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Electronic cigarettes for smoking cessation and reduction (Protocol)

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[Intervention Protocol]

Electronic cigarettes for smoking cessation and reduction

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The primary objective is to evaluate the efficacy of electronic cigarettes (ECs) for helping people who smoke to achieve long-term cessation.

The secondary objectives are to evaluate the efficacy of ECs for helping smokers to substantially reduce cigarette use and to assess potential adverse effects.

BACKGROUND

Throughout the document, two types of cigarettes are discussed: electronic and conventional. To avoid confusion, all mentions of smoking, smoking cessation, cigarette use, smoke intake etc. concern conventional cigarettes. When the text concerns electronic cigarettes, this will be spelled out, or an abbreviation of EC will be used.

Description of the condition

Stopping smoking is associated with large health benefits. Despite most smokers wanting to quit, few manage to succeed long term. Almost half who try to quit without support will not manage to stop for even a week, and less than 5% make it for a year (Hughes 2004).

Behavioural support and pharmacotherapies increase abstinence rates, but even with this additional support long-term quit rates remain low (Lancaster 2005; Stead 2005; Stead 2006; Hughes 2007; Stead 2008; Cahill 2012). One of the limitations of current treatments is that none adequately address the ritual and sensory aspects that smokers miss when they stop smoking (e.g. holding a cigarette in their hands, taking a puff, etc.) and the enjoyment people derive from smoking. Electronic cigarettes may be a way to overcome this limitation.

Whilst 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 mesolimbic dopamine system (Balfour 2004), there are other factors that contribute to tobacco dependence (Rose 2006). Sensory and behavioural cues appear to provide additional reinforcement of smoking behaviour (Rose 1993; Rose 2000) and over time have themselves become rewarding. There are several lines of evidence to support this. Smokers appear to have a preference for cigarette smoke compared to other forms of nicotine delivery. This, in part, is related to its speed of nicotine delivery, however even when nicotine is administered intravenously it does not provide the same level of satisfaction or reward as smoking (Westman 1996; Rose 2000). The local sensory effects (e.g. the 'scratch' in the back of the throat) may also be important for enjoyment. Numbing the sensations of cigarette smoke by anaesthetising 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). De-nicotinised cigarettes (DNCs), which have a very low content of nicotine (e.g. 0.08mg) and so have negligible or no central effects have also been investigated for their role in aiding smoking cessation (Walker 2009). Despite not delivering nicotine, DNCs were found to be satisfying over the initial few days of abstinence from nicotine (Pickworth 1999; Rose 2000; Donny 2007). They have also been shown to reduce tobacco withdrawal symptoms, including urges to smoke and low mood (Rose 2000; Donny 2009; Barrett 2010; Perkins 2010), and to improve long-term continuous abstinence rates in one study (Walker 2012). However, because DNCs are tobacco products that are smoked they are still associated with all of the health risks of inhaling tobacco smoke.

The ideal smoking cessation product would provide nicotine replacement and sensorimotor replacement without the health risks associated with the inhalation of tobacco smoke. The only pharmaceutical treatment available so far that combines both aspects is the nicotine inhalator. Disappointingly, the efficacy of the inhalator does not surpass that of the other nicotine replacement therapy (NRT) products (Hajek 1999). This may be at least in part due to the considerable effort (e.g. 20 minutes of continuous puffing) needed to provide nicotine blood concentrations consistent with other NRTs (Schneider 2001). Compliance with proper use of the inhalator is low compared to other NRTs (Hajek 1999). It is thus possible that any advantage of sensorimotor replacement is counterbalanced by low nicotine delivery. Additionally, the degree to which the inhalator mimics the sensations of smoking a cigarette is limited.

