistical analyses, biochemical assays, and analyses of e-cigarette solutions were supported by the Administrative and Laboratory cores of P50DA036151 (Yale TCORS) from the National Institutes of Health and the U.S. Food and Drug Administration Center for Tobacco Products. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or of the U.S. Food and Drug Administration."
Author declarations	"Ralitza Gueorguivea, PhD, discloses consulting fees for Palo Alto Health Sciences and Mathematica Policy Research and a provisional patent submission by Yale University: Chekroud, A. M., Gueorguieva, R., & Krystal, K. H. “Treatment Selection for Major Depressive Disorder” (filing date June 3, 2016, USPTO docket number Y0087.70116US00). The authors report no other financial relationships with commercial interests."
Notes	New for 2020 update.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Uncontrolled cohort study
Allocation concealment (selection bias)	High risk	Uncontrolled cohort study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Follow-up: 31/50 at week 8
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial record.

Van Staden 2013

Study characteristics

Methods	Design: Single-group within-subject design Recruitment: Participants from a military hospital in South Africa Setting: South Africa Study start date/ end date: Not specified
Participants	Total N: 15, mean age 38 years, smoked 20 cpd (range 10 - 30), for an average of 17 years (range 5 - 27) Total N: 13 completed the study (5 women) Inclusion criteria: • Adults who smoke daily, of at least 10 cpd Exclusion criteria: • History of lung disease Inclusion based on specific population characteristic: No

Van Staden 2013 *(Continued)*

	Motivated to quit: Not specified E-cigarette use at baseline: Not specified
Interventions	**EC: Cig-a-like** Participants were asked to use an EC only for 2 weeks (i.e. no cigarettes) EC: 'Twisp eGo' cartridge 0.8 ml containing 0.0144 mg of nicotine
Outcomes	The following measurements were taken at baseline and 2-week follow-up: • Blood pressure and pulse • Arterial and venous COHb and blood oxygen saturation
Study funding	"We are grateful for the sponsorship of the eGo e-cigarette packs by Twisp and also for the valuable advice and laboratory assistance given by Col. (Dr) J Lubbe, Chemical Pathologist, 1 Military Hospital, Pretoria with regard to the measurement of the cotinine levels. We also wish to acknowledge Professor Martin Veller for his insightful contributions during the preparation of this manuscript and also Dr Richard van Zyl-Smith for his assistance and review."
Author declarations	"The sponsor of the Twisp e-cigarette had no role in the design and conduction; the collection, analysis and interpretation of the study; or in the preparation, review or approval of the manuscript."
Notes	Dropouts (N = 2) were due to illness (headache and fever) and undertaking a military course associated with high stress and exposure to others smoking, making it difficult to abstain from cigarettes The paper states that the EC cartridge contained 0.8 ml of solution with 0.0144 mg of nicotine. This would be an unusually low concentration of nicotine and we have assumed an error in units where milligrams should have been grams (0.0144 grams of nicotine would make the concentration 18 mg/ml)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/15 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Veldheer 2019

Study characteristics

Methods	Design: Randomized parallel-assignment double-blind trial Setting: USA (2 sites) Recruitment: Community advertisements

Veldheer 2019 *(Continued)*

	Study start date: June 2015; Study end date: June 2018.
Participants	Estimated enrolment: 520 Total N: 263 in this analysis (520 planned overall; THIS INCLUDES ONLY THOSE FOLLOWED UP AT 1 AND 3 MONTHS) N per arm: sub: 72; EC: 191 Inclusion criteria: • Age 21 - 65 • Smoke > 9 cigarettes per day for at least 1 year • Smoke regular filtered cigarettes or machine-rolled cigarettes with a filter • CO measurement > 9 ppm at baseline • No serious quit attempt in the prior 1 month. This includes use of any FDA-approved smoking cessation medication (varenicline, bupropion (used specifically as a quitting aid), patch, gum, lozenge, inhaler, and nasal spray) in the past 1 month as an indication of treatment-seeking • Not planning to quit in the next 6 months • Interested in reducing cigarette consumption • Willing to attend visits weekly and monthly over a 9-month period (not planning to move, not planning extended vacation, no planned surgeries) • Read and write in English • Able to understand and consent Exclusion criteria: • Pregnant and/or nursing women • Unstable or significant medical condition in the past 12 months (recent heart attack or some other heart conditions, stroke, severe angina including high blood pressure if systolic > 159 or diastolic > 99 observed during screening) • Immune system disorders, respiratory diseases (exacerbations of asthma or COPD, require oxygen, require oral prednisone), kidney (dialysis) or liver diseases (cirrhosis), or any medical disorder/medication that may affect participant safety or biomarker data • Use of any non-cigarette nicotine delivery product (pipe, cigar, dip, chew, snus, hookah, e-cigs, strips, sticks) in the past 7 days • Uncontrolled mental illness or substance abuse or inpatient treatment for these in the past 6 months • History of difficulty providing or unwilling to provide blood samples (fainting, poor veins, anxiety) • No surgery requiring general anesthesia in the past 6 weeks • Use of an e-cig for 5 or more days in the past 28 days or any use in the past 7 days • Use of marijuana or any illicit drug/prescription drugs for non-medical use daily/almost daily, or weekly in the past 3 months per NIDA Quick Screen • Use of hand-rolled, roll-your-own cigarettes • Known allergy to propylene glycol or vegetable glycerin • Other member of household is currently participating/participated in the study 58% women; mean age 47; mean cpd 18; mean FTND: Not specified Motivated to quit: Interested in reducing cigarette intake but not planning to quit in next 6 months E-cigarette use at baseline: None
Interventions	**EC: Cig-a-like** For 24 weeks: 1) **Cigarette substitute**: QuitSmart cigarette substitute - plastic tube looks like a real cigarette, designed to provide the same draw resistance as a smoker's usual cigarette. No drug delivery. 2 cigarette substitutes and a product manual are provided to participants following randomization and replace-

Veldheer 2019 *(Continued)*

	ment products are provided throughout the intervention period (24 weeks). At baseline, associated user manual, research staff explain how to use product. Reduction goal to 50% at weeks 0 and 1, 75% at weeks 2 and 4, continue reducing onwards from there 2) **EC with no nicotine**: EGO e-cigarette. Cartomizers containing 0 mg/ml nicotine provided throughout the intervention period (24 weeks) Associated user manual, research staff explain how to use product. 3) As (2) but 8 mg/ml nicotine 4) As (2) but 36 mg/ml nicotine
Outcomes	Months 1, 3, 6, 9; (only 1 and 3 month available at time of extraction) Cessation: Conventional tobacco product use measured but measures not clear Adverse events and biomarkers: • Adverse events • Lung function • Blood pressure, pulse • CO, "exhaled breath condensate biomarkers of oxidative stress, glutathione and 8 Isoprostanes" – incl. carcinogenic nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK; via its metabolite NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) in urine], expired air carbon monoxide (CO), and nicotine (via its metabolite cotinine in urine) Other outcomes measured: • Weight • Cotinine • Tobacco use
Study funding	This study was funded by the National Institutes of Health (NIH) and the U.S. Food and Drug Administration (FDA) under Award Number P50DA036105. The content is solely the responsibility of the authors and does not necessarily represent the views of the NIH or FDA. The project [publication] was supported by CTSA award No. UL1TR000058 from the National Center for Advancing Translational Sciences. Its contents are solely the responsibility of the authors and do not necessarily represent official views of the National Center for Advancing Translational Sciences or the National Institutes of Health.
Author declarations	JF has done paid consulting for pharmaceutical companies involved in producing smoking cessation medications, including GSK, Pfizer, Novartis, J&J, and Cypress Bioscience. TE is a paid consultant in litigation against the tobacco industry and is named on a patent application for a device that measures the puffing behavior of electronic cigarette users. There are no competing interests to declare for other authors
Notes	Preliminary data from RCT; full results not yet available EC arms pooled in preliminary data available to us at time of writing Authors provided outcome data; Study listed as ongoing study Lopez 2016 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the assignment codes are made from separate randomization lists created in advance by the statistician for each site stratum."
Allocation concealment (selection bias)	Low risk	Quote: "Once a participant has been confirmed eligible for randomization, a computer procedure will assign the participant to the next condition on the list automatically."

Veldheer 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not blinded for non-EC arms but given similar level of support/product, so performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not blinded for non-EC arms but given similar level of support/product, so differential misreport judged unlikely
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dataset only includes those followed up at 1 and 3 months, which excludes 140 participants; breakdown by arm not provided
Selective reporting (reporting bias)	High risk	Results paper just preliminary results with all EC arms collapsed. Protocol and NCT record list different outcomes and study lengths.

Wadia 2016

Study characteristics	
Methods	Design: Uncontrolled experimental study Recruitment: Dental hospital staff were recruited – not specified how Setting: Dental hospital, UK Study start date: April 2015; Study end date: December 2015
Participants	Total N: 20 (18 of the 20 attended the reassessment visit) Inclusion criteria: • 18 - 65 years old • Systemically healthy • Smoked at least 10 cigarettes per day for at least 5 years • had at least 24 natural teeth (excluding third molars) and had no probing pocket depths over 4 mm at any site • did not wish to quit Exclusion criteria: • Participants were excluded if they had a systemic condition known to exacerbate or modulate periodontitis (for example, diabetes) • antibiotics had been taken in the previous 3 months • anti-inflammatory drugs or other medication likely to affect the periodontal tissues were taken routinely • if they were pregnant or a nursing mother % women, age, cpd and FTND: not specified. Motivated to quit: enrolled people who smoke who did not intend to quit smoking, but were prepared to attempt to substitute smoking with the use of e-cigarettes for 2 weeks E-cigarette use at baseline: not specified
Interventions	**EC: Refillable**

Wadia 2016 *(Continued)*

	Participants provided with a blu PROTM e-cigarette kit (Electric Tobacconist®), an extra bottle of blu PRO Tobacco™ e-Liquid (Electric Tobacconist) and written instructions. The e-Liquid was Classic Tobacco-flavoured and contained 18 mg of nicotine (medium strength). The participants agreed to substitute their regular smoking habits with the use of e-cigarettes for 2 weeks. They were asked to make a note of any cigarette smoking during the 2 weeks if complete abstinence was unsuccessful
Outcomes	2 weeks Adverse events and biomarkers: adverse effects Other outcomes measured: • Cigarette use • Dental outcomes
Study funding	Not specified
Author declarations	Not specified
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	No randomization
Allocation concealment (selection bias)	High risk	No randomization
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to follow-up
Selective reporting (reporting bias)	Low risk	All expected outcomes reported

Walele 2018

Study characteristics

Methods	Design: RCT (short-term, Cravo 2016) followed by cohort study (Walele 2018) in which all participants were given nicotine EC Recruitment: Community Setting: 2 centres in the UK (Covance Clinical Research Unit Ltd, Leeds and Simbec Research Ltd, Wales) Study start date: December 2013; Study end date: December 2016
Participants	420 participants Inclusion criteria differ per study phase: **Cravo 2016 (short-term RCT):** • 21 - 65 years of age

Walele 2018 *(Continued)*

- BMI 18 - 35 kg/m^2
- 5 - 30 cigarettes per day for at least 1 year (self-reported)
- in good health (determined by medical history, a physical examination, a 12-lead ECG, lung function tests and clinical laboratory evaluations)
- Established people who smoke (urinary cotinine ≥ 3 and exhaled CO ≥ 6 ppm)

Additional criteria for Walele 2018 (participants from Cravo 2016):

- Participants assessed by PI as being compliant in Cravo 2016 (e.g. having attended outpatient visits and having been compliant with study procedures)
- Participants had to be willing to use the study product as the only nicotine-containing product for the duration of the study, and, as deemed by PI, had to have no clinically significant abnormalities in 12-lead electrocardiogram, vital signs, spirometry and clinical laboratory assessments in the preceding study
- In addition, participants who were assigned to the conventional cigarette (CC arm) in Cravo 2016 had to be established people who smoke CCs, which was assessed by urinary cotinine levels (a score of 3 and above on a NicAlert™ test strip was considered positive), eCO levels (a readout > 6 ppm was considered positive) and by review of a smoking history questionnaire

Exclusion criteria:

Cravo 2016:

- Use of NRT, snuff or chewing tobacco in 14 days previous, or intended to use during study
- Trying to stop smoking or considering quitting
- Clinically-significant illness or disorder, history of drug or alcohol abuse within 2 years prior to study start
- Woman of "childbearing potential" unwilling to use "acceptable contraceptive measure" during study

Walele 2018 (participants from Cravo 2016):

- People who had taken or received any form of NRT, snuff or chewing tobacco during the previous study or intended to use it during this study, were excluded
- People with relevant illness history
- People with history of drug or alcohol abuse
- People with lung function test or vital signs considered unsuitable
- People who are trying to stop smoking
- Women who are pregnant, or unwilling to use acceptable contraceptive method for the duration of the study

Cravo 2016

Total N: 419 randomized, 408 analyzed (excludes 11 who were excluded prior to any product use)

N per arm: EVP: 306; Control: 102

45% women; mean age 34.6; Mean cpd: most 11 - 20 cpd (56% int, 62% control); Mean FTND: most moderate (57% int, 54% cont)

Motivated to quit: No

E-cigarette use at baseline: Not excluded based on prior EC use

Walele 2018

Total N: 209 (147 pre-EVP group; 62 pre-CC group)

45% women; mean age 36.6; mean cpd 2.6 (data from figure): Not reported; FTND: Not reported

Motivated to quit: As reported for Cravo 2016

Walele 2018 *(Continued)*

	E-cigarette use at baseline: Not reported
Interventions	**EC: Cig-a-like** **Cravo 2016** **EC**: EVP prototype (2.0% nicotine), developed by Fontem Ventures B.V. (Amsterdam, the Netherlands). Instructed to only use EVP for study period. It consisted of a rechargeable battery (voltage range of 3.0e4.2 V), an atomiser and a capsule (small cartridge) containing e-liquid. The capsules were replaceable and the battery and atomiser were reusable. Could choose between two different e-liquids, which differed solely in their flavor: a menthol-flavored e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule) and a tobacco-flavored e-liquid with 2.0% nicotine (2.7 mg nicotine/capsule) **Control**: Used their own usual conventional cigarette brand **Walele 2018** E-cigarette details: Commercially available Puritane™ (closed system EVP) consists of a lithium-ion rechargeable battery and a replaceable cartomiser comprising of an e-liquid reservoir pre-filled by the manufacturer, a heating element and a mouthpiece; 1.6% nicotine (16 mg/g) Available in tobacco or menthol. 2 weeks before baseline, participants had a familiarization session with Puritane™, where they could see and try the EVP
Outcomes	**Cravo 2016:** Weeks 1, 2, 4, 6, 8, 10 and 12 **Walele 2018:** starting on the last day of the previous trial): Months 1, 2, 3, 6, 9, 12, 15, 18, 21 and 24 Study centre visits for assessments Adverse events and biomarkers: • "adverse events" (coded using Medical Dictionary for Regulatory Activities version 16.1, 2013, collected via diary cards and questionnaires) • vital signs (systolic and diastolic blood pressure, pulse rate and oral temperature) • lung function (FEV, FEF, PEF, FEV) • urine biomarkers (nicotine equivalents (NEQs: nicotine, cotinine, nicotine-N-glucuronide, cotinine-Nglucuronide, trans 3'-hydroxycotinine and trans 3'-hydroxycotinine glucuronide); S-PMA; 3-HPMA; PG; total NNAL (NNAL þ NNAL-glucuronide)); exhaled CO • blood COHb Other outcomes measured: • Number of conventional cigarettes smoked • EVP capsules used • ECG (categorized them as normal, abnormal-not clinically significant (NCS) or abnormal-clinically significant (CS)) • MWS-R (revised Minnesota Nicotine Withdrawal Scale) • QSUBrief (Brief Questionnaire of Smoking Urges) questionnaires • clinical chemistry (blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase (GGT), sodium, potassium, chloride, calcium, inorganic phosphate, glucose, urea nitrogen (BUN), total bilirubin, creatinine, total protein, albumin, cholesterol (HDL, LDL, and total));clinical haematology (white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit (PCV), mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), platelet count, differential WBC);urinalysis (pH, protein, glucose, ketones, urobilinogen, blood and specific gravity)
Study funding	**Cravo 2016** "This work was funded and supported by Fontem Ventures B.V. Imperial Brands plc is the parent company of Fontem Ventures B.V. the

Walele 2018 *(Continued)*

	manufacturer of the EVP prototype used in this study" **Walele 2018** "This work was funded and supported by Fontem Ventures B.V. Imperial Brands Group plc is the parent company of Fontem Ventures B.V., the manufacturer of the EVP used in this study"
Author declarations	**Cravo 2016** "Dr. Cravo has nothing to disclose. Mrs Martin reports personal fees from Fontem Ventures B.V. during the conduct of the study; personal fees from Tobacco and pharmaceutical industries outside the submitted work. Dr. Sharma reports other from Fontem Ventures B.V. during the conduct of the study. Dr. Bush reports other from Fontem Ventures B.V. during the conduct of the study. Mrs Savioz reports personal fees from Fontem Ventures B.V. during the conduct of the study; personal fees from Tobacco and pharmaceutical industries outside the submitted work. Mr Craige has nothing to disclose. Mr Walele has nothing to disclose." **Walele 2018** (copied from Transparency documents) "Dr. Koch reports other from Fontem Ventures B.V., during the conduct of the study; Dr. Martin reports personal fees from Fontem Ventures B.V., during the conduct of the study; personal fees from Tobacco and pharmaceutical industries, outside the submitted work; Dr. O'Connell has nothing to disclose. Dr. Bush reports other from Fontem Ventures B.V., during the conduct of the study; Dr. Savioz reports personal fees from Fontem Ventures B.V., during the conduct of the study; personal fees from Tobacco and pharmaceutical industries, outside the submitted work; Dr. Walele has nothing to disclose."
Notes	Sponsor: Imperial Tobacco Group PLC Study listed as ongoing studies NCT02029196 and NCT02143310 in 2016 review update. Treated as single study in this review due to including the same participants, and no time lag between studies "The same subjects who participated in our previous clinical trial (ClinicalTrials.gov, #NCT02029196) conducted in the same centres, with another EVP (Cravo et al., 2016), were invited to participate the study by Walele 2018. All volunteering subjects were assigned to switch to using Puritane™, a closed system EVP, for two years, starting on the last day of the previous trial (End of Study [EoS] visit), which corresponded to the baseline visit of Walele 2018."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation was performed using an Interactive Web Response System (IWRS; Almac Clinical Technologies)”
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation was performed using an Interactive Web Response System (IWRS; Almac Clinical Technologies)”
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label, no blinding, differential levels of support/product use so performance bias cannot be ruled out
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label, no blinding, with differential levels of support/product use and subjective outcomes

Walele 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Cravo: 286/306 int (4.5% ltfp) and 101/102 (1% ltfp) control completed study but all who received product included in analysis. In EVP group, 14 withdrew consent, 2 experienced AEs, 1 death, 3 "other". CC group 1 AE Walele 2018: High 209/387 enrolled for study Walele 2018. A total of 102 participants (48.8%; EVP: 75/145 (51%); CC: 27/61 (43.5%) completed the study
Selective reporting (reporting bias)	Low risk	Cravo 2016: Low All anticipated outcomes reported (study registered prior to study completion) Walele 2018: Low All anticipated outcomes reported (study registered prior to study completion)

Walker 2020

Study characteristics	
Methods	Design: RCT Recruitment: National media advertising Setting: Community based, New Zealand Study start date: Recruitment between March 2016; Study end date: Aug 2018
Participants	N per arm: Patches-only group: 125; Patches plus nicotine e-cigarette group: 500; Patches plus nicotine-free e-cigarette group: 499 Inclusion criteria: • Eligible if they were living in New Zealand • 18 years or older • smoked tobacco (amount not specified) • Motivated to quit in the next 2 weeks • Able to provide verbal consent • Prepared to use any of the trial treatments • Had access to a telephone Exclusion criteria: • Pregnant or breastfeeding women • Had used an e-cigarette for smoking cessation for more than 1 week anytime in the past year • Currently using smoking cessation medication • Enrolled in another cessation program or study • Self-reported a history of severe allergies • Poorly-controlled asthma • Cardiovascular event in the 2 weeks before enrolment • Only 1 participant per household was permitted. 69% women; mean age 41.6; mean cpd 17.3; mean FTND 5.2 Motivated to quit: yes

Walker 2020 *(Continued)*

	E-cigarette use at baseline: Not reported but use of an e-cigarette for smoking cessation for more than 1 week anytime in the past year was an exclusion criterion
Interventions	**EC: Refillable** Moderate-intensity behavioral support was available for all participants immediately after randomization, then once a week for 6 weeks. This support consisted of 10 – 15 mins of withdrawal-oriented behavioral support and advice on using their allocated treatment, delivered proactively over the phone by researchers who had received standardized training in delivery of such support. Assigned to: 1) **Nicotine patch** for 14 weeks including 2 week prequit. 21 mg, 24-hr nicotine patch (Habitrol) 2) **Nicotine patch and nicotine-free EC** for 14 weeks. As 1, plus 14-week supply at no cost. A 2nd generation eVOD (Kangertech, Shenzhen GuangDong, China) starter kit, with a choice of 1 of 2 tobacco e-liquid flavors. Advised to start using the e-cigarette 2 weeks before their quit date, as and when necessary or desired, and in accordance with the manufacturer's written instructions, to become familiar with its use Participants were instructed to stop smoking from their quit date and continue with their allocated treatment for 12 weeks (ad libitum use of the e-cigarette), irrespective of any lapses to smoking 3) **Nicotine patch and nicotine EC** for 14 weeks. As above, but 18 mg/mL nicotine
Outcomes	Quit date, 1, 3, 6 and 12 months Continuous abstinence at 6 months with CO validation Adverse events and biomarkers: Known side-effects associated with e-cigarette use and nicotine patch use; SAEs Other outcomes measured: • Relapse • Self-reported treatment adherence • Tobacco withdrawal symptoms and urge to smoke • Urge to vape • Self-reported weight • Concomitant medication • Treatment cross-over • Use of other smoking cessation support or medication • Continued use of allocated treatment past 14 weeks • Changes in shortness of breath, cough, asthma, COPD, and mental health problems • Belief in ability to quit and remain tobacco-free • Smoking identity and views on their allocated treatment for smoking cessation and whether they would recommend it to other people who smoke who want to quit • In people still smoking at each follow-up call, outcomes were number of cigarettes smoked per day and reduction in smoking • Participants allocated e-cigarettes were asked about their urge to vape; whether they changed devices or e-liquid, or both; whether they accessed any e-cigarette support
Study funding	Funding: Health Research Council of New Zealand. "The sponsor of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."
Author declarations	NW, CB, MV, GL, ML, and VP report grants from the Health Research Council of New Zealand, during the conduct of the study. NW, CB, MV, and VP report grants from Pfizer, outside of the submitted work. GL chairs the organization End Smoking New Zealand, which advocates for harm reduction approaches to tobacco control. E-cigarettes were purchased from a New Zealand e-cigarette online retailer (NZVAPOR, https://www.nzvapor.com/), e-liquid was purchased from Nicopharm, Australia (https://www.nicopharm.com.au/), and nicotine patches were supplied by the New Zealand Government via

