Smoking cessation in individuals who use vaping as compared to traditional nicotine replacement therapies; protocol for a systematic review and meta-analysis

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Systematic Review Protocol

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Registration: In accordance with guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 27th, 2020. Registration number pending.

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Contributions

CP is the guarantor. CP, JZ, and ATK drafted the manuscript. CP, JZ and ATK contributed to the development of the selection criteria, the risk of bias assessment strategy, and data extraction criteria. MS developed the search strategy. CP, JZ and ATK will perform the statistical analysis. CP provided expertise on vaping. All authors read, provided feedback, and approved the final manuscript.

Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

Sources

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Rationale for review in the context of what is already known

Despite a significant lack of rigorous pharmacological testing, the use of electronic nicotine device systems (ENDS), otherwise known as vaping devices, has been aggressively marketed as an effective method to quit smoking. In Canada, 32% of current and former smokers report

having used ENDS as a smoking cessation aid¹. In addition to delivering nicotine to the user, ENDS are thought to replace some of the habitual behaviors and sensations associated with smoking, such as the action of bringing a cigarette to the mouth. By doing so, ENDS may provide coping mechanisms that other traditional nicotine replacement therapies do not offer, and therefore may help with the behavioral component of smoking reduction and/or cessation². While vaping is still believed to be less harmful than cigarette smoking for those who use it as a smoking cessation aid, the large number of emerging reports on the health impacts of vaping are worrisome. In addition, the evidence on the effectiveness of ENDS as a smoking cessation aid is mixed.

There are multiple vaping products on the market. First generation ENDS resemble the traditional cigarette and are often disposable. Nicotine delivery is less efficient as compared to later generation products³. Second generation products are refillable with an e-liquid and offer more efficient nicotine delivery³⁻⁴. Third and fourth generation products allow the user to modify the amount of nicotine delivered⁴. Pod products typically offer the highest amount of nicotine content, with users showing blood nicotine content similar to those observed in cigarette smokers⁵.

In 2016, a meta-analysis of 20 studies found that using ENDS had an opposite effect to the advertised one, and actually reduced the odds of cigarette smoking cessation by 28%⁶. However, in a recent randomized controlled trial investigating smoking cessation at one year, individuals randomized to nicotine containing e-cigarettes were found to be more likely to quit smoking than individuals randomized to using nicotine patches (18% compared to 9.9%, RR 1.83; 95% CI 1.30 to 2.58)⁷. A recent Cochrane review⁴ found that nicotine-containing e-cigarettes were more effective than non-nicotine containing e-cigarettes for smoking cessation, but was not able to compare ENDS products to traditional nicotine replacement therapies.

Little information is known about the long-term health impacts of ENDS and reports of acute toxicity have recently captured the public's attention. As of January 21st 2020, there were 2711 hospitalized cases of "e-cigarette, or vaping, product use associated lung injury" (EVALI) and 60 deaths associated with the use of ENDS in the US⁸, and 17 cases in Canada⁹. Other short-term adverse events reported with the use of ENDS include cardiovascular changes such as increased heart rate and blood pressure, cough, wheeze¹⁰, and mucus production⁵. Burn injuries have also been reported, as well as fatalities from drinking or injecting the e-liquid¹⁰.

There is no long-term data available on the relationship between ENDS and oral, respiratory, and cardiovascular health, as well as cancer. There is however available data linking the chemicals present in e-liquids with cellular DNA damage and carcinogenicity^{5,11}. There is some evidence that the use of ENDS is associated with increased asthma exacerbations¹². No human long-term data exists on the use of ENDS in pregnancy and their impact on the developing fetus.

Given the large number of smokers using ENDS as a potential smoking cessation tool, there is a need to review and synthesize the evidence of trials examining a head to head comparison of ENDS versus traditional nicotine replacement therapies for smoking cessation.

Explicit statement of questions the review will address with reference to participants, interventions, comparators, and outcomes

The objective of this review is to assess the effect of electronic nicotine delivery systems (ENDS) on cigarette smoking cessation as compared other types of nicotine replacement therapies. Harms secondary to the use of ENDS and other nicotine replacement therapies will also be explored.

Specify study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review

This systematic review was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines¹³, and follows a PRISMA-Protocol checklist. The protocol has been registered with the PROSPERO International prospective register of systematic reviews (CRD number pending).

Study Characteristics:

Randomized controlled trials in which ENDS were compared to non-electronic nicotine replacement therapies in smokers will be included. We restrict our inclusion to randomized controlled trials to minimize the risk of bias.

No language limits will be imposed. No date limits will be imposed either, although we do not anticipate studies published prior to 2003 since this is when the first e-cigarette was invented¹⁴. There will be no geographical restriction of studies.