Description of the intervention

Electronic cigarettes, commonly called "e-cigarettes" (EC), are devices similar in appearance to cigarettes, cigars or pipes, that, by means of a small electronic vaporiser, convert propylene glycol or glycerol, with or without nicotine and flavours that are stored in disposable or refillable cartridges, into a vapour intended for inhalation. ECs are currently being promoted to smokers as a means to reduce or cease their cigarette consumption, to use in smoke-free environments, and to replace conventional cigarettes with a safer alternative.

ECs are a realistic behavioural replacement for smoking. They provide sensations similar to smoking a cigarette by emitting a smoke-like mist, resembling a cigarette closely in appearance, and providing taste and throat sensations that are closer to smoking than those provided by the nicotine inhalator.

There are different types of ECs available from different manufacturers. They all vaporize propylene glycol or glycerol as a carriage medium for nicotine, but differ in nicotine content (Goniewicz 2012). This makes a blanket assessment of efficacy difficult. Any conclusions need to be related to the concrete type of EC tested.

The first studies showed that the brands of ECs tested delivered negligible amounts nicotine to naive users (Bullen 2010; Vansickel 2010). However, both studies suggested that these brands of ECs could alleviate urges to smoke. One study allowed a comparison of ECs and inhalator though its main objective was a comparison of ECs with and without nicotine. Puffing for 20 minutes on the inhalator and puffing for five minutes on ECs had similar effects on desire to smoke after overnight abstinence (Bullen 2010). Later studies that have measured nicotine pharmacokinetics in both experienced (Vansickel 2012a) and naive (Vansickel 2012b) EC users show a different picture, with blood nicotine levels similar to those achieved with smoking.

Why it is important to do this review

Anecdotally, smokers report using ECs to help them stop smoking. Health care providers want to know what advice they should give to service users. Since there are very few other prospective smoking cessation treatment improvements on the horizon this promising development deserves objective scrutiny.

The popularity of EC use is increasing globally. Many smokers report being aware of these devices (Kralikova 2012). Data from a population survey conducted in the UK suggest that almost 10% of smokers trying to quit are using ECs to aid their attempt (West 2012). Web-survey data from EC users suggested that over three

quarters are using the devices to quit smoking (Etter 2011). Data from a small (n = 40) prospective cohort study (Polosa 2011) and a larger (n = 300) randomised controlled trial (Caponnetto 2012) also suggest that ECs can aid smoking reduction and cessation in smokers who were unwilling to quit at the point of study enrolment.

The majority of users perceive ECs to be less toxic than smoking (Etter 2011). However, categorical statements about the toxicity of ECs are not currently possible because of the large number of devices and cartridge fluids available and new products entering the market almost daily. Furthermore, the potential harms of long-term use are as yet unknown. However, among those brands of EC that have been tested, levels of toxins have been found to be substantially lower than in cigarettes (Cahn 2011). For this reason, it is probably reasonable to assume that EC use is safer than smoking tobacco cigarettes. Some public health experts have called for ECs to be carefully regulated (Cobb 2011), citing arguments such as lack of quality control measures, possible harms of secondhand EC vapour, and concerns that the products may be a gateway to smoking and may undermine smoke-free legislation. Other commentators consider these arguments spurious (Wagener 2012). Such concerns and disagreements point to the importance of monitoring and summarising the current knowledge and facts.

Health care providers and regulators are curious to know if these devices can reduce the harms associated with smoking. The largest health gains are achieved from stopping smoking completely and as such the primary objective of this review is to determine the effectiveness of ECs in aiding smoking cessation. However, there is also an opportunity to investigate if the EC has potential to aid reduction in cigarette consumption in those smokers who are not ready, or are unable, to quit smoking. NRT, when used in people who are not ready to quit, has been found to approximately double the odds of achieving at least a 50% reduction in daily cigarette consumption compared to placebo, although this was not fully matched by reductions in markers of tobacco exposure. There thus remains some uncertainty about the health benefits of this approach (Stead 2007). Nevertheless, support is growing for the use of NRT to aid cigarette reduction, especially in the context of preparing smokers for quitting (Stead 2007). This review will therefore evaluate the efficacy of ECs to reduce cigarette use with a corresponding decrease in biochemical markers of tobacco exposure.