Walker 2020 *(Continued)*

	their contract with Novartis (Sydney, Australia). NZVAPOR also provided, at no cost to participants, online and phone support regarding use of the e-cigarettes. Neither NZVAPOR nor Nicopharm have links with the tobacco industry. None of the above parties had any role in the design, conduct, analysis, or interpretation of the trial findings, or writing of this publication.
Notes	Study listed as ongoing study NCT02521662 in the 2016 review update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence
Allocation concealment (selection bias)	Low risk	Quote: "We ensured allocation concealment because the statistician who generated the random allocation was not the person randomising participants."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Participants and researchers collecting outcome data were masked to the nicotine content of the e-liquid" but those allocated to patch only would be aware they did not have an E-cigarette Quote: "Third, while we attempted to minimise detection bias by masking the nicotine content of the e-liquid, we were only 30% successful, and thus some bias in favour of nicotine e-cigarettes could have occurred."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 50% lost to follow-up, similar rates of attrition between groups (within 20%)
Selective reporting (reporting bias)	Unclear risk	CO-verified abstinence at 12 months stated as a secondary outcome but data are not reported in the main text. However, state in the appendix that too few people in each group were followed up to 12 months (36/1124) so no data are presented for this time point

Yingst 2020

Study characteristics

Methods	Design: Cross-over study Recruitment: Participants were recruited from people living with HIV/AIDS (PLWHA) (who smoked) seeking care at the Penn State Health HIV Comprehensive Care Program Setting: USA Study start date:Not reported
Participants	Total N: 17; 41.2% female; mean age 49.1 (SD 8.8); mean cpd 16.9 (SD 7.9); mean CO 22.4 (13.1) E-cigarettes use at baseline: not reported Motivated to quit: No Inclusion criteria:

Yingst 2020 *(Continued)*

	• adult (age ≥ 18) • smokers (≥ 10 cigarettes daily) • not planning to quit smoking • documented history of a positive HIV status Exclusion criteria: not reported
Interventions	**EC: Cig-a-like; Refillable** **Cig-a-like device** (Blu), nicotine concentration 24 mg/ml. Propylene glycol/ vegetable glycerin ratio 70/30. Nicotine delivery 4.56 ng/ml after 20 puffs in 10 minutes **Button-operated device** (eGO), nicotine concentration 36 mg/ml. Propylene glycol/ vegetable glycerin ratio 70/30. Nicotine delivery 6.9 ng/ml after 10 puffs in 5 minutes (refillable)
Outcomes	Visits: baseline, day 7, day 14, day 21 CO measured (day 0, 7, 14, 21); adverse events (nausea, dizziness) Also: Number of tobacco cigarettes smoked per day (self-report); EC puffs per day (self-report)
Study funding	This study was supported by the National Institute on Drug Abuse of the National Institutes of Health under Award Number P50DA036107 and the Center for Tobacco Products of the U.S. Food and Drug Administration. JY is also funded by the Penn State Cancer Institute (PSCI) and TE is also supported by U54DA036105. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the Food and Drug Administration
Author declarations	JF has done paid consulting for pharmaceutical companies involved in producing smoking cessation medications, including GSK, Pfizer, Novartis, J&J, and Cypress Bioscience. TE is a paid consultant in litigation against the tobacco industry and the electronic cigarette industry and is named on a patent application for a device that measures the puffing behavior of electronic cigarette users
Notes	New for 2021 update

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Used 2 ENDS in a random order – not enough information
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Unable to blind, but interventions judged equally intensive
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective outcome- CO monitoring (CO < 10 ppm)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Unclear risk	Unclear what outcomes were prespecified

AE: adverse event; BMI: body mass index; CO: carbon monoxide; COT: cotinine; cpd: cigarettes per day; EC: electronic cigarette; ENDS: electronic nicotine delivery system; FTND: Fagerström Test for Nicotine Dependence; HRQoL: health-related quality of life; IQR: interquartile range; ITT: intention-to-treat; LTFU: lost to follow-up; MMT: methadone maintenance treatment; NEC: nicotine electronic cigarette; NRT: nicotine replacement therapy; PEC: placebo electronic cigarette; PP(A): point prevalence (abstinence); ppm: parts per million; SAE: serious adverse event; SD: standard deviation; SMI: serious mental illness; TQD: target quit date; UC: usual care

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adkison 2013	Although this study uses a prospective cohort design, no data on EC use were collected at baseline, with EC use data only being available at follow-up
Al-Delaimy 2015	Observational study with no intervention provided - included in previous versions, but excluded from 2020
Anonymous 2019	Commentary of included study (not primary study)
Battista 2013	Short-term EC use only
Bianco 2019	Ineligible intervention
Biener 2015	Cohort study, but EC use evaluated retrospectively only
Biondi-Zoccai 2019	Less than 1 week follow-up
Biondi-Zoccai 2020	Acute EC use only
Borderud 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Brose 2015	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Brown 2014a	Cross-sectional survey
Bullen 2010	Short-term EC use only
Bullen 2018	Withdrawn trial registry
Caponnetto 2019	Ineligible intervention
Cavarretta 2019	Less than 1 week follow-up
Chaumont 2018	Less than 1 week follow-up
Chaumont 2019	Ineligible intervention
Chausse 2015	Ineligible study design
Choi 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Chorti 2012	Short-term EC use only
Collins 2019	Ineligible intervention

Study	Reason for exclusion
Cook 2019	Commentary of included study (not primary study)
Cox 2019a	Short-term abstinence only (< 6 months)
Czogala 2012	Short-term EC use only
D'Ruiz 2017	Less than 1 week follow-up
Dawkins 2012	Short-term EC use only
Dawkins 2013a	Short-term EC use only
Dawkins 2014	Short-term EC use only
Douptcheva 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Dutra 2014	Cross-sectional survey
Eissenberg 2010	Short-term EC use only
Etter 2014	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Farsalinos 2012	Short-term EC use only
Farsalinos 2013a	Included people that had already stopped smoking conventional cigarettes
Farsalinos 2013b	Short-term EC use only
Farsalinos 2013c	Short-term EC use only
Farsalinos 2013d	Short-term EC use only
Flouris 2012	Short-term EC use only
Flouris 2013	Short-term EC use only
Gmel 2016	Cohort study, but EC use only evaluated retrospectively
Gottlieb 2019	Commentary of included study (not primary study)
Grana 2014b	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
James 2016	Follow-up at 12 weeks, AE data not collected
Kasza 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Kouretas 2012	Short-term EC use only
Kousta 2019	Commentary of included study (not primary study)
Lechner 2015	Less than 1 week follow-up

Study	Reason for exclusion
Lee 2014	Cross-sectional survey
Manzoli 2015	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Marini 2014	Short-term EC use only
Mayor 2019	Commentary of included study (not primary study)
Meltzer 2017	Ineligible intervention
Miura 2015	Tests a device which is not an EC
NCT02487953	Withdrawn trial registry
NCT03036644	Less than 1 week follow-up
NCT03575468	Ineligible intervention
NCT04107779	Less than 1 week follow-up
Nolan 2016	Short-term abstinence only (< 6 months)
NTR6224	Study terminated early, no usable results. Previously listed as ongoing
Palamidas 2014	Short-term EC use only
Pearson 2012	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Pokhrel 2013	Cross-sectional survey
Polosa 2014a	Observational study with no EC intervention provided - included in previous versions, but excluded from 2020
Popova 2013	Cross-sectional survey
Prochaska 2014	RCT but no EC intervention provided - included in previous versions, but excluded from 2020
Russo 2018	Ineligible study design
Schober 2014	Short-term EC use only
Siegel 2011	Retrospective survey of 222 EC users that responded to a survey sent to 5000 new users of the 'Blu' EC. Likely to be a self-selected sample
Song 2020	Ineligible patient population
St.Helen 2020	Wrong intervention
Stein 2019	Commentary of included study (not primary study)
Stower 2019	Ineligible study design
Tsikrika 2014	Short-term EC use only

Study	Reason for exclusion
Tucker 2018	Short-term abstinence only (< 6 months)
Tzatzarakis 2013	Short-term EC use only
Vakali 2014	Short-term EC use only
Valentine 2016	Less than 1 week follow-up
Van Heel 2017	Ineligible study design
Vansickel 2010	Short-term EC use only
Vansickel 2012	Short-term EC use only
Vansickel 2013	Short-term EC use only
Vardavas 2012	Short-term EC use only
Vickerman 2013	Cross-sectional survey
Voos 2019	Less than 1 week follow-up
Voos 2020	Ineligible study design
Wagener 2014	EC use for up to 1 week, but does not report on any adverse events
Walele 2016a	RCT but follow-up too short
Walele 2016b	RCT but follow-up too short
Yan 2015	Ineligible study design
Yuki 2017	Less than 1 week follow-up
Zhang 2019	Commentary of included study (not primary study)

EC: electronic cigarette

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12617001324303

Study name	Vaporised nicotine products versus oral forms of nicotine replacement therapy (NRT) products for tobacco smoking cessation among low-socioeconomic status (low-SES) people who smoke
Methods	Parallel, single-blinded, randomized controlled trial Setting: Australia Recruitment: Not stated.
Participants	Target sample size: 868 Inclusion criteria:

ACTRN12617001324303 *(Continued)*

- At least 18 years of age
- Current daily smoker
- Motivated and willing to make a quit attempt using medications (NRT/VNP)
- Speak English
- Able to provide verbal informed consent
- Receipt of government pension or allowance (proxy for low-SES)
- Have a phone we contact them on;
- Willing to complete 2 telephone check-in calls and baseline and follow-up telephone interviews

The term "current smoker" in this trial will refer to those who use either factory-made or roll-own cigarettes.

Exclusion criteria:

- Women who are pregnant, breastfeeding or planning to become pregnant in the next 12 months
- Current users of smoking cessation medications (i.e. NRT, bupropion [Zyban], clonidine, nortriptyline, electronic nicotine cigarettes)
- Those who are participating in another smoking cessation program or study

People will also be excluded if they report any of the following medical conditions in the previous 3 months: serious chronic lung diseases, arrhythmia, heart attack, stroke, or severe angina

Interventions	Vaporised nicotine product (VNP) arm: • Innokin Endura T18 Personal Vaporizer • e-liquid nicotine (18mg/ml nicotine) for 8 weeks • Quitline behavioral support • 3 flavors will be offered: tobacco, strawberry, menthol • Permitted to use the study product ad libitum throughout the day and encouraged to stop smoking completely, or reduce smoking if unable to stop completely • Participants will be provided with detailed instructions on how to use the e-cigarette device effectively Oral nicotine replacement therapy (NRT) arm: • 2 mg or 4 mg nicotine gum/lozenge for 8 weeks • Quitline behavioral support • Those receiving the lozenge will be instructed to use 9 - 15 lozenges per day, approximately 1 every 2 hours or when they have an urge to smoke • Those receiving the gum will be instructed to use 10 to 20 pieces per day for the 2 mg gum and 4 to 10 pieces per day for the 4 mg gum, approximately 1 every 2 hours or when they have an urge to smoke • Participants will be provided with detailed instructions on how to use the NRT effectively and encouraged to stop smoking completely, or reduce smoking if unable to stop completely
Outcomes	Primary outcome: Carbon monoxide-verified six-month continuous abstinence (smoking not more than 5 cigarettes) from the quit date (8 months from baseline) Secondary outcomes measured at 2-week and 6-week check-in calls and 8-month follow-up • Self-reported 7-day point prevalence abstinence • Self-reported continuous abstinence: defined as self-report of smoking not more than 5 cigarettes from the designated quit date • Self-reported number of cpd among people continuing to smoke • Self-reported 30-day PPA at each follow-up (self-report of having smoked no cigarettes (not even a puff)) • Mean reduction in number of cigarettes smoked per day based on participant self-report

ACTRN12617001324303 *(Continued)*

	• Proportion of participants that achieved a 50% reduction of baseline cigarette consumption based on participant self-report (8 months only) • Self-reported continued use of nicotine products to assess maintenance use and dual use (8 months only) Weekly text message surveys and check-in calls 2 weeks and 6 weeks into the treatment period. These check-in calls will also assess smoking status, short-term outcomes, and adverse events at these time points
Starting date	Anticipated start date: 30 April 2019
Contact information	Richard P Mattick, r.mattick@unsw.edu.au Alexandra Aiken, a.aiken@unsw.edu.au
Notes	

ACTRN12618000408280

Study name	A pragmatic randomized partial cross-over clinical trial of nicotine vaporizers added to standard care for smoking cessation and relapse prevention (CARP) among priority populations with comorbidities
Methods	Randomized controlled trial Setting: Australia Recruitment: Not stated

Participants	Target sample size: 810
	
	Inclusion criteria:
	
	• Diagnosed with or receiving treatment for a priority health conditions in the past 12 months
	• Aged 18+ years
	• Currently smoke 10+ cigarettes per day
	• Has capacity to consent, able to understand participant materials and follow study instructions and comply with study procedures (e.g. sufficient English language ability, able to operate the vaporiser device)
	• Willing to make a quit attempt at baseline according to randomized condition (Condition A to make quit attempt with nicotine vaporizer; Condition B to make quit attempt without nicotine vaporizer)
	• Has a referral to Quitline counseling and smoking cessation support program (standard care) but has not begun quit attempt (Note: Quitline referral can occur at time of study enrolment)
	
	Exclusion criteria:
	
	• Already begun quit attempt (i.e. post-quit day) at time of enrolment into trial or currently enrolled in another smoking cessation clinical trial or using varenicline or bupropion or used a nicotine vaporizer product in the last 30 days. NOTE: Use of nicotine replacement products not supplied in the trial (e.g. as part of quitline support) is not an exclusion criterion
	• Currently pregnant or breast-feeding or an intention to be during trial participation period;
	  * A urinary pregnancy test will be required where pregnancy is suspected
	  * Participants will be advised appropriate contraception should be used to avoid pregnancy during the trial with ongoing contraception options discussed
	• Has experienced cardiac-related chest pain, or another cardiovascular event or procedure in the last month, such as heart attack, stroke, insertion of stent, bypass surgery

ACTRN12618000408280 *(Continued)*

	• Hospitalized for a mental health condition in the last 30 days • Currently being treated with oxygen therapy • Diagnosed terminal illness (such as cancer) or debilitating condition that will limit ability to fully participate as determined by preregistration responses from participant or opinion of enrolling clinician
Interventions	• **Arm 1)** Referral to Quitline telephone smoking cessation counseling + **Nicotine patches** (15 mg/16-hr) delivered at baseline + **refillable nicotine vaporizer device** (2 x kits) + nicotine vaporising liquid (in high and low strength - high strength: nicotine 1.8% in Vegetable Glycerine and purified water; low strength: nicotine 0.6% in Vegetable Glycerine and purified water). 1 patch to be applied daily to skin for up to 84 days. The vaporizer with nicotine liquid is to be used as needed up to 3.5 mL per day to treat withdrawal symptoms for up to 2 years (concurrently with patches for the first 84 days) to assist smoking cessation and relapse prevention. Participants start on high-strength nicotine liquid and may decrease their dose to low strength to assist with dose reduction prior to stopping use of the vaporizer. • **Arm 2)** Referral to Quitline telephone smoking cessation counseling + **Nicotine patches** (15 mg/16-hr) + participant's choice of either **nicotine gum or nicotine lozenges** (up to 800 x 4 mg pieces to be used up to 8 per day) delivered at baseline. Between 6 - 9 months post-baseline - participants in Arm 2 who are smoking (either failed to quit or relapsed) will be offered: refillable nicotine vaporizer (2 x kits) + nicotine vaporizing liquid (in high and low strength - high strength: nicotine 1.8% in Vegetable Glycerine and purified water; low strength: nicotine 0.6% in Vegetable Glycerine and purified water) to make a second quit attempt. Participants start on high-strength nicotine liquid and may decrease their dose to low strength to assist with dose reduction prior to stopping use of the vaporizer at the discretion of the participant. Participants will have until 2 years from baseline to use the vaporizer for smoking cessation and relapse prevention
Outcomes	Primary outcomes: • Continuous abstinence from smoking from weeks 12 to 26 assessed at 26 weeks from baseline by self-report. Participants that self-report abstinence from smoking will be asked for a urine specimen for bioconfirmation. Urine specimens will be batch-tested for anabasine and cotinine at 6,12 and 21 month time points from baseline Secondary outcomes: • Continuous abstinence from smoking from weeks 12 to 52, assessed at week 52 from baseline • Continuous abstinence from smoking from weeks 12 to 104, assessed by self-report at week 104 from baseline • Continuous abstinence from smoking from weeks 40 to 52, assessed by self-report at 52 weeks from baseline • Continuous abstinence from smoking from weeks 92 to 104, assessed by self-report at 104 weeks from baseline • Number of adverse events measured by self-report at 12 weeks and 26 weeks from baseline Abstinence is assessed through study-specific survey questions in Module CS Combustible Smoking Questions – administered through electronic survey or structured telephone interview. Participants that self-report abstinence from smoking will be asked for a urine specimen for bioconfirmation. Urine specimens will be batch-tested for anabasine and cotinine at 6,12 and 21 month time points
Starting date	5 June 2018
Contact information	Malcolm Brinn, m.brinn@uq.edu.au Coral Gartner, c.gartner@uq.edu.au
Notes	

ACTRN12619001787178

Study name	Project NEAT: nicotinE As Treatment for tobacco smoking following discharge from residential withdrawal services
Methods	RCT Project NEAT: A randomized controlled trial to examine the efficacy of vaporised nicotine products and telephone quit line support compared with nicotine replacement therapy and telephone quit line support when used following discharge from a residential withdrawal services Setting: Australia (New South Wales, Queensland, Victoria) Recruitment 4 hospitals sites: Belmont Hospital, Belmont; St Vincent's Hospital, Darlinghurst; Turning Point Drug and Alcohol Centre, Richmond; Royal Brisbane & Womens Hospital, Herston
Participants	Target sample size: 926 Inclusion criteria: • Aged 18 or over • Daily tobacco smoker (10 or more cigarettes) on entering withdrawal unit • Accessing treatment from participating services • Want to quit smoking in the next 30 days • Has capacity to consent and able to understand the participant materials and follow the study instructions and procedure (e.g. sufficient English language ability and not too unwell as judged by medical staff). Exclusion criteria: • Pregnant or breast-feeding • Enrolled in another study • Scheduled to be transferred to a long-term residential rehabilitation service following discharge from the withdrawal unit • Used VNP (containing nicotine) in the last 30 days • Currently engaged in Quitline's call-back services • No ready access to a phone
Interventions	Condition One: Vaporised Nicotine Products and Quitline Condition Two: Current Best Practice Treatment for Tobacco Smoking (Combination Nicotine Replacement Therapy and Quitline)
Outcomes	9 months after inpatient withdrawal unit discharge: Self-reported 7 months continuous abstinence from tobacco smoking Biochemically-verified 7-month continuous abstinence from tobacco smoking 3 and 9 months after inpatient withdrawal unit discharge: 30-day point prevalence abstinence 7-day point prevalence abstinence Abstinence from all nicotine/ tobacco products
Starting date	Anticipated enrolment: 19 December 2019. Anticipated date last data collection 19 September 2022
Contact information	Prof Billie Bonevski, Billie.Bonevski@newcastle.edu.au

ACTRN12619001787178 *(Continued)*

Notes	Funding: National Health and Medical Research Council (grant number: G1800272), Canberra ACT 2601.

