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Oral nicotine pouches for cessation or reduction of use of other tobacco or nicotine products (Protocol)

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[Intervention Protocol]

Oral nicotine pouches for cessation or reduction of use of other tobacco or nicotine products

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ABSTRACT

Objectives

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

Primary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from combustible tobacco use (smoking)
- To evaluate the impact of oral nicotine products on the prevalence of combustible tobacco use

Secondary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from other non-combustible tobacco/commercial nicotine product use
- To evaluate the impact of oral nicotine products on the prevalence of use of other non-combustible tobacco/commercial nicotine products

BACKGROUND

Description of the condition

Combustible tobacco use (i.e. smoking) is the leading preventable cause of disease and death worldwide [1]. Other commercial products containing tobacco leaf or synthetic or naturally derived nicotine vary in popularity and harm profiles. Nicotine e-cigarettes are defined as handheld electronic vaping devices that produce an aerosol for inhalation formed by heating an e-liquid containing nicotine, flavourings and humectants [2]. They are considered to represent some risk to the user, particularly people who do not have a history of combustible tobacco use, but have also been proven to help people who smoke transition away from smoking, and are considerably less harmful than traditional cigarettes [2]. Heated tobacco products (HTPs) are designed to heat tobacco to a high enough temperature to release an aerosol, without burning it or producing smoke. They differ from e-cigarettes because they heat tobacco leaf/sheet rather than a liquid. Companies who make HTPs claim they produce fewer harmful chemicals than conventional cigarettes, but independent data on their harm profiles and impacts on combustible tobacco use remain inconclusive [3]. Smokeless tobacco products include snus (a pouch of powdered tobacco leaves placed under the lip) and chewing tobacco, which are products used orally that contain tobacco leaf. Because combustion is the cause of most of the deadly toxins users are exposed to through smoking, oral tobacco products, though still posing varying risks to users, are also considered less harmful than smoking [4, 5, 6, 7].

Smoking is addictive and deadly. Most adults who smoke want to stop, but many find it difficult to do so, even with evidence-based support [8, 9]. There remains an urgent need to identify new alternatives to support people in transitioning away from combustible tobacco use.

Description of the intervention and how it might work

Oral nicotine pouches (ONPs) are preportioned pouches sold in various flavours and nicotine strengths. They are similar in appearance and use to snus. Snus is a form of smokeless tobacco placed between the gum and lip, which is popular in Nordic countries, but whose sale is banned in the UK and EU countries excluding Sweden. However, unlike snus, nicotine pouches do not contain tobacco leaf. As a result, they are often marketed as being 'tobacco-free' [10]. Like nicotine e-cigarettes and pharmaceutical forms of nicotine replacement therapy (NRT), ONPs may have the potential to help people transition away from harmful forms of tobacco/nicotine product use by replacing them with a product that does not contain tobacco leaf and which, unlike e-cigarettes, does not involve inhalation into the lungs [2, 11].

Since their introduction to the market in 2016, ONPs have grown in popularity [12, 13, 14, 15, 16, 17]. Claims are being made regarding their potential to reduce harm in people who use other forms of tobacco/nicotine, and they are being marketed as a possible form of 'tobacco harm reduction', including by manufacturers.