OBJECTIVES

The primary objective is to evaluate the efficacy of electronic cigarettes (ECs) for helping people who smoke to achieve long-term cessation.

The secondary objectives are to evaluate the efficacy of ECs for helping smokers to substantially reduce cigarette use and to assess potential adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials in which smokers are randomised to electronic cigarettes (ECs) or a control condition and abstinence rates or changes in cigarette consumption are measured will be used to determine the efficacy of ECs in aiding smoking cessation and reduction. In the absence of such trials, the results from cohort follow-up studies will be considered as well.

Randomised cross-over trials and cohort follow-up studies will be included for assessment of adverse events.

Types of participants

People defined as current smokers at enrolment into the trial. Participants can be willing or unwilling to quit.

Types of interventions

EC versus alternative aids including NRT or no intervention. Trials comparing the efficacy of EC added to standard smoking cessation treatment (behaviour and/or pharmacological) with standard treatment alone will also be considered.

Types of outcome measures

Primary outcomes

Cessation at the longest follow-up point, which will be 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.

Secondary outcomes

Reduction in cigarette use at the longest follow-up point, which will be at least six months from start of intervention, measured on an intention-to-treat basis confirmed by a reduction in biomarkers of exposure (e.g. carbon monoxide, thiocyanate, and other markers of tobacco use) if reported.

Any data on adverse events, serious and non-serious, will be collected from included studies.

Search methods for identification of studies

Electronic searches

We will search the following databases

- Medline (OVID SP) (2004 to present)
- PsycINFO (OVID SP) (2004 to present)
- EMBASE (OVID SP) (2004 to present)
- CINAHL (EBSCO Host) (2004 to present)
- Cochrane Central Register of Controlled Trials
- Cochrane Tobacco Addiction Group's Specialised Register

The search terms will be broad and include e-cig$ OR elect$ cigar$ OR electronic nicotine. The search strategy for MEDLINE (Ovid SP) is shown in Appendix 1.

The search date parameters are limited to 2004 to present due to the fact that ECs were not available before 2004.

Searching other resources

We will search the reference lists of studies found in the literature search and the metaRegister of controlled trials database. We will also contact authors of known trials and other published EC studies.

Data collection and analysis

Selection of studies

All titles and abstracts obtained from the search will be independently pre-screened by two reviewers using a screening checklist. Where there is disagreement, the full text version will be obtained and the disagreement will be resolved by discussion with the third reviewer.

Full text versions of the potentially relevant papers will be obtained and will be independently screened for inclusion by two reviewers. Any disagreement will be resolved with the third reviewer.

Data extraction and management

The authors will develop a data extraction form. This will include the following fields:

- Author
- Date and place of publication
- 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
- Cigarette use per day
- Type of biochemical validation (if any)
- Adverse events
- Assessment time points
- Risk of bias in the domains specified below
- Additional comments

We will take a broad focus to detect a variety of adverse events (AEs). However, in order to address adverse effects in a more organized manner, we will enter the most commonly reported adverse effects to into meta-analyses to determine if there are any significant differences between EC and control groups.

Two reviewers will extract data from each included study into summary tables independently. The third reviewer will check the study summary data extraction against the original paper.

Data from the data extraction forms will be entered into RevMan software for analyses by one reviewer and checked by another.

Assessment of risk of bias in included studies

Two authors will independently assess the risk of bias following the approach recommended in the Cochrane Handbook for Systematic Reviews (Higgins 2011). This approach uses a domain-based evaluation that addresses seven different areas. These are: random sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other sources of bias.

Each author will summarise data for each domain and then assign a grade to reflect the risk of bias (low, high, or unclear risk). Disagreements will be resolved by discussion with the third author.