Begh 2019

Study name	Examining the effectiveness of general practitioner and nurse promotion of electronic cigarettes versus standard care for smoking reduction and abstinence in hardcore smokers with smoking-related chronic disease: protocol for a randomized controlled trial
Methods	Individually randomized, blinded, 2-arm trial Setting: General practices, England Recruitment: Primary care registries
Participants	Target sample: 320 (160 per arm) Inclusion criteria: • Participant is willing and able to give informed consent for participation in the study • Aged 18 years or above • Current smoker with a value of at least 10 ppm for exhaled CO and smokes a minimum of 8 cigarettes/8 g of tobacco per day (including pipe, cigars or tobacco roll-ups) • Diagnosed with 1 or more of the following chronic conditions: ischaemic heart disease, peripheral vascular disease, hypertension, diabetes mellitus (type 1 and type 2), stroke, asthma, COPD, chronic kidney disease, depression, schizophrenia, bipolar disorder or other psychoses Exclusion criteria: • GP believes that switching to e-cigarettes would not benefit the patient given their current medical condition • Currently using e-cigarettes, nicotine replacement therapy or other cessation therapies (e.g. bupropion, nortriptyline or varenicline) • Plans to stop smoking before or at the annual review • Currently enrolled in another smoking-related study or other study where the aims of the studies are incompatible • Cannot consent due to mental incapacity • Pregnant, breastfeeding or planning to become pregnant during the course of the study
Interventions	• Control: No additional support beyond standard care • Intervention: will receive GP- or nurse-led brief advice about e-cigarettes, **an e-cigarette starter pack** with accompanying practical support booklet, and telephone support from experienced vapers and online video tutorials
Outcomes	Months 2, 8 Primary outcomes: • 7-day PPA from smoked tobacco at 2 months; Self-reported abstinence from smoking—not even a puff—in the past 7 days, accompanied by a salivary anabasine concentration of < 1 ng/ml; exhaled CO as verification of abstinence (CO < 10 ppm) used, as necessary. Secondary outcomes: • Smoking reduction • 7-day PPA and prolonged abstinence at 8 months;

Begh 2019 *(Continued)*

	• Participant recruitment and follow-up, • Participant uptake and use of e-cigarettes, • Nicotine intake, • Contamination of randomization and practitioner adherence to the delivery of the intervention
Starting date	November 2016
Contact information	Rachna Begh, rachna.begh@phc.ox.ac.uk
Notes	

Berlin 2019

Study name	Randomized, placebo-controlled, double-blind, double-dummy, multicentre trial comparing electronic cigarettes with nicotine to varenicline and to electronic cigarettes without nicotine: the ECSMOKE trial protocol
Methods	3-arm randomized, placebo-controlled, multicentre, double-blind, double-dummy, parallel groups, phase III type trial Setting: Smoking cessation clinics of both academic and community hospitals Recruitment is either local (a) directly by the centres or centralized (b) using a web page and a centralized study-specific phone number and email address • People who smoke intending to quit smoking are recruited by advertisement in pharmacies, physicians' offices situated in the catchment area of each investigator's centre, by local newspapers and in public places of the centres' healthcare facilities • Candidates to participate can register by the study's website, unique email address and phone number. Registration is followed by a phone screening before dispatching to the study centres. Only 1 person by household will be recruited
Participants	Estimated enrolment: 650 participants Inclusion criteria: • People who smoke, at least 10 cpd (factory-made or roll-your-own) in the past year • Aged 18 – 70 years • Motivated to quit, defined as a score > 5 on a visual rating scale ranging from 0 (not motivated at all) to 10 (extremely motivated) • Signed written informed consent • Understanding and speaking French • Women of childbearing age can be included if they use an effective contraceptive method: either hormonal contraception or an intrauterine device started at least 1month before the first research visit • Individual affiliated to a health insurance system • Previous failure of NRT for smoking cessation Exclusion criteria: • Any unstable disease condition within the last 3 months defined by the investigator as major change in symptoms or treatments, such as recent myocardial infarction, unstable or worsening angina, severe cardiac arrhythmia, unstable or uncontrolled arterial hypertension, recent stroke, cerebrovascular disease, obliterative peripheral arterial disease, cardiac insufficiency, diabetes, hyperthyroidism, pheochromocytoma, severe hepatic insufficiency, history of seizures, severe depression, COPD • Any life-threatening condition with life expectancy of < 3 months

Berlin 2019 *(Continued)*

	• Alcohol use disorder defined as a score ≥ 10 on the Alcohol Use Disorders Identification Test (AUDIT)-C questionnaire (see below) • Abuse of or dependence on illegal drugs in the last 6 months, revealed by medical history • Regular use of tobacco products other than cigarettes • Current or previous (last 6 months) use of EC • Pregnant women • Breastfeeding women • Protected adults • Current or past 3 months participation in another interventional research • Current or past 3 months use of smoking cessation medication such as varenicline, bupropion, NRTs • Known lactose intolerance (placebo tablets contain lactose) • Hypersensitivity to the active substance or to any of the excipients • Known severe renal failure
Interventions	A) **EC without nicotine** (ECwoN) plus placebo tablets of varenicline (0.50mg) administered by oral route: placebo condition; B) **EC with nicotine** (ECwN) plus placebo tablets of varenicline: ECwN condition. V C) Reference: ECwoN plus 0.5 mg varenicline tablets: **varenicline condition**. Varenicline administered according to the marketing authorization E-cigarette details: • EC device Mini iStick kit (20 W) Eleaf, clearomiser: GS Air M with resistance of 1.5 ohm. To keep the blinding, the clearomizer's Pyrex window is of grey Colour not allowing to distinguish the coloration of the e-liquid containing nicotine. Liquid for EC is manufactured by GAIATREND SARL (www.gaiatrend.fr/fr/) • All participants will be delivered a short manual and a video specifically developed for this study explaining the use of EC. At each visit, participants receive verbal counseling about the use of the EC device and answers to their questions about handling the EC device Behavioural support: • Brief behavioral smoking cessation counseling for all participants is administered at all visits by the investigators specialized in smoking cessation. It is based on the national guidelines for smoking cessation Treatment duration: 1 week + 3 months
Outcomes	Week 2, 4, 8, 10, 12, 24 after target quit day Primary outcome: • Continuous smoking abstinence rate (CAR) (abstinence from conventional/combustible cigarettes) during the last 4 weeks (weeks 9 – 12) of the treatment period of 3 months Secondary outcomes: • Safety profile • PPA rate • CAR confirmed by urinary anabasine concentration • Changes in cpd consumption • Craving for tobacco and withdrawal symptoms with respect to baseline
Starting date	17 October 2018
Contact information	Ivan Berlin, ivan.berlin@aphp.fr

Berlin 2019 *(Continued)*

Notes	

Caponnetto 2014

Study name	Smoking cessation and reduction In schizophrenia (the SCARIS study)
Methods	3-arm prospective 12-m randomized controlled trial investigating efficacy and safety of EC Setting: psychiatric and smoking cessation centres, Italy Recruitment: local newspapers and radio/television advertisements
Participants	153 participants Inclusion criteria • Schizophrenic in stable phase of illness • Smoked at least 10 cpd over previous 5 years • Aged 18 - 65 • In good general health • Not currently attempting to quit smoke or wishing to do so in next 6m Exclusion criteria • Use smokeless tobacco or NRT • Pregnant or breastfeeding • Current or recent (1 yr) history of drug or alcohol abuse • Other significant co-morbidities
Interventions	12-wk supply of: • EC, high nicotine (24 mg) • EC, no nicotine (0 mg, with tobacco aroma) • PAIPO nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 weeks Outcome measures: • Smoking cessation • Smoking reduction (≥ 50% from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfactions with products
Starting date	September 2014
Contact information	Pasquale Caponnetto, p.caponnetto@unict.it
Notes	

Caponnetto 2020

Study name	Non-inferiority trial comparing cigarette consumption, adoption rates, acceptability, tolerability, and tobacco harm reduction potential in smokers switching to Heated Tobacco Products or electronic cigarettes: Study protocol for a randomized controlled trial
Methods	RCT 12 weeks
Participants	220 healthy people who smoke tobacco cigarettes
Interventions	Arm 1 - Heated Tobacco Products (HTPs) Arm 2 - E-cigarettes (ECs)
Outcomes	12-week study. Follow-up 24 weeks Biochemically-verified self-reported continuous abstinence at 12 weeks from the previous visit Secondary outcomes will include: smoking reduction from baseline, adoption rates and product acceptability, tolerability, changes in step test values and in the level of selected biomarkers of exposure in exhaled breath (i.e. eCO) and in spot urine samples A follow-up visit at 24 weeks to review product usage and smoking behavior under naturalistic condition of use
Starting date	Recruitment May 2019, enrolment is expected to be completed in November 2019 Results to be reported in 2020
Contact information	Pasquale Caponnetto, p.caponnetto@unict.it
Notes	NCT03569748 Funded by Philip Morris

Fraser 2015

Study name	An open-label randomized pragmatic policy trial examining effectiveness of short-term use of nicotine replacement therapy (NRT) vs short- or long-term use of NRT vs short- or long-term use of NRT or electronic nicotine delivery systems for smoking cessation in cigarette smokers
Methods	Phase 3 blinded RCT Setting: Australia Recruitment: commercial market research panel
Participants	Target sample size: 1600 • Current daily smoking (at least 6 cpd) • Can read and understand English • Agree to try samples of nicotine products • Willing to complete surveys • 18 years or older Exclusion criteria: • If currently treated for serious medical condition,

Fraser 2015 *(Continued)*

	• Pregnant or planning to become pregnant or breast-feed in next 12 m
Interventions	• a) Factsheet explaining relative harm of NRT compared to smoking, free sample of NRT, participant chooses preferences, has free for 3 weeks then offered at subsidized rate for further 6 m • b) As (a), but with additional information provided • c) As (a), but additional information on electronic cigarettes and emphasis on cessation, and may select electronic cigarettes as well as NRT
Outcomes	6 m and 12 m, self-report • Continuous abstinence • NRT and EC use • Interest in quitting smoking and in quitting NRT • Cigarette consumption • Product orders and use • Quit attempts
Starting date	February 2014
Contact information	Coral Gartner, c.gartner@uq.edu.au
Notes	

ISRCTN13288677

Study name	Can electronic cigarettes and nicotine replacement treatment help reduce smoking in smokers who struggle to quit?
Methods	Pilot single-centre randomized control trial Setting: Queen Mary University of London, UK Recruitment method not specified.
Participants	Target sample size: 200 Inclusion criteria: • 18 years or older • Able to provide written informed consent • History of failed quit attempts using stop-smoking medications or stop smoking services, or both • Willing to use their allocated harm-reduction strategy for at least 4 weeks Exclusion criteria: • Women who are pregnant or breastfeeding • Unable to read/write/understand English • Currently using EC or any stop-smoking products • Taking part in other interventional research • Have a strong preference to use or not to use NRT or EC
Interventions	1) **NRT arm:** • Will be shown and explained the NRT products available and encouraged to choose a product or product combination that suits their needs

ISRCTN13288677 *(Continued)*

	• Will receive a letter of recommendation as per standard practice and collect their chosen products at local pharmacies • Product use will be supervised and adjusted (if required) as part of the behavioral support package. As per local standard practice, NRT will be provided for up to 8 weeks 2) **EC arm:** • Will be shown and explained different EC products commonly used and asked to obtain the product of their choice, either using a voucher for up to GBP 35 to purchase EC at a local vape shop, purchase from other suppliers and claim a refund of up to GBP 35 upon providing a valid receipt, or choose from a limited selection at the smoking cessation clinic • Will be encouraged to try different products and liquids if the first purchase does not meet their needs, but after the initial purchase, participants will fund further supplies themselves (this is to mimic the provision of starter packs, an approach that is most likely to be used by routine services)
Outcomes	Participants contacted by phone at 1 week, 4 weeks and 24 weeks after the initial screening session Primary outcomes: • Cigarette consumption per day, assessed by self-report in the follow-up survey created for the purpose of the study at 1, 4 and 24 weeks post-quit date/preparation date. Those who report ≥ 50% smoking reduction will be validated with a CO reading in the clinic Secondary outcomes: • Use of allocated harm-reduction strategies • Strategy ratings • Changes in smoking behavior • Proportion of people still using allocated strategy at 6 months
Starting date	January 2017
Contact information	Marzena Orzol, m.orzol@qmul.ac.uk Katie Myers-Smith, katie.smith@qmul.ac.uk
Notes	

ISRCTN61193406

Study name	Do e-cigarettes help smokers quit when not accompanied by intensive behavioral support? A multi-center randomized controlled trial
Methods	RCT Setting: UK Multicenter. Participants will be recruited mainly from hospitals and GP practices across the UK by the Clinical Research Network. The study is being organized by Queen Mary University of London (QMUL) Researchers from QMUL will provide the study treatment and conduct follow-up calls
Participants	1170 people who smoke tobacco cigarettes Inclusion criteria: • Adult daily smokers who are motivated to stop smoking

ISRCTN61193406 *(Continued)*

	• Must own a mobile phone and be willing to try either an online or texting treatment package, or both, or an e-cigarette with or without telephone support. • Be happy to receive follow-up calls • Be able to read/write/understand English Exclusion criteria: • Women who are pregnant • Currently using an e-cigarette
Interventions	1. Control: NHS Quit Now program (QN) 2. E-cigarette starter pack with no ongoing support (EC) 3. EC starter pack with helpline support (EC+) The study will aim to use a refillable EC that is similar to the type used in a previous EC trial (One Kit - Innokin, UK Ecig Store), and one that is compliant with UK regulations, and not produced by a tobacco company
Outcomes	Follow-up at 4 weeks, 6 months and 12 months. CO at 6 and 12 months Primary outcome measure: Sustained smoking cessation at 6 months post-TQD. This is measured by asking participants if they have smoked since their TQD at the 6-month follow-up. To be counted as a 'quitter', participants must report smoking no more than 5 cigarettes since 2 weeks post-TQD with no smoking in the previous week, validated by carbon monoxide (CO) reading of < 8 ppm. Participants lost to follow-up will be counted as smokers Secondary outcome measures: • Validated sustained abstinence rates measured by asking smoking status and taking a carbon-monoxide reading at 12 months post-TQD • Validated sustained abstinence rates between 6 and 12 months, measured by asking smoking status and taking a carbon-monoxide reading at 6 and 12 months • Self-reported 7-day point-prevalence abstinence, measured by asking smoking status in last 7 days at 4 weeks, 6 months and 12 months post-TQD • Cigarette consumption in non-abstainers by vaping status, measured by questionnaire at four weeks, 6 and 12 months • Frequency and severity of urges to smoke and withdrawal symptoms, measured by questionnaire at 4 weeks post-TQD. • Weight, measured by asking weight at 4 weeks, 6 months and 12 months post-TQD • Respiratory symptoms, measured by questionnaire, at 4 weeks, 6 months and 12 months post-TQD • Treatment adherence and ratings, measured by questionnaire at 4 weeks (and 6 and 12 months for EC arms) • Adverse reactions to EC, measured by questionnaire at 4 weeks, 6 and 12 months post-TQD • Cost-effectiveness of the interventions, measured by questionnaires at baseline, 6 and 12 months • Smokers' and health-care professionals views and opinions of the helpline, measured by one-off qualitative interviews separate to the main trial.
Starting date	Overall trial start date: 01 September 2020 Trial end date: 31 May 2024 Not yet recruiting. Last edited 12 August 2020
Contact information	Dr Katie Myers Smith, katie.smith@qmul.ac.uk

ISRCTN61193406 *(Continued)*

Notes	

Klonizakis 2017

Study name	Smokers making a quit attempt using e-cigarettes with or without nicotine or prescription nicotine replacement therapy: impact on cardiovascular function (ISME-NRT) - a study protocol
Methods	Pragmatic, 3-group, randomized, assessor-blinded, single-centre trial Setting: Centre for Sport and Exercise Science (CSES) of Sheffield Hallam University, UK Recruitment: From the community in the wider Sheffield area will be by: i) low-cost newspaper and post-office advertisement, ii) posters in local pharmacies, libraries, mosques, churches, and clubs, iii) social media or search engine advertisement (Facebook, Google ads) iv) notices in newsletters or participation in outreach events of community organizations (such as Sheffield U3A and AGE UK), iv) a study website, and v) out-reach events in local ethnic community centres or places of worship
Participants	Estimated enrolment: 258 participants (86 participants arm) Inclusion Criteria: • Age > 18 years of either sex • People who smoke (at least 10 cpd for the past year) • Willing (by declaration) to attempt quit smoking by using the NHS services or e-cigarettes Exclusion Criteria: • Inability to walk • Recent (within 6 months) cardiovascular disease event (e.g. stroke, myocardial infarction) or cardiac surgery • Insulin-controlled diabetes mellitus or with co-existing skin conditions, leg ulcers, vasculitis or deep venous occlusion (as these may affect their cardiovascular function) • Pregnancy • Requiring major surgery during the course of the study) • Contra-indications/unsuitability for NRT • Current daily use of e-cigarettes • Currently undertaking a cessation attempt supported by a smoking cessation clinic • Unable to give informed consent
Interventions	• a) Complimentary **e-cigarette equipment** and refills (Tornado V5, Joyetech, Shenzhen, China) at allocation stage, together with instructions on the correct usage of e-cigarettes. They will also receive behavioral support for a 3-month period. The nicotine strength of Group A cartridges will be up to 18 mg/ml nicotine strength • b) As a), but with **nicotine-free liquid** • c) Referral to **NHS smoking cessation clinics** and will receive NRT in conjunction with behavioral support
Outcomes	Follow-up: Within 3 days of “quit date”, 3 and 6 months past quit date Outcome measures: • Macro-vascular function (FMD assessment) • Micro-vascular function • Smoking status at 3 and 6 months, self-reported and biochemically validated by exhaled air measurement of < 10 ppm CO

Klonizakis 2017 *(Continued)*

	• Change in CVD risk using Q-risk assessment • Health Economic effects using EQ5D-L • Total cholesterol and High Density lipoprotein via fingerprick blood sample • Participant experiences' assessment
Starting date	24 April 2017
Contact information	Markos Klonizakis, m.klonizakis@shu.ac.uk
Notes	

Murray 2020

Study name	Yorkshire Enhanced Stop Smoking (YESS) study: a protocol for a randomized controlled trial to evaluate the effect of adding a personalized smoking cessation intervention to a lung cancer screening program
Methods	RCT Setting: Yorkshire, UK
Participants	Anticipated recruitment: 1040 people who smoke tobacco cigarettes Participants are aged 55 – 80, registered with a general practitioner (GP) in the Leeds Clinical Commissioning Group area and registered as a current or ex-smoker in primary care databases Inclusion criteria: • Attended an lung health check (LHC) and consent to participate in the Yorkshire Lung Screening Trial (YLST) • have smoked within the last month • have an exhaled carbon monoxide (CO) reading ≥ 6 ppm • have agreed to see an SCP on the mobile unit Exclusion criteria: • Any individual who does not have an LDCT scan • or is unable to provide informed consent
Interventions	Arm 1: enhanced, personalized smoking cessation (SC) support package, including CT scan images. SC support over 4 weeks comprising behavioral support, pharmacotherapy and/or a commercially-available e-cigarette Arm 2: continued standard best practice.
Outcomes	Follow-up contact will be requested at 4 weeks, 3 months and 12 months, with a 2-week window to accommodate participant availability The primary objective is to measure 7-day point prevalent carbon monoxide (CO)-validated SC after 3 months Secondary outcomes include CO-validated cessation at 4 weeks and 12 months, self-reported continuous cessation at 4 weeks, 3 months and 12 months, attempts to quit smoking and changes in psychological variables, including perceived risk of lung cancer, motivation to quit smoking tobacco, confidence and efficacy beliefs (self and response) at all follow-up points
Starting date	January 2019 and December 2020 with follow-up data collection ending December 2021

Murray 2020 *(Continued)*

Contact information	Professor Rachael L Murray; rachael.murray@nottingham. ac.uk
Notes	

NCT01842828

Study name	Spain-UK-Czech E-cigarette Study (SUKCES)
Methods	Randomized controlled trial, open-label pilot study Setting: smoking cessation clinics in London, Madrid and Prague Recuitment: via smoking cessation clinics
Participants	220 people who smoke, seeking help to quit Inclusion criteria: • 18 or older • Want help to quit Exclusion criteria: • Pregnant or breastfeeding; • Enrolled in other research; • Currently using EC
Interventions	• Standard care plus **4 weeks EC supply** • **Standard care** only
Outcomes	• CO-validated continuous abstinence at 4 and 24 weeks post-TQD • Withdrawal symptoms at 1 and 4 weeks post-TQD • EC use • EC taste and satisfaction compared to conventional cigarettes • Adverse events
Starting date	December 2013
Contact information	Peter Hajek, p.hajek@qmul.ac.uk
Notes	

NCT01989923

Study name	Smoking cessation in women with gynecological conditions
Methods	Randomized controlled trial, open-label feasibility study Setting: hospital clinic, USA Recruitment: in clinic
Participants	30 women who smoke with cervical dysplasia

NCT01989923 *(Continued)*

	Inclusion criteria: • Women who smoke at least 10 cpd over past year • Diagnosis of cervical dysplasia, cervical cancer, and lower genital tract dysplasia and cancer • Aged 18 - 65 Exclusion criteria: • Previous diagnoses or treatment for cancer (except for non-melanoma skin cancer) • Stroke, heart disease, heart attack, or irregular heart beat • Pregnancy and lactation • Plan to continue to use other nicotine as well as study products • Uncontrolled hypertension • Using other stop-smoking medication • Taking prescription medicine for depression or asthma
Interventions	• **NRT patch** (21 mg for first 3 weeks, 14 mg for 2nd 3 weeks) plus nicotine gum (2 mg) or lozenges (2 mg) for 6 weeks • **EC device** ('Blu' Cig) with refills to last 6 weeks, number provided based on packs smoked a day x 1.5. Strength of EC reduced at 3 weeks Both groups receive identical cessation counseling
Outcomes	At 6 and 12 weeks via survey: • Cpd • PPA at 7 and 30 days • Smoking cessation • Participants' attitudes and beliefs towards treatments • Adherence
Starting date	June 2013
Contact information	Laura A Beebe, laura-beebe@ouhsc.edu
Notes	

NCT02004171

Study name	Electronic cigarettes or nicotine inhaler for smoking cessation
Methods	Randomized controlled trial, open-label safety/efficacy study Setting and recruitment not specified, USA
Participants	40 participants Inclusion criteria: • 18 - 60 years old • Meet DSM-IV criteria for nicotine dependence • Seeking treatment for smoking cessation • smoking at least 15 cpd Exclusion criteria:

NCT02004171 *(Continued)*

	• DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder • Current diagnosis of major depressive disorder • Current diagnosis for other psychiatric disorders that may require intervention over course of study • Receiving treatment for nicotine dependence • Pregnancy, lactation, or chance of pregnancy • Unstable medical condition • Substance abuse diagnosis • Use of cannabis or alcohol on more than 20 days in past 30 days • Suicide risk
Interventions	4 weeks: • **ECs** (2nd generation) with 24 mg nicotine cartridges, 1 - 2 cartridges daily • **Nicotine inhaler** with 10 mg cartridges, max 16 cartridges per day
Outcomes	Over 4 weeks: • cpd • Withdrawal • Benefits from smoking cessation (breathing, sense of taste and smell, physical fitness) • Adverse events • BMI
Starting date	December 2013
Contact information	Barney Vaughan, vaughan@nyspi.columbia.edu
Notes	

NCT02124187

Study name	Smoking cessation and reduction in depression (SCARID)
Methods	3-arm prospective 12-m randomized controlled trial investigating efficacy and safety of ECs
Participants	129 participants Inclusion criteria: • Diagnosis of major depressive disorder (MDD) (according to DSM-5 criteria) • Smoke ≥ 10 cpd (for at least the past 5 years) • age 18 - 65 years • In good general health • Unwilling to quit smoking in the next 30 days Exclusion criteria: • Use of smokeless tobacco or NRT or other smoking cessation therapies • Pregnancy or breastfeeding • Current or recent (< 1 yr) past history of alcohol or drug abuse or both • Active suicidal intention

NCT02124187 *(Continued)*

	• Other significant co-morbidities according to the Investigator's clinical assessment (e.g. cancer, acute myocardial infarction, unstable angina, severe cardiac arrhythmia, recent cerebrovascular incident, or severe atherosclerosis)
Interventions	12-wk supply of: • **EC 24 mg** nicotine • **EC 0 mg** nicotine • **Nicotine-free inhalator**
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 weeks Outcome measures: • Smoking cessation • Smoking reduction (≥ 50% from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfaction with products
Starting date	February 2015
Contact information	Pasquale Caponnetto p.caponnetto@unict.it
Notes	

NCT02398487

Study name	Head-to-head comparison of personal vaporizers versus cig-a-like: prospective 6-month randomized control design study (VAPECIG 2)
Methods	Randomized parallel-assignment open-label trial Setting: Italy, community
Participants	Estimated enrolment: 200 Inclusion criteria: • (People who smoke) in good general health • Committed to follow trial procedures Exclude if: • Recent vaping history (stopped vaping < 3 months ago) • Use of any other form of non-combustible nicotine-containing products (chewable tobacco or nicotine replacement therapy) • Symptomatic cardiovascular disease • Clinical history of asthma and COPD • Regular psychotropic medication use • Current or past history of alcohol abuse • Use of smokeless tobacco or nicotine replacement therapy • Pregnancy or breastfeeding.