Study Population:

The population of interest includes all traditional cigarette users, including adults, teenagers, children and pregnant women, regardless of their motivation to quit. To ensure broad eligibility, we will not restrict eligibility based on the amount of traditional cigarette use.

Intervention of interest:

The intervention of interest comprises of all types, models, and brands of ENDS, including, but not limited to, first-, second-, third-, and fourth generation ENDS, as well as pod delivery systems. Characteristics of the ENDS and e-liquid used, including type, flavor, nicotine content, will be recorded but will not affect study eligibility. Given the ever-growing variety of ENDS and e-liquid products, restricting eligibility based on these factors is likely to lead to the exclusion of potentially important new evidence.

Comparators:

All included studies must compare ENDS users with non-electronic nicotine replacement therapies. These may include, but are not limited to nicotine patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strips, microtabs⁷ and combination of products.

Outcomes:

Our primary outcome measure will be traditional cigarette smoking cessation, as smoking cessation is known to improve future health outcomes. Smoking cessation will be defined by abstinence from traditional cigarette smoking for any time period as reported in each included study regardless of whether abstinence is self-reported or biochemically validated.

Secondary outcomes will include adverse events associated with the intervention and comparator, reduction in the number of traditional cigarettes smoked in any given time period, participants' acceptance of therapy, and number of quit attempts.

Settings:

All health care and community settings will be included.

Describe intended information sources (electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage

The following databases will be searched: MEDLINE (1946- present) and Embase (1980- present) and the CENTRAL Trials Registry of the Cochrane Collaboration (most current issue) using the Ovid interface, ClinicalTrials.gov and WHO ICTRP trials registries. Searches will be limited to randomized controlled trials using validated search filters where appropriate, i.e. MEDLINE and Embase. Searches will be designed and conducted by a librarian experienced in systematic reviews, using a method designed to optimize term selection¹⁵ and will be informed by searches used in previous systematic reviews of vaping or nicotine replacement therapies⁴. Due to time constraints, the search will not be peer reviewed. Reference lists of included studies and any applicable review studies will also be searched to ensure that further studies meeting eligibility criteria will not be missed by the initial search strategy. Study authors will be contacted to obtain unreported data that may be useful to our study.

Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Ovid MEDLINE(R) ALL <1946 to January 16, 2020>

#	Searches	Results
1	Electronic Nicotine Delivery Systems/ or (e cig* or electr* cigar* or electronic nicotine).mp. or (vape or vaper or vapers or vaping).ti,ab,kf.	5548

2	exp "Tobacco Use Cessation Devices"/ or NRT.ti,ab,kf. or (nicotine adj2 (patch* or gum or nasal spray or lozenge* or tablet* or sublingual or replac*)).mp. or (nicotine adj3 therapy).mp.	6776
3	1 and 2	490
4	limit 3 to randomized controlled trial*	20

*The final search will include the full Highly Sensitive Search Strategy.

Data management. Describe the mechanisms that will be used to manage records and data throughout the review

Records retrieved by the electronic search will be downloaded and imported into a Reference Manager database for duplicate removal, and then uploaded to Covidence. Throughout the review, newly identified records will be integrated into the set for screening.

State the process that will be used for selecting studies through each phase of the review (screening, eligibility, and inclusion in meta-analysis)

Each title and abstract will be independently screened by two review authors against the eligibility criteria after piloting the inclusion criteria with a set of 5 records to be assessed by all reviewers¹⁶. For the remaining records, disagreements will be resolved by discussion and with a third reviewer. Full text of all studies deemed potentially eligible will be obtained and reviewed independently by two review authors to determine eligibility. Disagreements will also be resolved by discussion and with a third reviewer. The number of studies excluded, as well as the reason for exclusion, will be documented. The number of conflicts between reviewers' assessments will also be documented. Studies will be included in the meta-analysis if they have reported categorical data associated with the primary intervention effect of smoking cessation as a dichotomous outcome (e.g., odds ratio, relative risk, or risk difference) or if they have reported numerical data and narrative data for any of the secondary outcomes of interest: harms, reduction in the number of traditional cigarettes smoked in any given time period, participants' acceptance of therapy and number of quit attempts (e.g., mean difference). The meta-analysis for each outcome will be performed separately due to the different outcomes measured and the nature of the outcome data¹⁶.

Data collection process. Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators

For studies that fulfill the inclusion criteria, two reviewers will extract data into an electronic data collection form. The data collection form will be piloted by all reviewers with the same

two to four studies. The data collection form will then be revised as needed, based on feedback by the reviewers. Disagreement between reviewers will be resolved by discussion and with a third reviewer.