Why it is important to do this review

Due to the immense harm caused by smoking combustible tobacco cigarettes, there remains great interest in products that might reduce the burden of tobacco-related disease as well as, more recently, interest in products that might facilitate reductions in vaping. ONPs also have the potential to replace oral tobacco products such as snus, potentially exposing users to fewer harmful chemicals given the absence of tobacco leaf. Simultaneously, there are serious concerns regarding potential unwanted effects of ONPs, including on health, and on tobacco and nicotine use, with some people worrying that ONPs may perpetuate, rather than lessen, addictions to other tobacco and nicotine products. There is a high degree of uncertainty in the existing evidence base. Whereas there is a substantial amount of epidemiological evidence relating to tobacco pouches (i.e. snus) and their toxicant profiles, there is very little on ONPs without tobacco leaf. Though existing evidence suggests that ONPs may expose users to lower levels of toxicants than forms of inhaled or oral tobacco, many of the studies contributing to this evidence are funded by industries who produce ONPs, and independent studies have more equivocal findings [10]. There is also some evidence to suggest that the different characteristics of ONPs, including their flavours and nicotine content, may impact their effects [10]. ONPs are relatively new to the market and are an increasing focus for independent researchers and policymakers, meaning independent research in this area is likely to evolve quickly over the coming years. People who use tobacco, health professionals, and policymakers have all highlighted ONPs as a research priority.

OBJECTIVES

Primary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from combustible tobacco use (smoking)
- To evaluate the impact of oral nicotine products on the prevalence of combustible tobacco use

Secondary objectives

- To evaluate the benefits and harms of oral nicotine pouches when used to help people transition away from other non-combustible tobacco/commercial nicotine product use
- To evaluate the impact of oral nicotine products on the prevalence of use of other non-combustible tobacco/commercial nicotine products

METHODS

We will follow the Methodological expectations for Cochrane intervention reviews (MECIR) when conducting the review [18], and PRISMA 2020 for reporting [19].

Criteria for considering studies for this review

We will use different criteria for different objectives, following the approach taken in the Cochrane review of heated tobacco products [3], and delineated as follows.

- Benefits and harms: objectives relating to transitioning away from tobacco/other nicotine product use
- Prevalence: objectives relating to prevalence of tobacco/other nicotine product use

Types of studies

We will consider different study types for different objectives, following the approach taken in the Cochrane review of heated

tobacco products [3]. We will include studies regardless of setting, language, or publication status. We will restrict our searches to articles published from 2000, as ONPs were not available or in development before then.

Benefits and harms

For those objectives relating to transitioning away from tobacco/other nicotine product use (hereon referred to as 'benefits and harms studies'), we will restrict inclusion to individual-level and cluster-randomised controlled trials (RCTs) and randomised cross-over trials. We will not include quasi-randomised studies.

Prevalence

For objectives relating to the prevalence of tobacco/other nicotine product use (hereon referred to as 'prevalence studies'), we will consider interrupted and multiple time-series studies examining the population-level effect of ONPs on the prevalence of use of other tobacco/commercial nicotine products. Individual-level interventions involving ONPs may not be representative of the way most people use ONPs, which is without support from a researcher or trained specialist. Moreover, even if ONPs encourage switching away from tobacco/other commercial nicotine products, their impact on prevalence also depends on how they affect initiation of these products. We will use time-series studies to assess how changes in ONP prevalence are associated with changes in prevalence (or sales) of tobacco or other commercial nicotine products, acknowledging the limitation that associations might not reflect causal effects.

Types of participants

Benefits and harms

We will include people currently using any kind of commercial tobacco or nicotine product at baseline, other than exclusively using ONP.

In studies where only a subset of participants meet this criterion, but where all other criteria are met, we will include the study if information on the eligible subset is available either in the manuscript or via contact with study authors to obtain data on the subset of interest. Where this information is not available, we will include the study if more than 50% meet our eligibility criteria, and will note this as a limitation and conduct sensitivity analyses removing these studies.

Prevalence

For studies evaluating the impact of ONPs on the prevalence of use of other tobacco/nicotine products, we will consider any population, regardless of tobacco/nicotine product use status at baseline.

We will not exclude studies based on participants' demographic factors.

Types of interventions

Our intervention of interest is oral nicotine pouches (preportioned pouches similar in appearance to snus, but not containing tobacco leaf).

Benefits and harms

We will consider any intervention in which a person who uses another tobacco or nicotine product is instructed to use ONPs to help them reduce or quit their other tobacco/nicotine product use. We will consider studies comparing ONP-based interventions with the following comparator groups.