NCT02398487 *(Continued)*

Interventions	Comparison between 2 types of EC; 'personal vaporizers' and 'cig-a-like'
Outcomes	24 weeks: • Smoking cessation • smoking reduction
Starting date	October 2014
Contact information	Riccardo Polosa
Notes	

NCT02527980

Study name	E-cigarettes: dynamic patterns of use and health effects
Methods	Prospective observational study Setting: community, USA Recruitment: People who smoke and dual EC and cigarette users
Participants	Estimated enrolment: 450 Inclusion criteria: • ≥ 18 years old • No plans to quit smoking and/or EC use in the next 30 days • Not currently taking smoking cessation medication • Not currently in treatment for psychosis or bipolar disorder • Participants must report either that they have: smoked at least 5 cpd for the past 6 months and not used EC within the last 3 months ("exclusive smokers") or used nicotine-containing EC at least once a week for the past month and have smoked at least 5 cpd for the last 3 months ("dual users")
Interventions	"We will conduct a 2-year longitudinal cohort study comprising participants who smoke exclusively CCs (n = 175) and dual users of e-cigs and CCs (n = 275)"
Outcomes	"We will use state-of-the-art ecological momentary assessments to determine: 1) dynamic patterns of e-cig and CC use and related outcomes (e.g. dependence, withdrawal symptoms, CC quit attempts and quitting success); 2) episodic (affective, contextual, social) and stable person-factor (lifestyle factors, demographics) variables that covary meaningfully with e-cig and CC use and related outcomes; 3) biomarkers of tobacco and carcinogen exposure as well as other health-related outcomes (e.g. reduced pulmonary function)."
Starting date	September 2015
Contact information	PI Megan Piper
Notes	

NCT02590393

Study name	The role of nicotine and non-nicotine alkaloids in e-cigarette use and dependence
Methods	Randomized parallel-assignment double-blind trial Setting: Smoking research clinic, USA Recruitment: volunteers
Participants	Estimated enrolment: 375 Inclusion criteria: • Have no known serious medical conditions • Are 18 - 65 years old • Smoke an average of at least 10 cpd • Have smoked at least 1 cumulative year • Have an expired air CO reading of at least 10 ppm • Are able to read and understand English Exclude if: multiple, related to baseline health status
Interventions	• Switch to standard **nicotine EC** use for 8 weeks • Switch to **ECs with same nicotine but very low non-nicotine alkaloid levels** • Switch to **ECs with very low nicotine** and non-nicotine alkaloids
Outcomes	Primary: • CO levels at 8 weeks Secondary: • EC use • EC solution use • cigarette use, at 8 weeks
Starting date	May 2016
Contact information	Jed Rose
Notes	"This is not a smoking cessation study; People who smoke will not be asked to quit smoking, and e-cigarettes will not be used as a medical device or therapy."

NCT02635620

Study name	Changes in lung function parameters, bronchial reactivity, state of health and smoking behavior associated with changing from conventional smoking to electronic cigarettes
Methods	Prospective observational study Setting: Community, Germany Recruitment: Vape shops and smoking cessation clinics

NCT02635620 *(Continued)*

Participants	Estimated enrolment: 80 Inclusion criteria: • Smoking ≥ 5 years • Smoking ≥ 10 cpd • No intention to stop smoking within the last 3 months • Using EC with nicotine • No infection of airways at the time of measurements • EC group: intending to use EC • Control group: smoking cessation in the framework of a clinical conducted program Exclude if: • pregnancy or breastfeeding • not speaking German • known allergy • acute psychiatric diseases, suicidal tendency • drug/substance/alcohol abuse • severe internal diseases
Interventions	Comparison between: • People who smoke who intend to start **EC use** for the first time • 2) People who smoke who **intend to quit** smoking within a clinical conducted smoking cessation program
Outcomes	Primary: • Lung function • QoL • Respiratory tract inflammation
Starting date	October 2015
Contact information	Tobias Rüther
Notes	

NCT03589989

Study name	The ESTxENDS Trial- Electronic Nicotine Delivery Systems (ENDS/Vaporizer/E-cigarette) as an aid for smoking cessation. (ESTxENDS)
Methods	Randomized, parallel-assignment, open-label trial Setting: Switzerland Recruitment: Not specified
Participants	Estimated Enrolment: 1172 Inclusion criteria: • Informed consent as documented by signature • Persons aged 18 or older • Currently smoking 5 or more cigarettes a day for at least 12 months

NCT03589989 *(Continued)*

- Willing to try to quit smoking within the next 3 months
- Persons providing a valid phone number, a valid email address and/or a valid postal address.

Exclusion criteria:

- Known hypersensitivity or allergy to contents of the e-liquid
- Participation in another study with investigational drug within the 30 days preceding the baseline visit and during the present study where interactions are to be expected
- Women who are pregnant or breastfeeding
- Intention to become pregnant during the course of the scheduled study intervention, i.e. within the first 6 months of the study
- Persons having used ENDS regularly in the 3 months preceding the baseline visit
- Persons having used nicotine replacement therapy (NRT) or other medications with demonstrated efficacy as an aid for smoking cessation such as varenicline or bupropion within the 3 months preceding the baseline visit
- Persons who cannot attend the 6-month follow-up visit for any reason
- Cannot understand instructions delivered in person or by phone, or otherwise unable to participate in study procedures

Interventions

- a) ENDS (vaporizer/e-cig) and smoking cessation counseling will receive:
  - ENDS and nicotine-containing e-liquids, which they will be allowed to use ad libitum
  - Smoking cessation counseling: provided in person at the first clinical visit and then over the phone at the target quit date 1 week later and again at weeks 2, 4 and 8 after the target quit date. After 6 months, participants will be asked to come to a final clinical visit
  - Participants will be allowed to additionally use nicotine replacement therapy
- b) Control group will receive smoking cessation counseling only as provided for a). Participants will be allowed to additionally use nicotine replacement therapy

Outcomes

Primary outcome: Continuous smoking abstinence at 6 months post-quit date measured by:

- Self-report of having smoked no cigarettes from quit date, validated by urinary levels of anabasine. If anabasine is missing, validation by exhaled carbon monoxide (CO).

Seconday outcomes:

- Continuous smoking abstinence at 6 months post-quit date
  - Self-report of having smoked no cigarettes from quit date, validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled carbon monoxide (CO)
- Self-reported smoking abstinence allowing a 2-week`grace period' at 4, 8 weeks and 6 months post quit date
- Validated smoking abstinence allowing a 2-week`grace period at 6 months post quit date
  - validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO
  - validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO
- Self-reported smoking abstinence allowing up to 5 cigarettes at 1, 2, 4, 8 weeks and 6 months post-quit date
- Validated smoking abstinence allowing up to 5 cigarettes at 6 months post-quit date:
  - validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO
  - validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO
- Self-reported 7-day PPA at 1, 2, 4, 8 weeks and 6 months post-quit date
- Validated 7-day PPA at 6 months post-quit date
  - Confirmation of having smoked no cigarettes in the past 7 days, validated by urinary levels of anabasine. If anabasine is missing validation by exhaled CO
  - Confirmation of having smoked no cigarettes in the past 7 days, validated by urinary levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol). If NNAL is missing, validation by urinary levels of anabasine or exhaled CO

NCT03589989 *(Continued)*

	• Number of cpd at baseline, target quit date, 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported • Change in number of cpd at baseline, 6 months post-quit date, self-reported. Successful reduction defined as 50% reduction in cpd • Use of any other smoking cessation products (NRT) at 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported • Withdrawal at baseline and 6 months • Fagerström Test for Nicotine Dependence at baseline and 6 months • Swiss EQ-5D at baseline and 6 months • Use of any ENDS at 1, 2, 4, 8 weeks and 6 months post-quit date, self-reported • Most common adverse events using ENDS at 1, 2, 4, 8 weeks and 6 months post-quit date
Starting date	16 July 2018
Contact information	Reto Auer, reto.auer@biham.unibe.ch Anna Schöni, anna.schoeni@biham.unibe.ch
Notes	Linked trials: NCT03603340; NCT03603353; NCT03612336; NCT03612375; NCT03612453; NCT03612544; NCT03632421; NCT03938298

NCT03700112

Study name	An open-label, randomized cross-over study comparing nicotine pharmacokinetics of seven electronic cigarette products and one traditional cigarette across two delivery (10 puff and ad-libitum) conditions, in healthy adult smokers.
Methods	Open-label, randomized cross-over trial Setting and recruitment not specified, New Zealand
Participants	Estimated enrolment: 24 Inclusion criteria: • Male or female aged 18 to 60 years of age inclusive • BMI between 18 to 35 kg/m^2 inclusive • Healthy based on medical history and screening assessments, in the opinion of the Investigator • Current smoker of at least 8 cigarettes per day on average • Has been smoking for at least 12 months prior to screening. Brief periods of non-smoking (e.g. up to ~7 consecutive days due to illness, trying to quit, participation in a study where smoking was prohibited) are permitted at the discretion of the Investigator • Able to participate, and willing to give written informed consent and comply with study restrictions Exclusion criteria: • Clinically-relevant medical or psychiatric disorder, in the opinion of the Investigator • Clinically-significant abnormality on screening ECG • Sustained blood pressure recordings at screening of < 90 mmHg or > 150 mmHg for systolic blood pressure, or < 50 mmHg or > 90 mmHg for diastolic blood pressure • Sustained resting heart rate of > 100 or < 40 beats per minute at screening • Positive result for urine drugs of abuse test or alcohol breath test at screening. If a positive urine drug test is observed, and it is believed the positive urine test is due to prescription drugs, the PI should obtain documentation that a) confirms the person's use of the prescribed medication, and b) the prescribed medication will cause a false positive drug test

NCT03700112 *(Continued)*

	• Clinically-significant abnormality in laboratory test results at screening, in the opinion of the Investigator • Exposure to an investigational drug in a clinical trial within 1 month prior to Assessment Day 1 • Blood or plasma donation of > 500 mL within 1 month prior to Assessment Day 1 • Positive urine pregnancy test at screening or Assessment Day 1 in women • Any clinically-significant concomitant disease or condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the participant in this study
Interventions	• JUUL Virginia Tobacco flavored 5.0% ENDS; consumed using 10 puffs delivery method, ad-libitum • PMI iQOS Heat sticks - Regular consumed using 10 puffs delivery method, ad-libitum • Reynolds VUSE Solo ENDS - Original consumed using 10 puffs delivery method, ad-libitum • Imperial MyBlu ENDS - Original consumed using 10 puffs delivery method, ad-libitum • Altria MarkTen ENDS - Bold Classic consuming using 10 puffs delivery method, ad-libitum • MLV PHIX ENDS - Original Tobacco consumed using 10 puffs delivery method, ad-libitum • NJOY Daily EXTRA ENDS - Rich Tobacco consumed using 10 puffs delivery method, ad-libitum • Altria Marlboro combustible cigarette - Red consumed using 10 puffs delivery method, ad-libitum
Outcomes	Day 48 Outcomes: • Nicotine PK parameters calculated from the individual plasma concentrations • Exhaled CO • Level of user satisfaction measured by Modified Product Evaluation Scale • Characterize consumption of 8 x E-cigarettes/cigarettes products by collecting total number of puffs for each e-cigarette
Starting date	7 December 2018
Contact information	Study director: Concetta Carbonaro Responsible party: Juul Labs, Inc.
Notes	

NCT03962660

Study name	Harm reduction for tobacco smoking with support of tobacco-replacing electronic nicotine delivery systems (HaRTS-TRENDS)
Methods	Parallel, randomized controlled trial Setting: USA Recruitment: from prominent Housing First programs serving chronically homeless people who are often multiply affected by psychiatric, medical and substance-use disorders. The proposed sample will be recruited from a highly vulnerable and marginalized population in a tight-knit urban community
Participants	Estimated enrolment: 94 Inclusion criteria: • Having a history of chronic homelessness according to the widely-accepted federal definition

NCT03962660 *(Continued)*

	• Being a current DESC client living in 1 of DESC's participating permanent supportive housing projects • Being between 21 - 65 years of age • Being a daily smoker (> 4 cigarettes/day in the past year with a breath CO ≥ 6 ppm or salivary cotinine test at level 1 if CO < 6 ppm) • Having adequate English language skills to understand verbal information and communicate in the study Exclusion Criteria: • Use of other tobacco products besides cigarettes ≥ 9 days in the past month • Refusal or inability to consent to participation in research • Constituting a risk to the safety and security of other clients or staff.
Interventions	• Intervention: HaRTS-TRENDS: 4 individual sessions delivered in the context of the interventionist's pragmatic harm-reduction mindset paired with a compassionate, advocacy-oriented "heart-set" or style. It comprises the delivery of 4 manualized components, including * a) participant-led tracking of preferred smoking outcomes, * b) elicitation of participants' harm-reduction goals and their progress toward achieving them, * c) discussion of the relative risks of various nicotine delivery systems, * d) instruction in using ENDS. Additionally, HaRTS-TRENDS entails provision of commercially available ENDS. • Standard care: The 4-session, individual standard care control condition entails the well-documented and evidence-based 5 As intervention (i.e. Ask about nicotine use, Assess use, Advise to quit smoking, Assist with exploring current smoking/planning smoking cessation, Arrange follow-up). Part of arranging follow-up is the recommendation to call the smoking quit line, which can supply additional counseling and nicotine replacement therapy
Outcomes	Primary outcomes, measured across the 12-month follow-up: • Biologically-verified nonsmoking (i.e. self-reported nonsmoking if corresponding CO measure is < 8) in the past 7 days • Urinary concentration of a tobacco-specific nitrosamine Secondary outcomes, measured across the 12-month follow-up: • Self-reported smoking intensity is the mean number of cigarettes participants report smoking per day in the 7 days prior to the assessment • Self-reported smoking frequency is the number of days participants report smoking in the 7 days prior to the assessment • CO level • Urinary cotinine • FEV1% • 10-item Clinical COPD Questionnaire • EQ-5D-5L Other outcomes: • Smoking craving • Side effects of ENDS
Starting date	9 May 2019
Contact information	Tatiana M Ubay, tatiubay@uw.edu
Notes	

NCT04063267

Study name	Electronic cigarettes as a harm reduction strategy in individuals with substance use disorder
Methods	Parallel, randomized trial Recruitment/Setting: Not specified
Participants	Estimated enrolment: 240 Inclusion criteria: • Smokes at least 10 cpd • Meet DSM-V AUD and/or OUD within the past year, interested in reducing cpd • Able to provide consent • Use a cell phone, are willing/able to receive and respond to daily text messages about their cigarette use and e-cigarette use on their cell phone • Provide 1 additional contact, and are willing to use an e-cigarette for 3 weeks Exclusion criteria: • Pregnant and/or breast feeding (self-reported) • Currently using smoking cessation medications (including other forms of NRT, bupropion, or varenicline) • enrolled in a smoking cessation program or another cessation trial • Have used an e-cigarette in the past 14 days • Have used any other tobacco products (pipe, cigar, cigarillos, snuff, chewing tobacco, rolling tobacco, or hookah/shisha) in the past 30 days • Report having a history of asthma, other airways diseases, or heart disease
Interventions	**E-cigarettes arm:** • Participants will be encouraged to substitute e-cigarettes for combustible cigarettes in order to reduce nicotine withdrawal symptoms **Nicotine Replacement Therapy** arm: • Nicotine patches and gum to last them the first week based on their baseline recorded smoking. Participants will be advised to use both a 21 mg nicotine patch and 4 mg nicotine for cravings
Outcomes	Proportion of participants who achieve 50% reduction in cpd at 3 weeks
Starting date	15 September 2019
Contact information	NYU Langone Health, Scott.Sherman@nyulangone.org
Notes	

NCT04231838

Study name	A randomized controlled international multicentre study evaluating changes in metabolic syndrome in smokers with type 2 diabetes mellitus after switching from tobacco cigarettes to combustion-free nicotine delivery systems: DIASMOKE Study Short title: Metabolic syndrome in diabetic smokers using cigarettes & combustion-free nicotine delivery systems (DIASMOKE)

NCT04231838 *(Continued)*

Methods	RCT Setting: Italy
Participants	576 participants Inclusion criteria: Participants will be required to satisfy all of the following criteria at the screening visit, unless otherwise stated: • Participants will be: 1.1. over 23 years of age • T2DM Patients will have: 2.1. body mass index (BMI) between 17.6 and 32.0 kg/m^2, inclusive 2.2. body weight exceeding 50 kg (men) or 40 kg women 2.3 6.5 < HbA1C < 10 3.2. completion of proforma (CRF) 3.3. lab assessment as outlined in the CRF • Participants will be willing to refrain from eating/drinking prior to screening and check-in at each study visit. • Participants will be regular smokers of at least 10 cigarettes/day (max 30 cigarette/day) • Participants will have smoked for at least 5 consecutive years prior to screening • Participants must have a saliva cotinine level > 10 ng/mL or an exhaled breath CO (eCO) level > 7 ppm at screening • Participants in Arm A who continue to smoke will be willing to use their own brand/type cigarettes • Participants in Arm B will be willing to use the study products (THP product or e-cigarette) provided to them during the study Exclusion Criteria: Participants will be excluded at the screening visit based on the following criteria: • Women who are pregnant or breastfeeding. This will be confirmed at screening and at visit 1. Any woman who becomes pregnant during this study will be withdrawn • People with a history of recent acute decompensation of their disease requiring treatment within 4 weeks prior to visit 1 • People who have a significant history of alcoholism or drug/chemical abuse within 24 months prior to screening, as determined by the investigator • People who are still participating in another clinical study (e.g. attending follow-up visits) or who have participated in a clinical study involving administration of an investigational drug (new chemical entity) in the past 3 months prior to first product use • People who have, or who have a history of, any clinically-significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematological or other major disorder that, in the opinion of the investigator or their appropriately qualified designee, would jeopardize the safety of the person or impact on the validity of the study results • People who regularly use any nicotine (e.g. e-cigarettes, NRT) or tobacco product (e.g. HTPs, oral smokeless) other than their own cigarettes within 14 days of screening At screening and prior to enrolment, all patients will be offered a locally-available free smoking cessation program as per local guidelines. Those who express the intention of booking for the cessation program together with those who, at screening, are planning to quit smoking in the next 6 months, will not be recruited into the study. Patients taking part in the study will be informed that they are free to quit smoking and withdraw from the study at any time. Any person who decides to quit smoking will be directed to local stop smoking services.
Interventions	Arm A: tobacco cigarettes (continuing smoking their own tobacco cigarette brand) Arm B: switching to using combustion-free nicotine delivery systems (C-F NDS)
Outcomes	Time frame: 3 months, 6 months, 1 year and 2 years

NCT04231838 *(Continued)*

	Change in metabolic syndrome prevalence Change in plasma glucose Change in triglycerides Change in high-density lipoprotein (HDL) Change in waist circumference
Starting date	Estimated start date: 17 September 2020. Estimated primary completion September 2021. Estimated study completion March 2025
Contact information	Daniela Saitta, PhD, daniela.saitta@eclatrbc.it Riccardo Polosa, PhD, polosa@unict.it
Notes	

NCT04238832

Study name	Impact of non-cigarette tobacco product formulation on reinforcement value and use in current smokers Short title: Salt-Based E-cigarette
Methods	RCT Setting: USA, South Carolina
Participants	30 participants Inclusion criteria: • daily cigarette smoker • interested in using non-cigarette tobacco product • have a smartphone that can receive text messages and has access to the internet or have an e-mail account they check daily (necessary for daily diary completion) Exclusion criteria: • additional tobacco use criteria • additional medical criteria
Interventions	Salt base nicotine Free base nicotine
Outcomes	Most preferred product [Time Frame: Lab Visit 2, occurring approximately 1 week after the initial screening/baseline visit] Participants complete a preference assessment in which they choose between the salt liquid, free-base liquid, or a traditional cigarette in a series of trials. The outcome of this assessment is the product chosen most often by each participant Cigarettes per day [Time Frame: Week 2 of study] The average number of cigarettes smoked per day during the 1 week sampling period. Biomarkers (i.e. expired CO, cotinine) will corroborate self-reported indices of use

NCT04238832 *(Continued)*

Starting date	23 June 2020. Estimated completion August 2021
Contact information	Tracy Smith, smithtra@musc.edu
Notes	

NCT04452175

Study name	Official title: Cigarette consumption after switchinG to high or low Nicotine strENght E-cigaretteS In Smokers with Schizophrenia spectrum disorders: a 12-month randomized, double-blind multicentre trial Brief title: Cigarette consumption after switchinG to high or low nicotine strENght E-cigaretteS In Smokers with Schizophrenia (GENESIS)
Methods	RCT Multicenter: Italy, Russia, Ukraine, UK Collaborators: • Juul Labs, Inc. • St. Petersburg State Pavlov Medical University • Bashkir State Medical University • Ukrainian Institute on Public Health Policy • University of Surrey • Eclat Srl
Participants	Estimated enrolment: 260 Inclusion criteria: • Adult (> 18 yrs) • Regular smoking (> 10 cigarettes a day; for at least 1 year) • Exhaled breath CO (eCO) level > 7 ppm • Not currently attempting to quit smoking or wishing to do so in the next 30 days; this will be verified at screening by the answer ''NO'' to the question ''Do you intend to quit in the next 30 days?'' • Schizophrenia spectrum disorder diagnosis (schizophrenia, delusional disorder, schizoaffective disorder, personality disorder, schizoid personality disorder, etc) by DSM-V criteria • Understand and provide informed consent • Able to comply with all study procedures Exclusion criteria: • Institutionalized patients • Acute decompensation of Schizophrenia spectrum disorder symptoms within the past month • Change in antipsychotic treatment within the past month • No recent history of hospitalization for any serious medical condition within 3 months prior to screening, as determined by the investigator • Myocardial infarction or angina pectoris within 3 months prior to screening, as determined by the investigator • Current poorly-controlled asthma or COPD • Pregnancy, planned pregnancy or breastfeeding. Any female participant who becomes pregnant during this study will be withdrawn • People who have a significant history of alcoholism or drug/chemical abuse within 12 months prior to screening, as determined by the investigator.