List and define all variables for which data will be sought (PICO, funding) and any pre-planned data assumptions and simplifications

The abstracted data will include the following:

- 1- study characteristics: author names, year of publication, country of study, study setting, study design, sample size, number of participants that were analyzed, number of participants loss to follow up, ties with tobacco industry, funding of study
- 2- participant characteristics: age range, mean age, gender, pregnancy status, motivation to quit, duration of traditional cigarette smoking, amount of traditional cigarette smoking, previous quit attempts, previous experience with non-electronic nicotine replacement therapies, previous use of ENDS, health state
- 3- intervention characteristics: type of ENDS, model of ENDS, brand of ENDS, generation of ENDS, type of e-liquid, nicotine content, flavor, training on use of ENDS, amount of ENDS supplies given to participants, frequency of use
- 4- comparator characteristics: type of nicotine replacement therapy used, dose, frequency of use, training on use of nicotine replacement therapy, amount of supplies given to participants, combination of products
- 5- outcomes: smoking cessation / abstinence proportion between treatment groups, length of cessation, relapse, reduction in cigarette smoking, dual use of ENDS and cigarette, dual use of nicotine replacement therapy and cigarette, type, frequency, and severity of harms related to ENDS, type, frequency and severity of harms related to nicotine replacement therapies, acceptance of therapy, adherence to assigned intervention

Authors will be contacted to obtain relevant missing data.

List and define all outcomes for which data will be sought, including prioritisation of main and additional outcomes, with rationale

The primary outcome to be extracted is smoking cessation as measured by abstinence from traditional cigarette smoking. We anticipate that different follow-up time points from the designated quit date will be used to assess the smoking cessation outcome, otherwise defined as abstinence from traditional cigarette smoking. The follow-up time points will be divided to short-term (less than six month) or long-term (six months and up). The last follow-up abstinence measurement¹⁷ of each study will be extracted for this review's primary outcome synthesis. Multiple definitions for abstinence exist¹⁷ and all will be included in our review. Continuous abstinence is defined as abstinence since an intervention or event.

Prolonged abstinence corresponds to sustained abstinence after a quit date, with or without a grace period¹⁸. Point prevalence abstinence refers to not smoking for a specific period of time prior to a follow up^{18,19}. If multiple measures of abstinence are reported in a given study, the cessation outcome for the longest reported consecutive period will be included in our meta-analysis. Abstinence can either be self-reported or biochemically validated. Saliva cotinine level

tends to be a preferred method of biochemical validation, however, carbon monoxide monitoring can also be used¹⁸.

For the secondary outcome of harms, the adverse events of interest will include but will not be limited to withdrawal symptoms, respiratory symptoms (e.g., phlegm production), and adverse reactions (nausea, sleep disturbance, throat or mouth irritation or any other unexpected reactions)⁷. Harms will be summarized narratively, and a synthesis will be done if there is adequate data to support the analysis. For the secondary outcomes 'reduction in the number of traditional cigarettes smoked' and 'number of quit attempts in the follow-up period', outcomes will be standardized between studies by dividing the number of traditional cigarettes smoked and the number of quit attempts by the follow-up period to allow the results to be combined from the studies. Participants' acceptance of therapy will be synthesized narratively.

Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both: state how this information will be used in data synthesis

Two reviewers will conduct the risk of bias assessment independently for each study and at the study level. Any disagreement will be resolved by discussion and with a third reviewer. All the assessors have training in epidemiology and bias assessment. This systematic review will include only randomized controlled trials so the risk of bias will be assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)¹⁶. The tool is structured to cover five domains through which bias might be introduced into the results. The five domains are:

- (1) bias arising from the randomization process;
- (2) bias due to deviations from intended interventions;
- (3) bias due to missing outcome data;
- (4) bias in measurement of the outcome;
- (5) bias in selection of the reported result.

Studies at high risk of bias will be excluded from the primary synthesis. Sensitivity analyses including all studies will be performed to show how conclusions might change if studies at high risk of bias were included.

Describe criteria under which study data will be quantitatively synthesized

Studies will be included in the meta-analysis if they have reported categorical data associated with the primary intervention effect of smoking cessation as a dichotomous outcome (e.g., odds ratio, relative risk, or risk difference) or they have reported numerical data for the secondary outcomes of interest of harms, reduction in the number of traditional cigarettes smoked in any given time period, and number of quit attempts (e.g., mean difference). The meta-analysis for each outcome will be performed separately due to the different outcomes measured and the nature of the outcome data.

Should data be available, we will perform separate analyses for different periods of follow-up and the follow-ups will be divided into short term (less than six month) or long-term (six months and up).

If data are appropriate for synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)

We plan to analyze dichotomous data by calculating the risk ratio, using the longest follow-up time reported. The risk ratio is more easily interpretable than the odds ratio and the intervention effect will not be overestimated and misinterpreted when the risk ratio is used, especially when the risk of event is common ($>20\%$)¹⁶. The risk ratio will be calculated as such: (Number of individuals abstaining from cigarette smoking in intervention/Number of individuals in intervention)/(Number of individuals abstaining from cigarette smoking in the control group/Number of individuals in the control group)

95% confidence intervals will be calculated.