Measures of treatment effect

Dichotomous data will be analysed by calculating the risk ratio (RR) using the longest follow-up data reported. We will use a dichotomous approach for change in cigarette consumption and CO in expired breath, where changes will be categorized as reduction by 50% or more, or no change/reduction <50%.

Continuous data (other measures of tobacco exposure) will be analysed by comparing the difference between the mean change from baseline to the longest follow-up point in the intervention and control groups.

Unit of analysis issues

Data on smoking outcomes will only be extracted from randomised controlled trials. In the case of cluster-randomised controlled trials we will extract, where available, a direct estimate of the required effect from an analysis that properly accounts for the cluster design. Where such data are unavailable we will perform an approximately correct analysis if the required information can be extracted (Higgins 2011).

In the case of trials with multiple arms, we will combine all relevant experimental intervention groups of the study into a single group, and combine all relevant control intervention groups into a single control group.

For adverse events, data from cross-over trials will also be included in meta-analysis using paired data obtained from reports.

Dealing with missing data

We will use a conservative approach for missing data for smoking outcomes. Regarding smoking cessation, missing data will be considered as smoking. Regarding smoking reduction, missing data will be considered as no reduction. The proportion of people affected by adverse events will be based upon the number of people available for follow-up, and not the number randomised.

Assessment of heterogeneity

We will assess the clinical and methodological diversity between studies to guide our decision as to whether data should be pooled. This decision will also be guided by the degree of statistical heterogeneity, assessed by calculating the I^2 statistic. We will consider a value of greater than 50% as substantial heterogeneity.

Assessment of reporting biases

If there are at least ten studies, we will assess reporting bias using funnel plots. These plots show the relationship between the effect estimates from individual studies against their size or precision. The greater degree of asymmetry of these plots, the greater the risk of reporting bias.

Data synthesis

We will provide a narrative summary of the included studies and where appropriate will pool these data in meta-analyses. For dichotomous data, a fixed-effect Mantel-Haenszel model will be used to calculate the risk ratio with 95% confidence intervals. Where substantial heterogeneity exists a random effects model will be used.

We will calculate the summary estimates for continuous outcomes (e.g. biomarkers of tobacco exposure) using the inverse variance approach, also with 95% CI. Change-from-baseline measurements and final measurements will be combined for continuous outcomes if the mean difference is used to express the summary results, following the Cochrane Handbook (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

Where data allow, subgroup analyses will be undertaken to investigate differences between studies, such as:

- Intensity of behavioural support used
- Type of control (e.g. placebo EC, nicotine NRT)
- Type of participants (e.g. experience of EC use)

Sensitivity analysis

We will undertake sensitivity analyses to assess the effect of removing studies with a high risk of bias.

ACKNOWLEDGEMENTS

We would like to thank Jamie Hartmann-Boyce and Lindsay Stead for their feedback on the draft protocol.

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APPENDICES

Appendix 1. MEDLINE search strategy

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. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. electronic nicotine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

4. 1 OR 2 OR 3

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of this review protocol.

DECLARATIONS OF INTEREST

CB and HM conducted a study of ECs funded by an EC manufacturer (Ruyan Group) but designed and conducted independently of the sponsors. CB and HM are investigators on an on-going EC trial funded by the Health Research Council of New Zealand that uses product supplied at no charge from PGM international.

HM and PH have received research funding from and/or provided consultancy to manufacturers of smoking cessation medications including GSK, Pfizer, Novartis and McNeill.

SOURCES OF SUPPORT

Internal sources

- Queen Mary University of London, UK.

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

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

  provides salary, office space and library resources for CB

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Electronic Nicotine Delivery Systems [adverse effects] [instrumentation]; *Smoking Prevention; Cohort Studies; Nicotine [administration & dosage]; Nicotinic Agonists [administration & dosage]; Publication Bias; Randomized Controlled Trials as Topic; Smoking [epidemiology]; Smoking Cessation [*methods]

MeSH check words

Humans; Middle Aged