NCT04452175 *(Continued)*

	• Accepting to take part in a smoking cessation program • People who regularly use any recreational nicotine (e.g. e-cigarettes,) or tobacco product (e.g. tobacco heated products, oral smokeless) other than their own cigarettes within 30 days of screening • People who have used smoking cessation therapies (e.g. varenicline, bupropion, or NRT) within 30 days of screening • People who are still participating in another clinical study (e.g. attending follow-up visits) or who have recently participated in a clinical study involving administration of an investigational drug (new chemical entity) within the past 3 months • People who have, or who have a history of, any clinically-significant neurological, gastrointestinal, renal, hepatic, cardiovascular, psychiatric, respiratory, metabolic, endocrine, hematological or other major disorder that, in the opinion of the investigator or their appropriately qualified designee, would jeopardize the safety of the participant or impact on the validity of the study results
Interventions	• Experimental: HIGH 5%. Intervention: JUUL E-CIGARETTE • Active Comparator: LOW 1.7%. Intervention: JUUL E-CIGARETTE
Outcomes	Primary outcomes: • Rates of participants with continuous smoking abstinence at 6 months; Time Frame: 24 weeks • Self-reported continuous smoking abstinence at 6 months from the previous visit, biochemically-verified by exhaled CO measurements of ≤ 7 ppm Secondary outcomes • Rates of participants with continuous smoking abstinence at 12-month [Time Frame: 52 weeks] • Rates of participants with continuous smoking reduction at 6-month [Time Frame: 24 weeks] • Rates of participants with continuous smoking reduction at 12-month [Time Frame: 52 weeks] • Proportion of AEs [Time Frame: 24 weeks] • Absolute change in PANSS [Time Frame: 24 weeks] • Absolute change in mCEQ [Time Frame: 24 weeks] • Absolute change in Chester Step Test-derived values [Time Frame: 24 weeks] • Change in App-derived endpoints (self-rated mental health -SRMH). [Time Frame: 24 weeks]
Starting date	October 2020. Estimated completion date March 2022
Contact information	Pasquale Caponnetto, p.caponnetto@unict.it
Notes	

NCT04649645

Study name	International randomized controlled trial evaluating changes in oral health in smokers after switching to combustion-free nicotine delivery systems (SMILE)
Methods	RCT Setting: multicenter: Italy, Moldova, Poland, UK and Indonesia
Participants	Estimated enrolment 606 participants Inclusion criteria: • Demonstrate understanding of the study and willingness to participate in the study by providing a signed written informed consent • Healthy, not taking regular medications for chronic medical conditions

NCT04649645 *(Continued)*

- Adults, age at least 18 years old
- Presence of at least 10 natural anterior teeth in total (cuspid to cuspid, lower and upper jaw)
- Presence of at least 18 'scorable' teeth with scorable facial and lingual surfaces. Teeth that are grossly carious, orthodontically banded, exhibiting general cervical abrasion and/or enamel abrasion, and third molars will not be included in the tooth count
- Willingness and ability to comply with the requirements of the study including installing an APP on their digital device, e.g. smart phone or tablet

For Arms A and B, participants have to be:

- Regular smokers, defined as: smoked for at least 5 consecutive years prior to screening. Smoked > 10 and < 30 cigarettes per day (cpd).with an exhaled breath carbon monoxide (CO) level ≥ 7 ppm at screening
- willing to regularly use any nicotine or tobacco product other than their own conventional cigarettes brand within 14 days prior to screening
- willing to change to use of study products or if randomized to Arm A continuing to use their own brand of conventional cigarettes for the whole duration of the study

For Arm C, participants have to be:

- Never-smokers, defined as:never smoked or who have smoked < 100 cigarettes in their lifetime and none in the 30 days prior to screening.with an exhaled breath CO level < 7 ppm at screening
- willing to not smoke or use any form of tobacco or nicotine-containing products for the whole duration of the study

Exclusion criteria:

- Pregnancy
- Presence of extensive crown or bridge work, dental implants, and/or rampant decay (per Investigator/Examiner discretion)
- Significant oral soft tissue pathology or any type of gingival overgrowth, other than plaque-induced gingivitis and mild periodontitis (Stage I)
- Moderate-to-severe periodontitis (Stage II, III and IV) based on 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions, which require:Detectable Interdental Clinical Attachment Loss (CAL) ≥ 3 mm at ≥ 2 non-adjacent teeth. Buccal or Oral CAL ≥ 3 mm with pocketing ≥ 5 mm detectable at ≥ 2 teeth
- Removable dentures or fixed and removable orthodontic appliance (except fixed lingual wires)
- Significant history of alcoholism or drug abuse (other than tobacco/nicotine) within 24 months prior to screening, as determined by the Investigator
- A course of treatment with any medications or substances (other than tobacco/nicotine) which:interfere with the cyclo-oxygenase pathway (e.g. anti-inflammatory drugs including aspirin and ibuprofen) within 3 days prior to each visit.are known to have antibacterial activity (e.g. antibiotics) within 7 days prior to each visit

Interventions	Standard Arm (Arm A): own tobacco cigarette brand Intervention Arm (Arm B): combustion-free nicotine delivery system (C-F NDS) Control Arm (Arm C): no smoking or use of any nicotine/tobacco products
Outcomes	Oral health parameters and teeth appearance, comparing short- and long-term impact on periodontal health between smokers continuing with conventional cigarette smoking, those switching to combustion-free nicotine delivery systems (C-F NDS), and never-smokers over 18 months
Starting date	Not yet recruiting (last updated February 2021) Estimated study start date Feb 2021. Primary completion date Feb 2023. Completion April 2023
Contact information	Principal investigator: Antonio Pacino, DDS, Addendo srl, Catania, Italy

NCT04649645 *(Continued)*	info@addendo.net
Notes	

BMI: body mass index; CAR: continuous abstinence rate; CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; cpd: cigarettes per day; CVD: cardiovascular disease; EC: electronic cigarette; ECG: electrocardiogram; FTND: Fagerström Test for Nicotine Dependence; NNAL: carcinogen found in tobacco smoke; NRT: nicotine replacement therapy; PP(A): point prevalence (abstinence); QoL: quality of life; TQD: target quit date; wk: week; yr: year

DATA AND ANALYSES

Comparison 1. Nicotine EC versus NRT

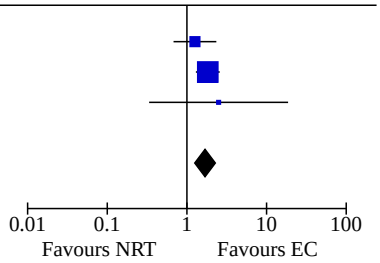
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Smoking cessation	3	1498	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [1.25, 2.27]
1.2 Adverse events	2	485	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.80, 1.19]
1.2.1 4 weeks	1	29	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.31, 1.73]
1.2.2 6 months	1	456	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.22]
1.3 Serious adverse events	2	727	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.77, 2.41]
1.3.1 4 weeks	1	29	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.3.2 1 year	1	698	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.77, 2.41]
1.4 Carbon monoxide (ppm)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 8 weeks	2	136	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-1.94, 0.62]
1.5 Heart rate (bpm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Blood oxygen saturation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 3-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 NNAL (pmol/mg creatinine))	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10 2-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.10.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11 HMPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.11.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12 PheT (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13 CEMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.13.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14 AAMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.14.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15 FEV1 (ml)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.15.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.16 FEV1/FVC (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.16.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1: Nicotine EC versus NRT, Outcome 1: Smoking cessation

Study or Subgroup	EC Events	EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bullen 2013	21	289	17	295	27.2%	1.26 [0.68 , 2.34]
Hajek 2019	79	438	44	446	70.6%	1.83 [1.30 , 2.58]
Lee 2018	5	20	1	10	2.2%	2.50 [0.34 , 18.63]
Total (95% CI)		**747**		**751**	**100.0%**	**1.69 [1.25 , 2.27]**
Total events:	105		62			

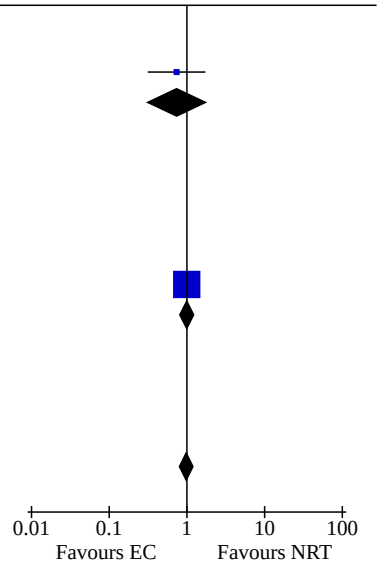
Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Nicotine EC versus NRT, Outcome 2: Adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 4 weeks						
Lee 2018 (1)	7	19	5	10	6.1%	0.74 [0.31 , 1.73]
Subtotal (95% CI)		**19**		**10**	**6.1%**	**0.74 [0.31 , 1.73]**
Total events:	7		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
1.2.2 6 months						
Bullen 2013	107	241	96	215	93.9%	0.99 [0.81 , 1.22]
Subtotal (95% CI)		**241**		**215**	**93.9%**	**0.99 [0.81 , 1.22]**
Total events:	107		96			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**260**		**225**	**100.0%**	**0.98 [0.80 , 1.19]**
Total events:	114		101			

Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.21 (P = 0.83)
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%

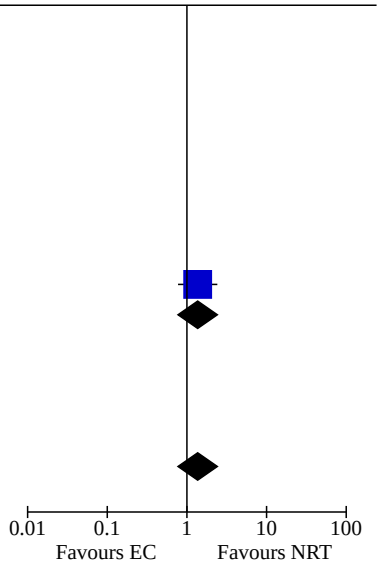


Footnotes

(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

Analysis 1.3. Comparison 1: Nicotine EC versus NRT, Outcome 3: Serious adverse events

Study or Subgroup	EC Events	EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 4 weeks						
Lee 2018 (1)	0	19	0	10		Not estimable
Subtotal (95% CI)		**19**		**10**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.3.2 1 year						
Hajek 2019	27	356	19	342	100.0%	1.37 [0.77 , 2.41]
Subtotal (95% CI)		**356**		**342**	**100.0%**	**1.37 [0.77 , 2.41]**
Total events:	27		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**375**		**352**	**100.0%**	**1.37 [0.77 , 2.41]**
Total events:	27		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Not applicable						

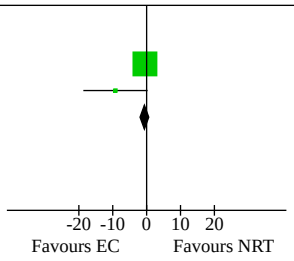


Footnotes

(1) Data at 4 weeks post-operation; time from baseline not defined and likely to differ between participants

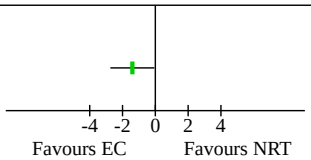
Analysis 1.4. Comparison 1: Nicotine EC versus NRT, Outcome 4: Carbon monoxide (ppm)

Study or Subgroup	Nicotine EC Mean	Nicotine EC SD	Nicotine EC Total	NRT Mean	NRT SD	NRT Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 8 weeks								
Hatsukami 2020	-9.1	2.9	58	-8.6	3.9	52	98.2%	-0.50 [-1.80 , 0.80]
Lee 2018	-2.1	12.2	18	7.1	11	8	1.8%	-9.20 [-18.68 , 0.28]
Subtotal (95% CI)			**76**			**60**	**100.0%**	**-0.66 [-1.94 , 0.62]**
Heterogeneity: Chi² = 3.18, df = 1 (P = 0.07); I² = 69%								
Test for overall effect: Z = 1.01 (P = 0.31)								
Test for subgroup differences: Not applicable								



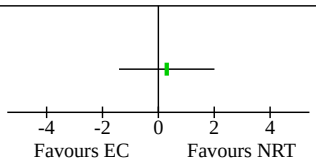
Analysis 1.5. Comparison 1: Nicotine EC versus NRT, Outcome 5: Heart rate (bpm)

Study or Subgroup	Nicotine EC Mean	Nicotine EC SD	Nicotine EC Total	NRT Mean	NRT SD	NRT Total	Mean Difference IV, Fixed, 95% CI
1.5.1 8 weeks							
Hatsukami 2020	-4.6	3.9	58	-3.2	3.3	53	-1.40 [-2.74 , -0.06]



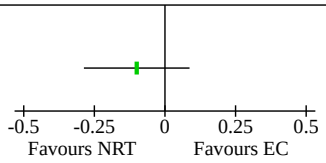
Analysis 1.6. Comparison 1: Nicotine EC versus NRT, Outcome 6: Systolic blood pressure

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.6.1 8 weeks								
Hatsukami 2020	1.6	3.8	58	1.3	5.2	53	0.30 [-1.41 , 2.01]	



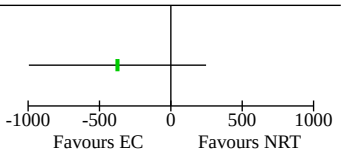
Analysis 1.7. Comparison 1: Nicotine EC versus NRT, Outcome 7: Blood oxygen saturation

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.7.1 8 weeks								
Hatsukami 2020	0.2	0.5	57	0.3	0.5	53	-0.10 [-0.29 , 0.09]	



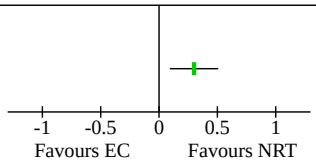
Analysis 1.8. Comparison 1: Nicotine EC versus NRT, Outcome 8: 3-HPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.8.1 8 weeks								
Hatsukami 2020	-2681	1523	58	-2307	1788	53	-374.00 [-994.76 , 246.76]	



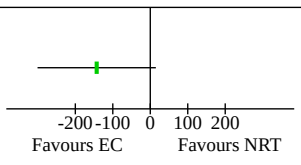
Analysis 1.9. Comparison 1: Nicotine EC versus NRT, Outcome 9: NNAL (pmol/mg creatinine))

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.9.1 8 weeks								
Hatsukami 2020	-0.6	0.5	57	-0.9	0.6	53	0.30 [0.09 , 0.51]	



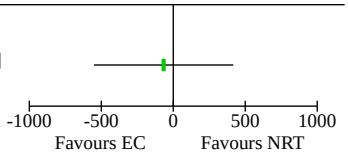
Analysis 1.10. Comparison 1: Nicotine EC versus NRT, Outcome 10: 2-HPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.10.1 8 weeks								
Hatsukami 2020	-249	525	58	-106	303	53	-143.00 [-300.83 , 14.83]	



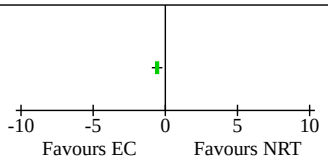
Analysis 1.11. Comparison 1: Nicotine EC versus NRT, Outcome 11: HMPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.11.1 8 weeks								
Hatsukami 2020	-2061	1069	58	-1994	1478	53	-67.00 [-550.76 , 416.76]	



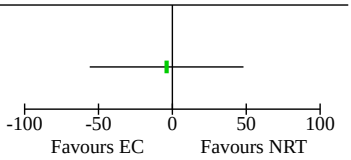
Analysis 1.12. Comparison 1: Nicotine EC versus NRT, Outcome 12: PheT (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.12.1 8 weeks								
Hatsukami 2020	-0.56	0.73	56	0.01	1.16	53	-0.57 [-0.94 , -0.20]	



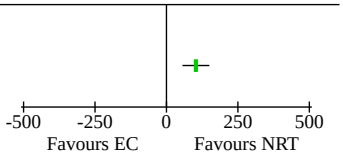
Analysis 1.13. Comparison 1: Nicotine EC versus NRT, Outcome 13: CEMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.13.1 8 weeks								
Hatsukami 2020	-266.4	136	58	-262.5	143	53	-3.90 [-55.93 , 48.13]	



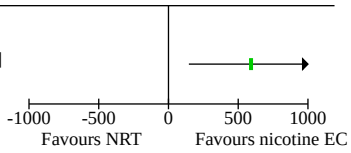
Analysis 1.14. Comparison 1: Nicotine EC versus NRT, Outcome 14: AAMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
1.14.1 8 weeks								
Hatsukami 2020	-144	114	58	-247	134	51	103.00 [55.95 , 150.05]	



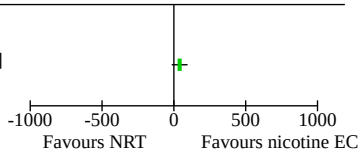
Analysis 1.15. Comparison 1: Nicotine EC versus NRT, Outcome 15: FEV1 (ml)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.15.1 8 weeks							
Lee 2018	292	503	18	-300	549	8	592.00 [146.22 , 1037.78]



Analysis 1.16. Comparison 1: Nicotine EC versus NRT, Outcome 16: FEV1/FVC (%)

Study or Subgroup	Nicotine EC Mean	SD	Total	NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.16.1 8 weeks							
Lee 2018	2	10.5	18	-38.1	79.2	8	40.10 [-15.00 , 95.20]

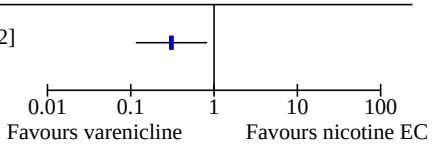


Comparison 2. Nicotine EC versus varenicline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.2 Serious adverse events	1	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2.1 12 weeks	1	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

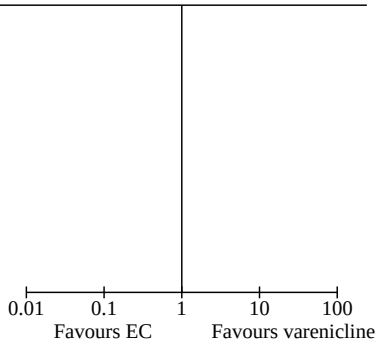
Analysis 2.1. Comparison 2: Nicotine EC versus varenicline, Outcome 1: Smoking cessation

Study or Subgroup	Nicotine EC Events	Total	Varenicline Events	Total	Risk Ratio M-H, Fixed, 95% CI
Ioakeimidis 2018	4	27	13	27	0.31 [0.11 , 0.82]



Analysis 2.2. Comparison 2: Nicotine EC versus varenicline, Outcome 2: Serious adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Varenicline Events	Varenicline Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 12 weeks						
Ioakeimidis 2018 (1)	0	27	0	27		Not estimable
Subtotal (95% CI)		**27**		**27**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**27**		**27**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Footnotes