We will not use risk difference to measure the absolute effect as we anticipate this measure to be different across the studies due to the different study characteristics. Continuous data for the secondary outcomes will be analyzed through mean differences between groups as the same scales are likely to be used. In the event that different scales are used, the standardized mean differences will be computed¹⁶. Data will be extracted from studies with individuals as the unit of randomization.

Random-effects meta-analyses will be done for each outcome (dichotomous and continuous) for each time period¹⁶. The random effects (DerSimonian and Laird) method will be used to provide the pooled effect estimate for dichotomous outcomes. The inverse-variance random-effects and the mean difference approach (using standard deviations and sample sizes) to assign the weight given to each study will be used for continuous outcomes. Summary statistics of dichotomous and continuous data for each treatment group will be entered into RevMan to allow for the effect estimates to be calculated. Skewed data will be checked for the continuous outcomes and if necessary, study authors will be contacted to provide appropriate data summaries for the studies to allow transformation of data to reduce skew. If review authors are unable to obtain missing data, participants with missing data will be considered as still smoking, as per the conservative approach recommended by the Cochrane Tobacco Addiction group⁴. The proportion of adverse events reported will however be based on the number of people available for outcome assessment. For the reduction of number of cigarettes smoked and number of quit attempts, missing data will be imputed as zero so as to use the most conservative estimate.

Funnel plots of effect estimate against standard error will be used to assess for the possibility of reporting bias. Testing for funnel plot asymmetry will be undertaken if ten or more studies are included in the meta-analysis.

We anticipate there will be heterogeneity among the studies due to the clinical diversity in patient characteristics and the intervention and comparator used. In addition, methodological diversity and thus statistical heterogeneity are also anticipated¹⁶. A p value of 0.10 for the chi-squared test (Cochrane Q) to assess whether the observed differences of intervention effects from each study are due to chance alone will be used as an indicator for heterogeneity. In

addition, the I^2 statistic will be calculated to assess for heterogeneity and an I^2 of larger than 50% will be deemed as evidence of heterogeneity following the assessment of the magnitude and direction of effects and the p value. This will however be interpreted with caution as we anticipate that there will be few studies available for the meta-analysis. We do not anticipate that there will be rare events or small cells for any of the studies.

Describe any proposed additional analyses (sensitivity or subgroup analyses, meta-regression)

Sensitivity analyses will be conducted to determine if the results of the meta-analyses are robust after excluding studies that have outlying results. We will also perform a sensitivity analysis using odds ratio instead of risk ratio as the summary statistic. In addition, we will consider running a sensitivity analysis excluding small studies (number of participants ≤ 20) since using random effects meta-analysis will give more weight to smaller studies compared to using fixed effect meta-analysis¹⁶.

Meta-regression will only be performed if there are more than ten studies to provide ten observations per covariate to investigate heterogeneity and random-effects meta-regression will be used to account for residual heterogeneity of the intervention effects¹⁶. Covariates of study characteristics that will be considered for meta-regression include: study country, eligibility criteria of smokers by smoking amount, eligibility criteria of smokers motivated versus unmotivated to quit, whether training was provided, study blinding, method used to assess abstinence.

Subgroup analyses will be undertaken, if enough data is available, to investigate whether the effect of the intervention of interest is modified by the following factors:

- Age category of participants (children and teenagers vs adults)
- Smoking intensity (heavy smokers vs light smokers); heavy smokers are defined as individuals smoking ≥ 25 cigarettes per day²⁰
- Limiting comparator to nicotine patches
- Limiting primary outcome measure to biochemically validated smoking cessation
- Smoking cessation at ≤ 6 months since smoking cessation is defined as sustained abstinence for at least 6 months²¹
- Industry funding

If quantitative synthesis is not appropriate, describe the type of summary planned

A narrative summary of all included studies will be provided for each outcome that cannot be included in the quantitative synthesis. All studies will be included in the narrative synthesis, but studies with high risk of bias will be identified as such. Outcome information will be included in the summary of findings table.

Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)

Clinical and methodological diversity will be explored through careful review of included studies. Statistical heterogeneity will be explored through the use of the I^2 statistic. Funnel

plots of effect estimate against standard error will be used to assess for the possibility of reporting bias. Testing for funnel plot asymmetry will be undertaken if ten or more studies are included in the meta-analysis.

Describe how the strength of the body of evidence will be assessed (such as GRADE)

A summary of findings table will be presented for the primary outcome of traditional smoking cessation as well as for the secondary outcome of adverse events, reduction in the number of traditional cigarettes smoked in any given time period, participants' acceptance of therapy and number of quit attempts. The five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias)¹⁶ will be assessed independently by two review authors to assess the quality of evidence for each outcome, and to draw conclusions about the robustness of evidence within the review.

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