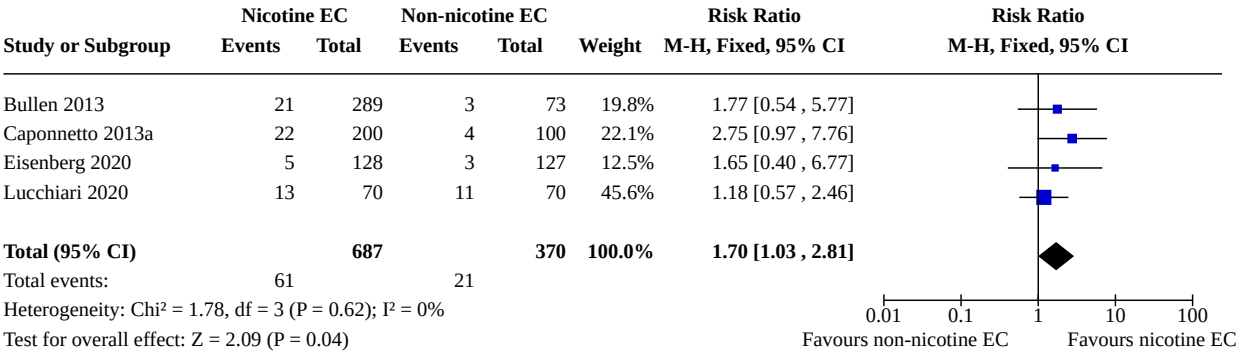
(1) n followed up not reported; n randomised used as denominators

Comparison 3. Nicotine EC versus non-nicotine EC

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.1 Smoking cessa-tion	4	1057	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.03, 2.81]
3.2 Adverse events	3	601	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.11]
3.2.1 1 week	1	48	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.27, 8.19]
3.2.2 6 months	1	298	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.71, 1.34]
3.2.3 12 weeks	1	255	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.94, 1.08]
3.3 Serious adverse events	4	494	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.15, 2.44]
3.3.1 1 week	1	48	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.2 4 weeks	1	74	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3.3 24 weeks	1	255	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.15, 2.44]
3.3.4 1 year	1	117	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Carbon monoxide (ppm)	2	171	Mean Difference (IV, Fixed, 95% CI)	-2.44 [-3.91, -0.97]
3.4.1 2 weeks	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-3.00, 2.20]
3.4.2 12 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-5.18, -1.62]
3.5 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

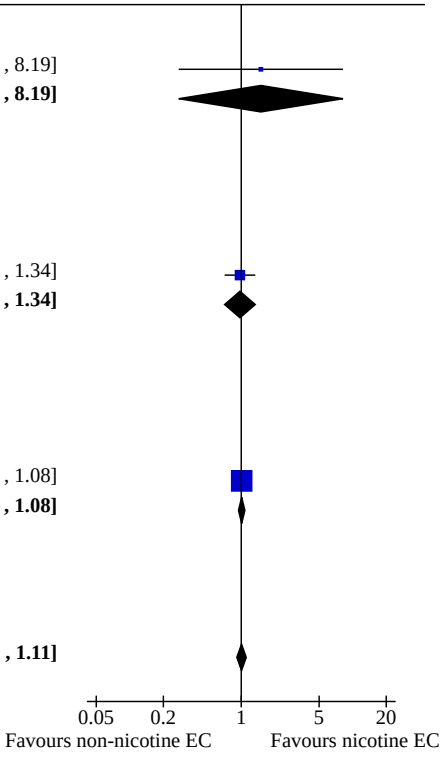
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
3.5.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.6.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7 FeNO (ppb)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.7.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8 FEV1 (l)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.8.1 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9 FVC (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.9.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10 FEV1/FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.10.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 1: Smoking cessation



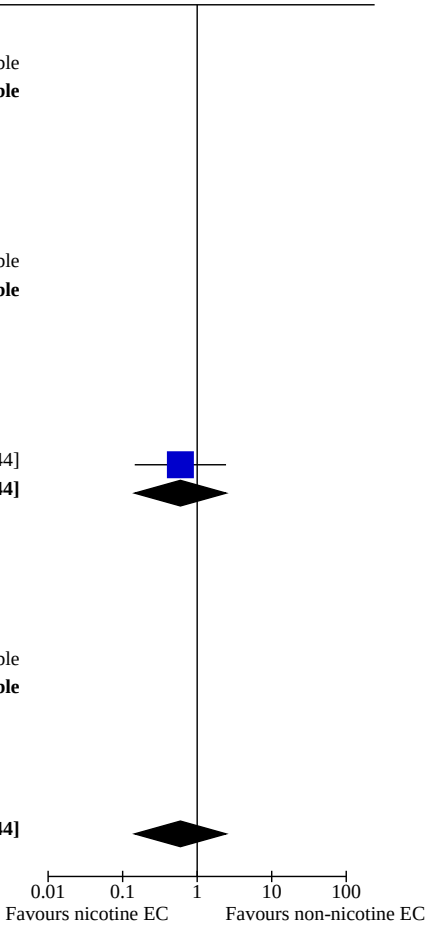
Analysis 3.2. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 2: Adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Non-nicotine EC Events	Non-nicotine EC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 1 week						
Meier 2017	3	24	2	24	1.2%	1.50 [0.27 , 8.19]
Subtotal (95% CI)		**24**		**24**	**1.2%**	**1.50 [0.27 , 8.19]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
3.2.2 6 months						
Bullen 2013	107	241	26	57	25.9%	0.97 [0.71 , 1.34]
Subtotal (95% CI)		**241**		**57**	**25.9%**	**0.97 [0.71 , 1.34]**
Total events:	107		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.17 (P = 0.87)						
3.2.3 12 weeks						
Eisenberg 2020	120	128	118	127	72.9%	1.01 [0.94 , 1.08]
Subtotal (95% CI)		**128**		**127**	**72.9%**	**1.01 [0.94 , 1.08]**
Total events:	120		118			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
Total (95% CI)		**393**		**208**	**100.0%**	**1.01 [0.91 , 1.11]**
Total events:	230		146			
Heterogeneity: Chi² = 0.26, df = 2 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 0.26, df = 2 (P = 0.88), I² = 0%						



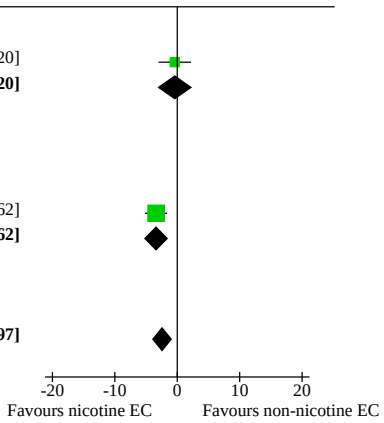
Analysis 3.3. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 3: Serious adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Non-nicotine EC Events	Non-nicotine EC Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 1 week						
Meier 2017	0	24	0	24		Not estimable
Subtotal (95% CI)		**24**		**24**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.2 4 weeks						
George 2019	0	37	0	37		Not estimable
Subtotal (95% CI)		**37**		**37**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.3.3 24 weeks						
Eisenberg 2020	3	128	5	127	100.0%	0.60 [0.15 , 2.44]
Subtotal (95% CI)		**128**		**127**	**100.0%**	**0.60 [0.15 , 2.44]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
3.3.4 1 year						
Caponnetto 2013a	0	72	0	45		Not estimable
Subtotal (95% CI)		**72**		**45**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**261**		**233**	**100.0%**	**0.60 [0.15 , 2.44]**
Total events:	3		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: Not applicable						



Analysis 3.4. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 4: Carbon monoxide (ppm)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.4.1 2 weeks								
Felicione 2019	-1.9	3.4	14	-1.5	3.2	11	32.0%	-0.40 [-3.00 , 2.20]
Subtotal (95% CI)			**14**			**11**	**32.0%**	**-0.40 [-3.00 , 2.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
3.4.2 12 weeks								
Caponnetto 2013a (1)	-6	6.4	76	-2.6	4.5	70	68.0%	-3.40 [-5.18 , -1.62]
Subtotal (95% CI)			**76**			**70**	**68.0%**	**-3.40 [-5.18 , -1.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.74 (P = 0.0002)								
Total (95% CI)			**90**			**81**	**100.0%**	**-2.44 [-3.91 , -0.97]**
Heterogeneity: Chi² = 3.48, df = 1 (P = 0.06); I² = 71%								
Test for overall effect: Z = 3.25 (P = 0.001)								
Test for subgroup differences: Chi² = 3.48, df = 1 (P = 0.06), I² = 71.3%								

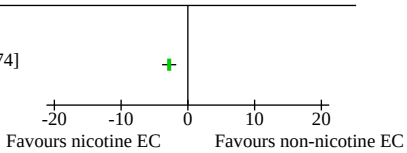


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.5. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 5: Heart rate

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.5.1 12 weeks							
Caponnetto 2013a (1)	-1.7	3.4	73	1.1	3	68	-2.80 [-3.86 , -1.74]

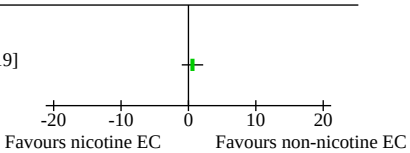


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.6. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 6: Systolic blood pressure

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.6.1 12 weeks							
Caponnetto 2013a (1)	-3.9	5.7	73	-4.5	3.8	68	0.60 [-0.99 , 2.19]

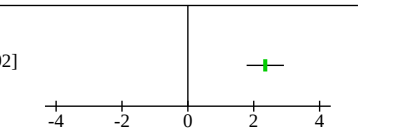


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.7. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 7: FeNO (ppb)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.7.1 12 weeks							
Caponnetto 2013a (1)	2.8	1.7	49	0.45	1	41	2.35 [1.78 , 2.92]

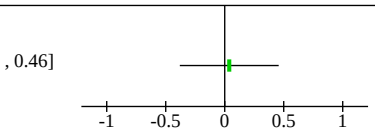


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.8. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 8: FEV1 (l)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Std. Mean Difference IV, Fixed, 95% CI
3.8.1 12 weeks							
Caponnetto 2013a (1)	0	0.3	47	-0.01	0.2	41	0.04 [-0.38 , 0.46]

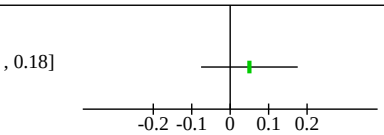


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.9. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 9: FVC (l)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.9.1 12 weeks							
Caponnetto 2013a (1)	-0.02	0.3	47	-0.07	0.3	41	0.05 [-0.08 , 0.18]

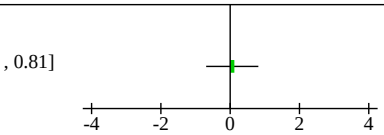


Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Analysis 3.10. Comparison 3: Nicotine EC versus non-nicotine EC, Outcome 10: FEV1/FVC

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
3.10.1 12 weeks							
Caponnetto 2013a (1)	0.96	2	47	0.9	1.6	41	0.06 [-0.69 , 0.81]



Footnotes

(1) Data is 2.4% nicotine compared to no-nicotine; 1.8% nicotine arm reported elsewhere

Comparison 4. Nicotine EC versus behavioural support only/no support

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.1 Smoking cessation	5	2561	Risk Ratio (M-H, Fixed, 95% CI)	2.70 [1.39, 5.26]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 Adverse events	4	765	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [1.12, 1.32]
4.2.1 12 weeks	2	657	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [1.11, 1.30]
4.2.2 16 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.67, 2.07]
4.2.3 6 months	1	58	Risk Ratio (M-H, Fixed, 95% CI)	11.00 [0.64, 190.26]
4.3 Serious adverse events	6	1011	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.33, 4.09]
4.3.1 4 to 6 weeks	2	246	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3.2 12 weeks	1	408	Risk Ratio (M-H, Fixed, 95% CI)	3.69 [0.21, 66.17]
4.3.3 16 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.3.4 6 months	2	307	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.16, 3.10]
4.4 Carbon monoxide (ppm)	8		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.1 3 to 4 weeks	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.2 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.3 8 weeks	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.4 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.4.5 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5 Heart rate (bpm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.5.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6 Systolic blood pressure	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.1 6 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.2 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.6.3 4 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7 Blood oxygen saturation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.7.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8 3-HPMA (SMD)	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.8.1 8 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected

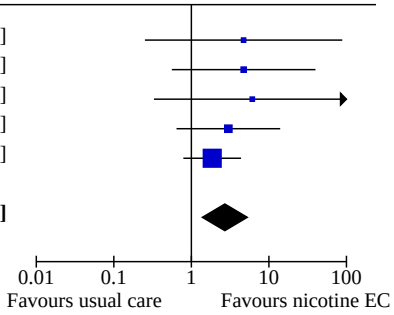
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.8.2 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9 NNAL (SMD)	4		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.1 3 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.2 8 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.3 12 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.9.4 6 weeks	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.10 2-HPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.10.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.11 HMPMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.11.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.12 PheT (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.12.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.13 CEMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.13.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14 AAMA (pmol/mg creatinine)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.14.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15 S-PMA (nanograms)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.15.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.16 FVC (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.16.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.17 FEV1 (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.17.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.18 FEF 25-75 (litres/second))	2	555	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.18, 0.06]
4.18.1 6 weeks	1	168	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.28, 0.00]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.18.2 12 weeks	1	387	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
4.19 PEF 25-75 (litres/minute)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.19.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 1: Smoking cessation

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dawkins 2020	3	48	0	32	5.3%	4.71 [0.25 , 88.30]
Eisenberg 2020	5	128	1	121	9.2%	4.73 [0.56 , 39.88]
Halpern 2018	4	1199	0	813	5.3%	6.11 [0.33 , 113.24]
Holliday 2019 (1)	6	40	2	40	17.8%	3.00 [0.64 , 13.98]
Lucchiari 2020	13	70	7	70	62.4%	1.86 [0.79 , 4.38]
Total (95% CI)		**1485**		**1076**	**100.0%**	**2.70 [1.39 , 5.26]**
Total events:	31		10			

Heterogeneity: Chi² = 1.45, df = 4 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.92 (P = 0.003)
Test for subgroup differences: Not applicable

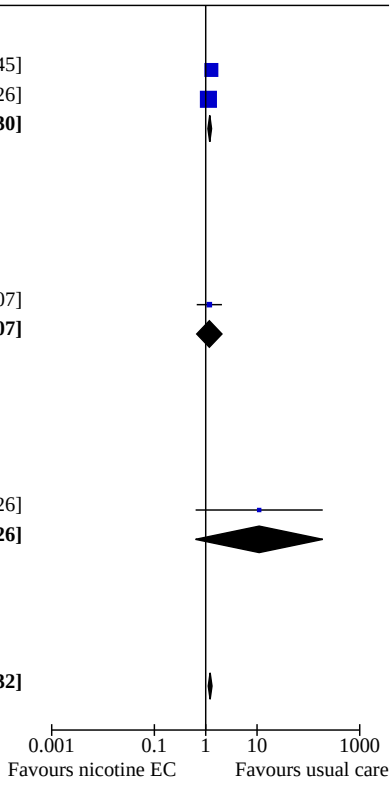


Footnotes

(1) Although participants were given a choice of nicotine concentration including 0 mg, none of the participants chose the non-nicotine e-liquid

Analysis 4.2. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 2: Adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 12 weeks						
Eisenberg 2020	120	128	88	121	40.8%	1.29 [1.15 , 1.45]
Walele 2018	271	306	80	102	54.1%	1.13 [1.01 , 1.26]
Subtotal (95% CI)		**434**		**223**	**94.9%**	**1.20 [1.11 , 1.30]**
Total events:	391		168			
Heterogeneity: Chi² = 2.61, df = 1 (P = 0.11); I² = 62%						
Test for overall effect: Z = 4.41 (P < 0.0001)						
4.2.2 16 weeks						
Carpenter 2017 (1)	20	34	8	16	4.9%	1.18 [0.67 , 2.07]
Subtotal (95% CI)		**34**		**16**	**4.9%**	**1.18 [0.67 , 2.07]**
Total events:	20		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.57)						
4.2.3 6 months						
Holliday 2019 (2)	5	29	0	29	0.2%	11.00 [0.64 , 190.26]
Subtotal (95% CI)		**29**		**29**	**0.2%**	**11.00 [0.64 , 190.26]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
Total (95% CI)		**497**		**268**	**100.0%**	**1.22 [1.12 , 1.32]**
Total events:	416		176			
Heterogeneity: Chi² = 5.04, df = 3 (P = 0.17); I² = 41%						
Test for overall effect: Z = 4.70 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.33, df = 2 (P = 0.31), I² = 14.1%						



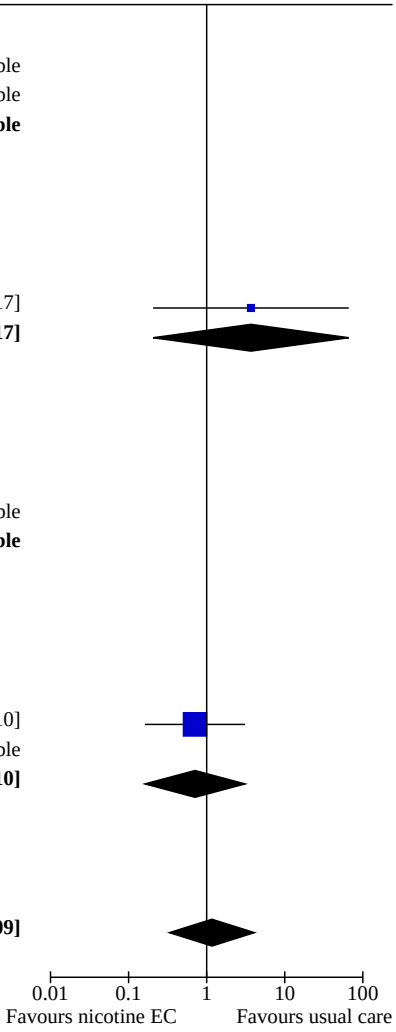
Footnotes

(1) 24mg EC arm included here; 16mg data reported elsewhere

(2) Participants offered choice of nicotine or no-nicotine EC; all chose nicotine-containing EC

Analysis 4.3. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 3: Serious adverse events

Study or Subgroup	Nicotine EC Events	Nicotine EC Total	Usual care Events	Usual care Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 4 to 6 weeks						
George 2019	0	37	0	40		Not estimable
Pulvers 2020	0	115	0	54		Not estimable
Subtotal (95% CI)		**152**		**94**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.2 12 weeks						
Walele 2018	5	306	0	102	15.4%	3.69 [0.21 , 66.17]
Subtotal (95% CI)		**306**		**102**	**15.4%**	**3.69 [0.21 , 66.17]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.89 (P = 0.38)						
4.3.3 16 weeks						
Carpenter 2017 (1)	0	34	0	16		Not estimable
Subtotal (95% CI)		**34**		**16**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.4 6 months						
Eisenberg 2020	3	128	4	121	84.6%	0.71 [0.16 , 3.10]
Holliday 2019 (2)	0	29	0	29		Not estimable
Subtotal (95% CI)		**157**		**150**	**84.6%**	**0.71 [0.16 , 3.10]**
Total events:	3		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**649**		**362**	**100.0%**	**1.17 [0.33 , 4.09]**
Total events:	8		4			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Chi² = 0.99, df = 1 (P = 0.32), I² = 0%						



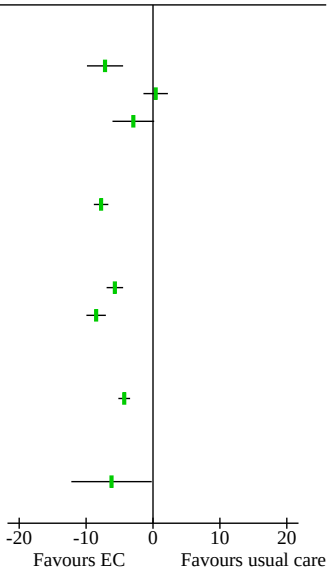
Footnotes

(1) Data from 24mg arm (0 events in 16mg arm as well)

(2) Participants offered choice of nicotine or no-nicotine EC; all chose nicotine-containing EC

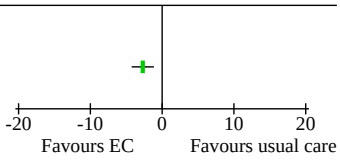
Analysis 4.4. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 4: Carbon monoxide (ppm)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.4.1 3 to 4 weeks							
Carpenter 2017	-2.47	5.37	42	4.7	4.8	19	-7.17 [-9.87 , -4.47]
Dawkins 2020	-2.8	4	39	-3.2	3.1	21	0.40 [-1.43 , 2.23]
Ozga-Hess 2019	-6.64	5.3	18	-3.7	3.93	16	-2.94 [-6.05 , 0.17]
4.4.2 6 weeks							
Pulvers 2020	-8.13	2.75	114	-0.37	3.59	54	-7.76 [-8.84 , -6.68]
4.4.3 8 weeks							
Adriaens 2014	-11.6	2	31	-5.9	2	15	-5.70 [-6.93 , -4.47]
Hatsukami 2020	-9.1	2.9	58	-0.6	3.6	32	-8.50 [-9.95 , -7.05]
4.4.4 4 months							
Ikonomidis 2020	-6.9	1.6	20	-2.6	1.2	20	-4.30 [-5.18 , -3.42]
4.4.5 6 months							
Holliday 2019	-12	11	29	-5.8	12.3	29	-6.20 [-12.21 , -0.19]



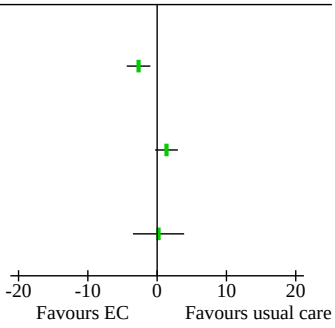
Analysis 4.5. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 5: Heart rate (bpm)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.5.1 8 weeks							
Hatsukami 2020	-4.6	3.9	58	-1.9	3.4	32	-2.70 [-4.25 , -1.15]



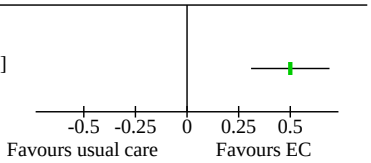
Analysis 4.6. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 6: Systolic blood pressure

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.6.1 6 weeks							
Pulvers 2020	1.07	5.68	114	3.75	5.03	54	-2.68 [-4.38 , -0.98]
4.6.2 8 weeks							
Hatsukami 2020	1.63	3.8	58	0.28	3.8	32	1.35 [-0.29 , 2.99]
4.6.3 4 months							
Ikonomidis 2020	-0.6	5.6	20	-0.8	6.3	20	0.20 [-3.49 , 3.89]



Analysis 4.7. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 7: Blood oxygen saturation

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.7.1 8 weeks							
Hatsukami 2020	0.2	0.5	57	-0.3	0.4	32	0.50 [0.31 , 0.69]



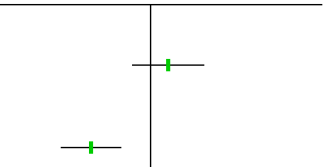
Analysis 4.8. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 8: 3-HPMA (SMD)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Std. Mean Difference IV, Fixed, 95% CI
4.8.1 8 weeks							
Hatsukami 2020 (1)	-2681	1523	58	1142	1846	32	-2.31 [-2.86 , -1.75]
4.8.2 12 weeks							
Walele 2018 (2)	-530	1272.5	284	96	1142.9	100	-0.50 [-0.73 , -0.27]

Footnotes
(1) measured as pmol/mg creatinine
(2) Measured as micrograms

Analysis 4.9. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 9: NNAL (SMD)

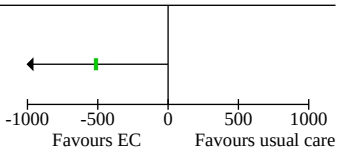
Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Std. Mean Difference IV, Fixed, 95% CI
4.9.1 3 weeks							
Carpenter 2017 (1)	1.59	79.2	41	-21.3	96.5	19	0.27 [-0.28 , 0.81]
4.9.2 8 weeks							
Hatsukami 2020 (2)	-0.6	0.5	57	-0.2	0.3	31	-0.90 [-1.36 , -0.44]
4.9.3 12 weeks							
Walele 2018 (3)	-76	189.2	284	6	163.3	100	-0.45 [-0.68 , -0.22]
4.9.4 6 weeks							
Pulvers 2020	-65.91	39.41	114	14.23	39.62	54	-2.02 [-2.41 , -1.63]



Footnotes
(1) Measured as pg/ml
(2) Measured as pmol/mg creatinine
(3) Measured as nanograms

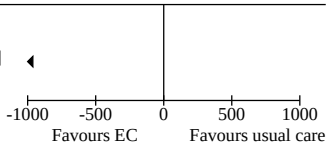
Analysis 4.10. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 10: 2-HPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.10.1 8 weeks								
Hatsukami 2020	-249	525	58	264	1424	32	-513.00 [-1024.55 , -1.45]	



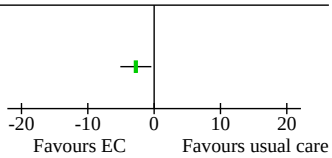
Analysis 4.11. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 11: HMPMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.11.1 8 weeks								
Hatsukami 2020	-2061	1069	58	1397	2896	32	-3458.00 [-4498.43 , -2417.57]	



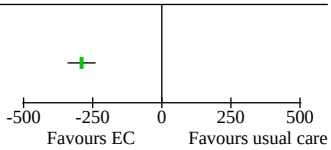
Analysis 4.12. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 12: PheT (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.12.1 8 weeks								
Hatsukami 2020	-0.56	0.72	56	2.2	6.72	32	-2.76 [-5.10 , -0.42]	



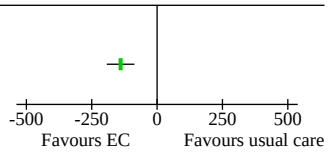
Analysis 4.13. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 13: CEMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.13.1 8 weeks								
Hatsukami 2020	-266.4	136	58	23.8	105.9	32	-290.20 [-340.91 , -239.49]	



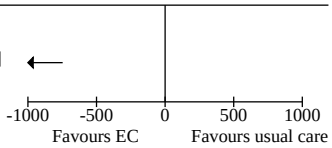
Analysis 4.14. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 14: AAMA (pmol/mg creatinine)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.14.1 8 weeks								
Hatsukami 2020	-144	114	58	-4.4	127	32	-139.60 [-192.49 , -86.71]	



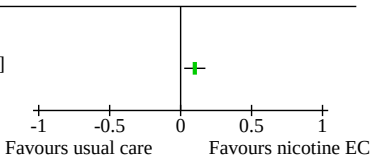
Analysis 4.15. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 15: S-PMA (nanograms)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.15.1 12 weeks								
Walele 2018	-1340	3426.3	284	31	2451.5	100	-1371.00 [-1995.23 , -746.77]	



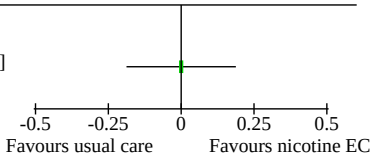
Analysis 4.16. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 16: FVC (litres)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.16.1 12 weeks								
Walele 2018	-0.1	0.4	286	-0.2	0.3	101	0.10 [0.03 , 0.17]	



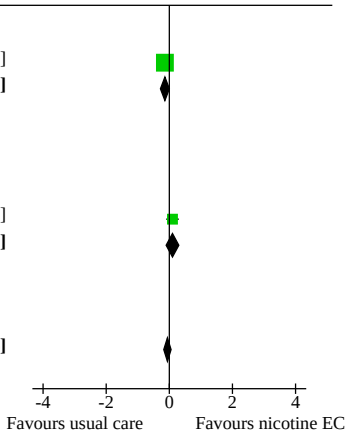
Analysis 4.17. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 17: FEV1 (litres)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
4.17.1 12 weeks								
Walele 2018	-0.1	0.9	286	-0.1	0.8	101	0.00 [-0.19 , 0.19]	



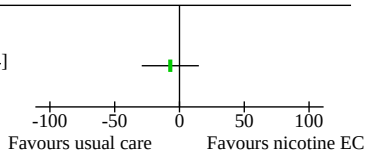
Analysis 4.18. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 18: FEF 25-75 (litres/second))

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.18.1 6 weeks								
Pulvers 2020	-0.11	0.43	114	0.03	0.44	54	66.8%	-0.14 [-0.28 , 0.00]
Subtotal (95% CI)			**114**			**54**	**66.8%**	**-0.14 [-0.28 , 0.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.94 (P = 0.05)								
4.18.2 12 weeks								
Walele 2018	-0.1	0.4	286	-0.2	1	101	33.2%	0.10 [-0.10 , 0.30]
Subtotal (95% CI)			**286**			**101**	**33.2%**	**0.10 [-0.10 , 0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
Total (95% CI)			**400**			**155**	**100.0%**	**-0.06 [-0.18 , 0.06]**
Heterogeneity: Chi² = 3.68, df = 1 (P = 0.06); I² = 73%								
Test for overall effect: Z = 1.02 (P = 0.31)								
Test for subgroup differences: Chi² = 3.68, df = 1 (P = 0.06), I² = 72.8%								



Analysis 4.19. Comparison 4: Nicotine EC versus behavioural support only/no support, Outcome 19: PEF 25-75 (litres/minute)

Study or Subgroup	Nicotine EC Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
4.19.1 12 weeks							
Walele 2018	11.7	75.9	286	18.8	103.6	101	-7.10 [-29.14 , 14.94]



Comparison 5. Nicotine EC + NRT versus non-nicotine EC + NRT

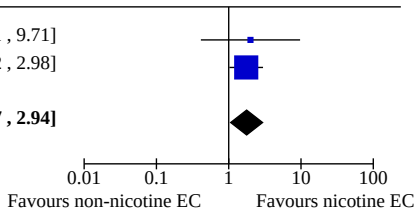
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Smoking cessation	2	1039	Risk Ratio (M-H, Fixed, 95% CI)	1.77 [1.07, 2.94]
5.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.2.1 12 weeks	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.3.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.4 Carbon monoxide (ppm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.4.1 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.5 FeNO (ppb)	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-7.23, 6.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.5.1 6 months	1	30	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-7.23, 6.51]
5.6 FEV1 (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.10]
5.6.1 6 months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.01, 0.10]
5.7 FVC (%)	1	32	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.03, 0.09]
5.7.1 6 months	1	32	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.03, 0.09]

Analysis 5.1. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 1: Smoking cessation

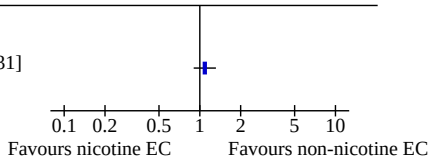
Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	Non-nicotine EC + NRT Events	Non-nicotine EC + NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Baldassarri 2018	4	20	2	20	9.1%	2.00 [0.41 , 9.71]
Walker 2020	35	500	20	499	90.9%	1.75 [1.02 , 2.98]
Total (95% CI)		**520**		**519**	**100.0%**	**1.77 [1.07 , 2.94]**
Total events:	39		22			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable



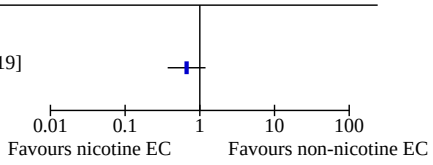
Analysis 5.2. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 2: Adverse events

Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	Non-nicotine EC + NRT Events	Non-nicotine EC + NRT Total	Risk Ratio M-H, Fixed, 95% CI
5.2.1 12 weeks					
Walker 2020	138	317	116	290	1.09 [0.90 , 1.31]



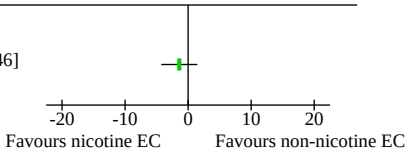
Analysis 5.3. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 3: Serious adverse events

Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	Non-nicotine EC + NRT Events	Non-nicotine EC + NRT Total	Risk Ratio M-H, Fixed, 95% CI
5.3.1 6 months					
Walker 2020	18	500	27	499	0.67 [0.37 , 1.19]



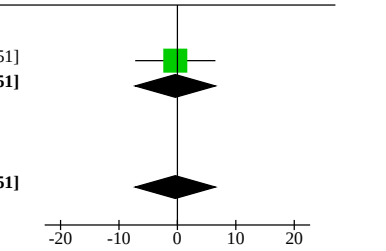
Analysis 5.4. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 4: Carbon monoxide (ppm)

Study or Subgroup	Nicotine EC + NRT Mean	SD	Total	Non-nicotine EC + NRT Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.4.1 8 weeks							
Baldassarri 2018	-9.5	3.9	13	-8.1	3.4	12	-1.40 [-4.26 , 1.46]



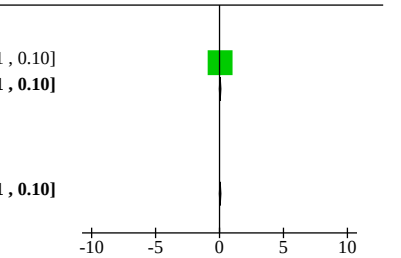
Analysis 5.5. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 5: FeNO (ppb)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.5.1 6 months								
Baldassarri 2018	2.75	10.5	12	3.11	7.45	18	100.0%	-0.36 [-7.23 , 6.51]
Subtotal (95% CI)			**12**			**18**	**100.0%**	**-0.36 [-7.23 , 6.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
Total (95% CI)			**12**			**18**	**100.0%**	**-0.36 [-7.23 , 6.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
Test for subgroup differences: Not applicable								



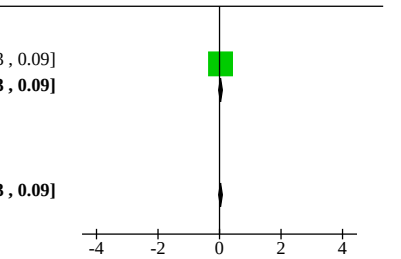
Analysis 5.6. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 6: FEV1 (%)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.6.1 6 months								
Baldassarri 2018	0.0085	0.057	13	-0.037	0.097	19	100.0%	0.05 [-0.01 , 0.10]
Subtotal (95% CI)			**13**			**19**	**100.0%**	**0.05 [-0.01 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.10)								
Total (95% CI)			**13**			**19**	**100.0%**	**0.05 [-0.01 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.67 (P = 0.10)								
Test for subgroup differences: Not applicable								



Analysis 5.7. Comparison 5: Nicotine EC + NRT versus non-nicotine EC + NRT, Outcome 7: FVC (%)

Study or Subgroup	Nicotine EC Mean	SD	Total	Non-nicotine EC Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
5.7.1 6 months								
Baldassarri 2018	0.0108	0.065	13	-0.0216	0.103	19	100.0%	0.03 [-0.03 , 0.09]
Subtotal (95% CI)			**13**			**19**	**100.0%**	**0.03 [-0.03 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.09 (P = 0.28)								
Total (95% CI)			**13**			**19**	**100.0%**	**0.03 [-0.03 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.09 (P = 0.28)								
Test for subgroup differences: Not applicable								

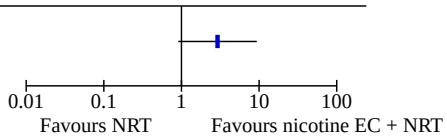


Comparison 6. Nicotine EC + NRT versus NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2 Adverse events	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.2.1 12 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.3 Serious adverse events	3	682	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.46, 3.42]
6.3.1 5 weeks	1	7	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3.2 12 weeks	1	50	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.30]
6.3.3 6 months	1	625	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.39, 3.27]

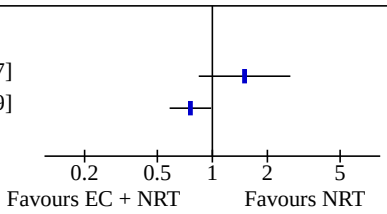
Analysis 6.1. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 1: Smoking cessation

Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
Walker 2020	35	500	3	125	2.92 [0.91 , 9.33]



Analysis 6.2. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 2: Adverse events

Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
6.2.1 12 weeks					
Guillaumier 2018 (1)	15	25	10	25	1.50 [0.84 , 2.67]
Walker 2020	138	317	31	54	0.76 [0.58 , 0.99]

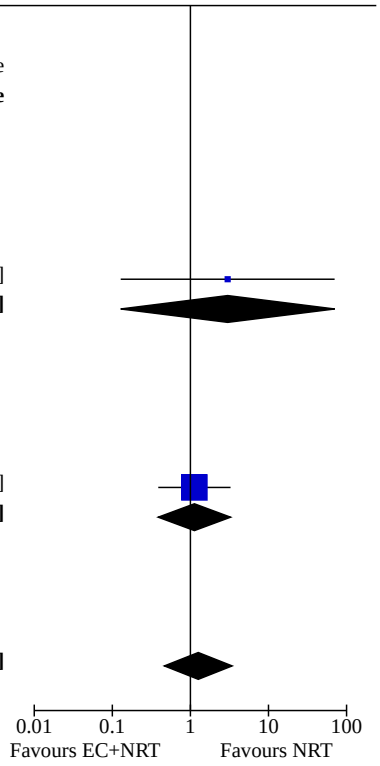


Footnotes

(1) NRT not matched between arms

Analysis 6.3. Comparison 6: Nicotine EC + NRT versus NRT, Outcome 3: Serious adverse events

Study or Subgroup	Nicotine EC + NRT Events	Nicotine EC + NRT Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.3.1 5 weeks						
NCT02918630	0	3	0	4		Not estimable
Subtotal (95% CI)		**3**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.3.2 12 weeks						
Guillaumier 2018 (1)	1	25	0	25	7.2%	3.00 [0.13 , 70.30]
Subtotal (95% CI)		**25**		**25**	**7.2%**	**3.00 [0.13 , 70.30]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.49)						
6.3.3 6 months						
Walker 2020	18	500	4	125	92.8%	1.13 [0.39 , 3.27]
Subtotal (95% CI)		**500**		**125**	**92.8%**	**1.13 [0.39 , 3.27]**
Total events:	18		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.83)						
Total (95% CI)		**528**		**154**	**100.0%**	**1.26 [0.46 , 3.42]**
Total events:	19		4			
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² = 0%						



Footnotes

(1) NRT not matched between arms

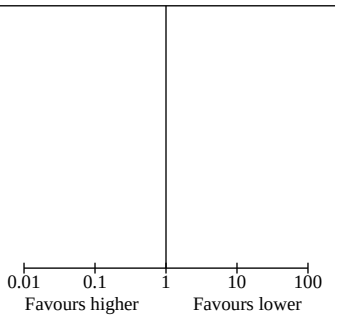
Comparison 7. Higher versus lower nicotine content

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.1 Serious adverse events	1	72	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.1.1 1 year	1	72	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 Carbon monoxide (ppm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.2.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.3 Heart rate	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.3.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.4 Systolic blood pressure	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
7.4.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5 FeNO (ppb)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.5.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6 FEV1 (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.6.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7 FVC (l)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.7.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8 FEV1/FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.8.1 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

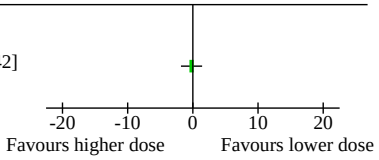
Analysis 7.1. Comparison 7: Higher versus lower nicotine content, Outcome 1: Serious adverse events

Study or Subgroup	Higher nicotine content Events	Total	Lower nicotine content Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 1 year						
Caponnetto 2013a	0	35	0	37		Not estimable
Subtotal (95% CI)		**35**		**37**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**35**		**37**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



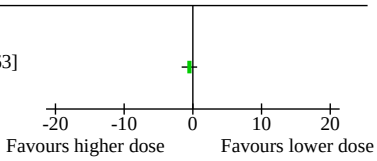
Analysis 7.2. Comparison 7: Higher versus lower nicotine content, Outcome 2: Carbon monoxide (ppm)

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.2.1 12 weeks							
Caponnetto 2013a	-6	6.4	76	-5.8	3.4	79	-0.20 [-1.82 , 1.42]



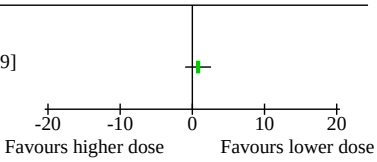
Analysis 7.3. Comparison 7: Higher versus lower nicotine content, Outcome 3: Heart rate

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.3.1 12 weeks							
Caponnetto 2013a	-1.7	3.4	73	-1.2	3.6	75	-0.50 [-1.63 , 0.63]



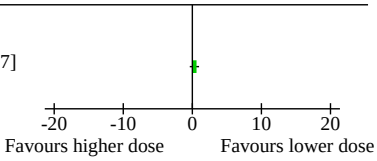
Analysis 7.4. Comparison 7: Higher versus lower nicotine content, Outcome 4: Systolic blood pressure

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.4.1 12 weeks							
Caponnetto 2013a	-3.9	5.7	73	-4.7	5.4	75	0.80 [-0.99 , 2.59]



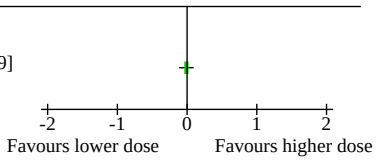
Analysis 7.5. Comparison 7: Higher versus lower nicotine content, Outcome 5: FeNO (ppb)

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.5.1 12 weeks							
Caponnetto 2013a	2.8	1.7	49	2.5	1.6	44	0.30 [-0.37 , 0.97]



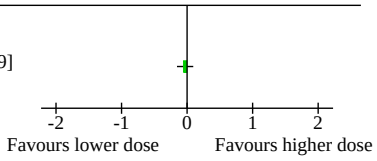
Analysis 7.6. Comparison 7: Higher versus lower nicotine content, Outcome 6: FEV1 (l)

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.6.1 12 weeks							
Caponnetto 2013a	0	0.3	47	0.01	0.2	43	-0.01 [-0.11 , 0.09]



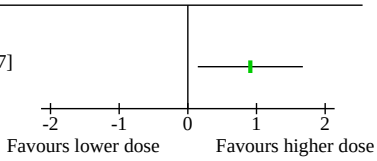
Analysis 7.7. Comparison 7: Higher versus lower nicotine content, Outcome 7: FVC (l)

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
7.7.1 12 weeks							
Caponnetto 2013a	-0.02	0.3	47	0.01	0.3	43	-0.03 [-0.15 , 0.09]



Analysis 7.8. Comparison 7: Higher versus lower nicotine content, Outcome 8: FEV1/FVC

Study or Subgroup	higher dose Mean	SD	Total	lower dose Mean	SD	Total	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
7.8.1 12 weeks								
Caponnetto 2013a	0.96	2	47	0.05	1.7	43	0.91 [0.15 , 1.67]	



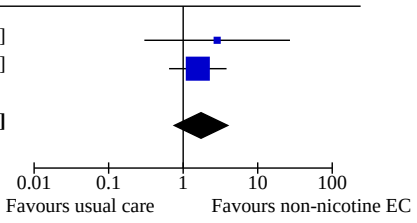
Comparison 8. Non-nicotine EC versus behavioural support only/no support

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Smoking cessation	2	388	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.76, 3.96]
8.2 Adverse events at 12 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.3 Serious adverse events at 24 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Non-nicotine EC versus behavioural support only/no support, Outcome 1: Smoking cessation

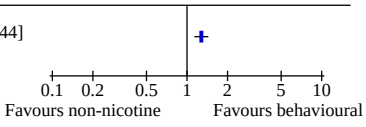
Study or Subgroup	Non-nicotine EC Events	Total	Usual care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Eisenberg 2020	3	127	1	121	12.8%	2.86 [0.30 , 27.10]	
Lucchiari 2020	11	70	7	70	87.2%	1.57 [0.65 , 3.82]	
Total (95% CI)		**197**		**191**	**100.0%**	**1.74 [0.76 , 3.96]**	
Total events:	14		8				

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable

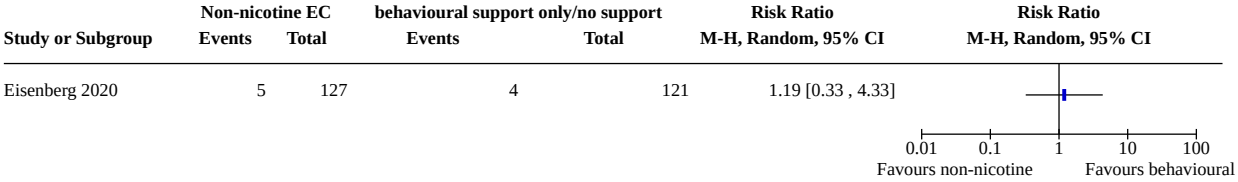


Analysis 8.2. Comparison 8: Non-nicotine EC versus behavioural support only/no support, Outcome 2: Adverse events at 12 weeks

Study or Subgroup	Non-nicotine EC Events	Total	behavioural support only/no support Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Eisenberg 2020	118	127	88	121	1.28 [1.13 , 1.44]	



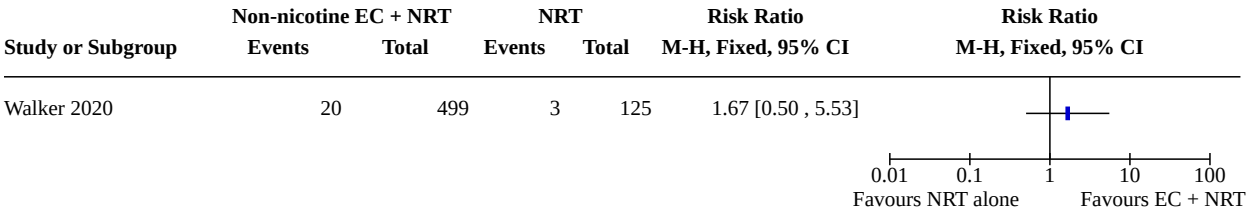
Analysis 8.3. Comparison 8: Non-nicotine EC versus behavioural support only/no support, Outcome 3: Serious adverse events at 24 weeks



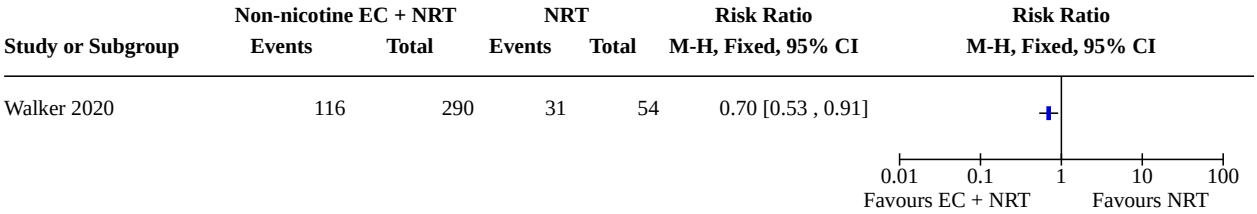
Comparison 9. Non-nicotine EC + NRT versus NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3 Serious adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.3.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 1: Smoking cessation

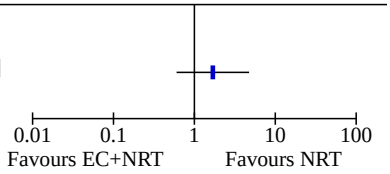


Analysis 9.2. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 2: Adverse events



Analysis 9.3. Comparison 9: Non-nicotine EC + NRT versus NRT, Outcome 3: Serious adverse events

Study or Subgroup	Non-nicotine EC + NRT Events	Non-nicotine EC + NRT Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
9.3.1 6 months					
Walker 2020	27	499	4	125	1.69 [0.60 , 4.74]

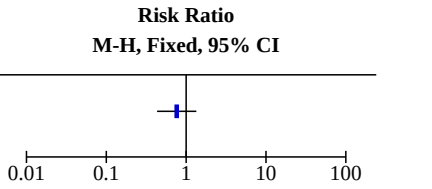


Comparison 10. Non-nicotine EC versus NRT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Smoking cessation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.2.1 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.3 Serious adverse events	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3.1 6 months	1	132	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 10.1. Comparison 10: Non-nicotine EC versus NRT, Outcome 1: Smoking cessation

Study or Subgroup	Non-nicotine EC Events	Non-nicotine EC Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
Lee 2019 (1)	16	75	21	75	0.76 [0.43 , 1.34]

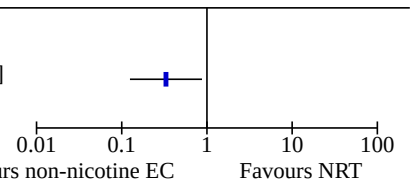


Footnotes

(1) 0.01 mg/ml of nicotine in e-liquid

Analysis 10.2. Comparison 10: Non-nicotine EC versus NRT, Outcome 2: Adverse events

Study or Subgroup	Non-nicotine EC Events	Non-nicotine EC Total	NRT Events	NRT Total	Risk Ratio M-H, Fixed, 95% CI
10.2.1 6 months					
Lee 2019 (1)	5	71	13	61	0.33 [0.12 , 0.87]

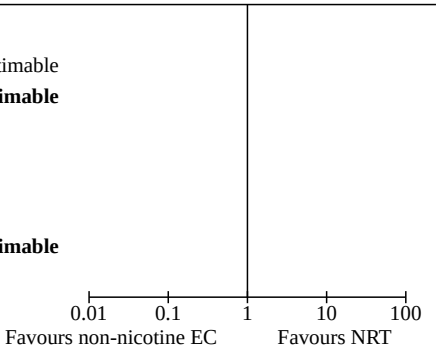


Footnotes

(1) 0.01 mg/ml of nicotine in e-liquid; length of follow-up not defined but presumably over study period

Analysis 10.3. Comparison 10: Non-nicotine EC versus NRT, Outcome 3: Serious adverse events

Study or Subgroup	Non-nicotine EC Events	Non-nicotine EC Total	NRT Events	NRT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 6 months						
Lee 2019 (1)	0	71	0	61		Not estimable
Subtotal (95% CI)		**71**		**61**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**71**		**61**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Footnotes

(1) 0.01 mg/ml of nicotine in e-liquid; length of follow-up not defined but presumably over study period

ADDITIONAL TABLES

Table 1. Summary of proportion of participants abstinent from smoking at 6+ months follow-up: cohort studies of nicotine EC

Study	Motivated or unmotivated to quit smoking?	% abstinent				
Cohort studies		**6-month**	**12-month**	**18-month**	**24-month**	**Notes**
Adriaens 2014 [a]	Unmotivated to quit	19.6% (10/51)	-	-	-	Data from 8-month follow-up
Bell 2017	"Willing to attempt to quit"	26.6% (8/30)	-	-	-	-
Caponnetto 2013b	Unmotivated to quit	-	14% (2/14)	-	-	-
Ely 2013 [b]	Motivated to quit	44% (21/48)	-	-	-	-
Pacifici 2015	Unmotivated to quit	-	53% (18/34)	-	-	-
Polosa 2011	Unmotivated to quit	23% (9/40)	-	15% (6/40)	13% (5/40)	-
Polosa 2014b	Unmotivated to quit	36% (18/50)	-	-	-	-
Polosa 2015	Not defined	42% (30/71)	41% (29/71)	-	-	-

[a]Technically an RCT but observational for purposes of EC analysis.
[b]All participants (N = 48) used an EC, but 16 also used bupropion and 2 used varenicline.

APPENDICES

Appendix 1. Protocol for living systematic review

Justification for 'Living Review' status

Living systematic reviews (LSRs) offer a new approach to updating reviews, in which the review is continually updated by incorporating relevant new evidence as it becomes available (Brooker 2019). Previous versions of this Cochrane Review of electronic cigarettes (ECs) for smoking cessation have informed policy worldwide (Hartmann-Boyce 2016; McRobbie 2014). This update has found high degrees of uncertainty (low- and very low-certainty evidence) for most outcomes, due to the small number of included randomized controlled trials, and the resulting imprecision in effect estimates. This means that some conclusions are likely to change substantially as new evidence emerges.

On average, Cochrane Reviews are updated every three to four years. For EC, where the evidence base is rapidly evolving, this schedule impedes the ability of the review to provide the most up-to-date evidence to decision-makers. As EC use, availability, and design changes, policymakers are frequently drawing on this review to inform decisions, so it is imperative that it is up-to-date to ensure decisions are being made on the basis of the entirety of the evidence. Regular updates have the potential to strengthen the existing conclusions of the review or to change conclusions where conflicting evidence or evidence on new outcomes emerges (e.g. comparisons between EC and other interventions; longer-term safety data).

Objective of the change to 'Living Review' status

To implement approved Cochrane LSR methods to provide an up-to-date, accessible, engaging and unbiased review of the evidence on the effect and safety of using EC to quit smoking.

LSR methodological considerations

The methods outlined below are specific to maintaining this review of *Electronic cigarettes for smoking cessation* as an LSR on the Cochrane Library. These methods will be 'active' immediately upon publication of this update. Core review methods, such as the criteria for considering studies in the review and assessment of risks of bias, are unchanged and are detailed in the main body of the review. Below we outline the methods for which specific considerations apply as a result of the change to 'living' status.

Search methods for identification of studies

We will conduct database searches monthly, beginning December 2020. These searches will be of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, and clinical trial registries, as detailed in the main body of the review. The funders of this LSR – Cancer Research UK (CRUK) - already run monthly searches of the EC evidence and so we will work alongside their health information officer to ensure that we are identifying all the relevant literature with our searches. We will review our search strategies on an ongoing basis every 12 months, as indexing terms and keywords may change, and new search filters may be published. Such changes will be managed by input from experienced information specialists.

Selection of studies

We will immediately screen any new citations retrieved by the monthly searches using Covidence, undertaking dual screening of title and abstract, and then full text, by independent review authors. Where we find multiple citations of the same study we will group them into one study record with a single study ID. One review author (AB) will contact corresponding authors of potentially relevant ongoing studies as they are identified and ask them to advise when results are available, or to share early or unpublished data. Based on the information and projected timescales shared, we will contact corresponding authors on an ongoing basis to retrieve new evidence as it becomes available.

Data synthesis

Whenever we identify new studies relevant to the review, we will extract the relevant data and assess risks of bias as detailed in the main body of the review. We will highlight availability of this new evidence on both the Cochrane Library and on our own dedicated website. We will incorporate the new data into meta-analyses and tables in the Revman (Review Manager 2020) and supplementary data files, and carry out GRADE assessments (GRADEpro GDT). We will conduct a full update of the review (full incorporation and interpretation of all new data within the review and re-publishing) when the accumulating evidence leads to changes in any one of:

- The direction of effect or clinical significance of the findings for one or more outcomes;
- The certainty (e.g. GRADE rating) of one or more outcomes;
- The availability of studies investigating new settings, populations, interventions, comparisons or outcomes.

Formal sequential meta-analysis approaches will not be used for updated meta-analyses, in line with Cochrane guidance for LSRs.

Future updates of review methods

The LSR approach acknowledges that reviews may cease to need to be 'living' over time, as the review findings become stable, or the question is no longer a priority for decision-makers (Brooker 2019). Eighteen months into this review's 'living' status (March 2022) we will

evaluate the LSR approach, including the likely benefits of and challenges to continuing this methodology for this evidence base, and whether such an approach remains warranted. If the evidence is high certainty for all outcomes and all comparisons at that point, meaning further studies are judged very unlikely to impact the effect estimate, we would consider ceasing living mode for this review. If, as is more likely, some or all outcomes are not yet certain, we will facilitate discussions within the author team and Cochrane, as well as engaging with a wider PPI panel and key decision-makers, e.g. policymakers, in order to determine next steps. If the decision is made to continue in living mode, we will review, and if necessary revise, the living review methods described in this Appendix before continuing.

Appendix 2. Toxins/carcinogen names and abbreviations

Abbreviation	Name
-	1-Hydroxyfluorene
-	1-Hydroxyphenanthrene
-	1-Hydroxypyrene
2-HPMA	2-hydroxypropylmercapturic acid
-	2-Hydroxyfluorene
-	2-Hydroxyphenanthrene
-	2-Naphthol
-	3-, 4-Hydroxyphenanthrenes
3-HPMA	3-hydroxypropylmercapturic acid
-	3-Hydroxyfluorene
AAMA	*N*-acetyl-*S*-(carbamoylethyl)-L-cysteine (synonym: 2-carbamoylethylmercapturic acid)
CEMA/CNEMA	2-cyanoethylmercapturic acid; referred to as 'acrylonitrile' in Pulvers 2018
-	Formic acid
HEMA	2-hydroxyethylmercapturic acid
HMPMA/HPMMA	3-hydroxy-1-methyl propylmercapturic acid
MHBMA	2-hydroxy-3-buten-1-ylmercapturic acid
MMA	N-nitrosodimethyamine
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
PheT	Phenanthrene tetraol
PMA	phenylmercapturic acid; referred to as 'benzene' in Pulvers 2018
S-PMA	S-phenylmercapturic acid

Appendix 3. MEDLINE search strategy - 2020 update

1. exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw.

2. (e-cig$ or ecig$ or electr$ cigar$ or electronic nicotine).mp. or (vape or vapes or vaporizer or vapourizer or vaporiser or vapouriser or vaper or vapers or vaping).ti,ab. or exp Electronic Nicotine Delivery Systems/

3. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

4. exp animals/ not humans.sh.

5. 3 not 4

6. 2 and 5

7. 1 and 2

8. 6 or 7

9. smoking cessation.mp. or exp Smoking Cessation/

10. tobacco cessation.mp. or "Tobacco-Use-Cessation"/

11. (nicotine dependence or tobacco dependence).mp.

12. exp Smoking/th

13. "Tobacco-Use-Disorder"/

14. Smoking reduction/ or Smoking reduction.mp.

15. exp Pipe smoking/ or exp Tobacco smoking/ or exp Tobacco Products/

16. ((quit$ or stop$ or ceas$ or giv$ or abstain* or abstinen*) adj5 (smoking or smoke* or tobacco)).ti,ab.

17. exp Tobacco/ or exp Nicotine/

18. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 8 and 18

Appendix 4. MEDLINE search strategy - pre-2020

1. e-cig$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. electr$ cigar$.mp.
3. electronic nicotine.mp.
4. (vape or vaper or vapers or vaping).ti,ab.
5. 1 OR 2 OR 3 OR 4

Identical terms used for other databases.

Line 4 added to search strategy for 2016 update.

WHAT'S NEW

Date	Event	Description
15 April 2021	New search has been performed	Updated with six new included studies and new data from one previously included study. Most recent search 1 Feb 2021.
15 April 2021	New citation required and conclusions have changed	6 new included studies added (Czoli 2019; Ikonomidis 2020; Ozga-Hess 2019; Pulvers 2020; Scheibein 2020; Yingst 2020), cer-

Date	Event	Description
		tainty in finding of no difference in adverse events between nicotine EC and non-nicotine EC updated to moderate (from low). First study of pod EC device included.

HISTORY

Protocol first published: Issue 11, 2012
Review first published: Issue 12, 2014

Date	Event	Description
1 April 2021	Amended	This is a Living Systematic Review. We run and screen searches monthly. Last search date 1st April 2021. In addition to the studies identified from March 2021 we found two new ongoing studies and one paper linked to a study already included in the review. We will incorporate these into the review as part of a future update.
17 March 2021	Amended	This is a Living Systematic Review. We run and screen searches monthly. Last search date 1st March 2021. Studies identified in March are not included in this version of the review, but will be incorporated into a subsequent version. We found four new included studies, five new ongoing studies and five papers linked to studies already included in the review. The four new included studies were all conference abstracts; three of which were identified from the SRNT 2021 abstract book (SYM2A, SYM2B, PH-353; www.srnt.org/page/2021_Meeting). The fourth is available here: dx.doi.org/10.1016/j.drugalcdep.2015.07.1091.
4 February 2021	Amended	This is a Living Systematic Review. We run and screen searches monthly. Last search date 1st February 2021. In addition to the studies identified from our December 2020 and January 2021 searches we found one paper linked to a study already included in the review (Lucchiari 2020), and have preliminary results from a study listed as ongoing (Begh 2019). We will incorporate this paper and data into the review as part of a future update.
20 January 2021	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 4th January 2021. In addition to the studies identified from our December 2020 searches we found four new completed studies, one new ongoing study and one paper linked to a study already included in the review. These studies and papers will be incorporated into the review at the next update. DOIs for the four new included studies are as follows: Ozga-Hess et al. 2019: 10.1016/j.addbeh.2019.106105; Pulvers et al. 2020: 10.1001/jamanetworkopen.2020.26324; Scheibein 2020: 10.1186/s12954-020-00406-y; Yingst et al. 2020: 10.1080/09540121.2019.1687835
15 December 2020	Amended	This is a Living Systematic Review. Searches are run and screened monthly. Last search date 1st December 2020. Searches found 3 new completed studies, 11 new ongoing studies and 9 papers linked to studies already included in the review. These studies and papers will be incorporated into the review at the next update. DOIs for the three new included studies are as fol-

Date	Event	Description
		lows: Czoli et al:10.1093/ntr/nty174; Bonevski et al: 10.1093/ntr/ntaa143; Eisenberg et al: 10.1001/jama.2020.18889 .
20 July 2020	New citation required and conclusions have changed	Strength of evidence increased for existing comparisons; new comparisons added
20 July 2020	New search has been performed	New searches run January 2020. 35 new studies added. Living systematic review protocol incorporated
14 December 2016	Amended	Clarification on outcome data from Adriaens - no changes to conclusions
23 June 2016	New search has been performed	Update search run January 2016, 11 new included studies added. Reduction removed as outcome, now covered in Harm Reduction review.
23 June 2016	New citation required but conclusions have not changed	11 new included studies added; no changes to conclusions.

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of this review.
For this update, JHB, NL, CN, RB, PH, NR, ARB, HMR screened studies and/or extracted data.
JHB and ARB entered data for analysis.

DECLARATIONS OF INTEREST

RB holds an NIHR grant, however this did not directly fund this current work. She is principal investigator of an ongoing study listed in this review.

CB was principal investigator on the ASCEND e-cigarette trial reported in the Cochrane review and a co-investigator on the ASCEND II trial and several other studies included in the review. CB has provided consultancy for J&J KK (Japan) on NRT products. CB reports research grants from the Health Research Council of NZ, the Heart Foundation of NZ and the NZ Ministry of Health. He has recently led a project funded by Pfizer (NZ) on chronic disease management.

ARB's work on this review has been supported by Cancer Research UK Project Award funding. This is not deemed a conflict of interest.

PH provided consultancy for and received research funding from Pfizer, a manufacturer of stop-smoking medications. He was principal investigator on one of the trials included in this review and co-investigator on other relevant studies.

JHB has received support for this work from the Cochrane Review Support Programme and the University of Oxford's Returning Carer's Fund. Neither of these are deemed conflicts of interest.

NL has received payment for lectures on systematic review methodology, and has been an applicant on project funding to carry out priority setting and systematic reviews in the area of tobacco control (NIHR funded). None of this is deemed a conflict of interest.

HM has received honoraria for speaking at smoking cessation educational events and sitting on an advisory board organized by Pfizer.

CN has no known conflicts of interest.

NR has received royalties from UpToDate, Inc., for chapters on electronic cigarettes and occasional fees from academic hospitals or professional medical societies for lectures on smoking cessation that include discussion of electronic cigarettes. Dr. Rigotti was an member of the committee that produced the 2018 National Academies of Science, Engineering, and Medicine's Consensus Study Report on the Public Health Benefits of E-cigarettes. She was unpaid for this work. Outside the topic of e-cigarettes, Dr. Rigotti has received honoraria from Achieve Life Sciences for consulting about cytisine. NR is a consultant for Achieve LifeSciences, which is developing an investigational smoking cessation medication for FDA approval (cytisine) and her institution (MGH) receives a grant from the company as a site for a clinical trial testing the safety and efficacy of cytisine. NR has received travel reimbursement (but no honoraria) from Pfizer for attending advisory boards regarding varenicline. NR holds grants from NIH for research work.

AT's work on this review has been supported by the Cochrane Review Support Programme and the University of Oxford's Returning Carer's Fund. Neither of these are deemed conflicts of interest.

TT has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Queen Mary University of London, UK

  provides salary, office space and library resources for HM and PH
- The University of Auckland, New Zealand

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- University of Oxford, UK

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External sources

- NIHR, UK

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- Cancer Research UK, UK

  Cancer Research UK project award funding to support living systematic review

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol did not specify a minimum follow-up period for data on adverse events. As of the 2016 update, we have changed the Methods section to clarify that we will exclude follow-up data at less than a week.

The original version of this review included reduction as a secondary outcome. The 2016 update removed reduction as an outcome, to bring the review into line with other reviews of cessation treatments produced by the Cochrane Tobacco Addiction Group and to prevent substantial overlap with the update of the Group's review of interventions for harm reduction.

As prespecified in the 2016 update, in the 2020 update we excluded non-intervention studies. In the 2020 update, we also added in an appendix with a protocol setting out our plans to convert this review into a living systematic review in the future.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Cohort Studies; *Electronic Nicotine Delivery Systems; *Nicotine [administration & dosage]; *Nicotinic Agonists [administration & dosage]; Publication Bias; Randomized Controlled Trials as Topic; Smoking [epidemiology]; Smoking Cessation [*methods] [statistics & numerical data]; *Smoking Prevention; Tobacco Use Cessation Devices; Vaping

MeSH check words

Humans; Middle Aged