- No or minimal intervention, or a co-intervention also delivered to the intervention group (e.g. if both groups receive the same behavioural support, and the intervention group is also randomised to an ONP intervention)
- Interventions providing another commercial tobacco or nicotine product, for example, snus, non-snus oral tobacco, heated tobacco products, or electronic cigarettes
- Interventions providing pharmacotherapies designed to facilitate smoking cessation, including but not limited to medicinal nicotine replacement therapy, bupropion, cytisine, and varenicline
- 'Placebo' ONPs; in other words, pouches designed to mimic ONPs but which do not contain nicotine
- Experimental cigarettes with altered characteristics, e.g. very low nicotine content cigarettes
- Another ONP intervention, for example, different product, duration, dose, or instructions for use

Prevalence

For studies evaluating the impact of ONPs on the prevalence of use of other tobacco/nicotine products, we will consider the introduction of ONPs to the market or the time point where ONPs began gaining popularity as the intervention of interest. For multiple time-series studies, we will consider the extent to which changes in the prevalence of ONP use were associated with changes in the prevalence of use of other tobacco/commercial nicotine products (or sales of these products as a proxy), after adjusting for other influences that could affect changes in the prevalence of use of these products at the population level. For these studies, the comparisons of interest could be the following.

- Earlier versus later time periods
- Cross-jurisdictional comparisons
- Synthetic control groups
- Any combination of the above

Outcome measures

Studies must report measuring at least one of the critical or important outcomes listed below in order to be included in the review.

Critical outcomes

- Benefits: smoking abstinence at the longest follow-up point available, at four-week follow-up or longer. Where studies provide multiple definitions of abstinence, we will prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We will use intention-to-treat analyses assuming participants with missing data at follow-up are non-abstainers.
- Harms: number of people reporting serious adverse events (SAEs) at one week or longer. If multiple follow-up periods are reported, we will use data from the one closest to the end

of the intervention. We define SAEs as medical incidents that are potentially life-threatening, require hospitalisation, result in disability or death, or a combination of these.

- Prevalence: change in the prevalence of smoking, measured as the proportion of people in a given locality that report smoking, over a defined time period. Where multiple time periods are provided, we will use the outcome at the longest follow-up. If relevant, we will include sales as a proxy for prevalence, but it should be considered as an indirect measure of prevalence, because people can reduce their tobacco consumption without quitting.

Important outcomes

Benefits and harms

- Biomarkers of toxicant and carcinogen exposure at one week or longer (including measures of exposure to tobacco-specific N-nitrosamines, polycyclic aromatic hydrocarbons, volatile organic compounds, and carbon monoxide). We will extract all biomarkers fitting this definition. Each biomarker will be its own outcome (i.e. biomarkers will not be combined in composite measures). If multiple follow-up periods are reported, we will use data from the one closest to the end of the intervention.
- Biomarkers of harm at one week or longer (including lung function, blood pressure, heart rate, heart rate variability, blood oxygen saturation, and markers of oxidative stress and inflammation). If multiple follow-up periods are reported, we will use data from the one closest to the end of the intervention.
- Number of people reporting adverse events (AEs) at one week or longer. If multiple follow-up periods are reported, we will use data from the one closest to the end of the intervention. We define AEs as medical problems – e.g. cough, headache, dry mouth – that do not fulfil the above criteria to be considered serious.
- Change in tobacco or commercial nicotine product use from baseline, at the longest follow-up point available, at four-week follow-up or longer (e.g. change in cigarettes per day). This will be grouped by product class, including: combustible tobacco; heated tobacco products; e-cigarettes; non-combustible products containing tobacco leaf (e.g. snus, chewing tobacco). We will use intention-to-treat analyses assuming participants with missing data at follow-up have not changed their use from baseline.
- Other tobacco or commercial nicotine product abstinence at the longest follow-up point available, at four-week follow-up or longer. This will be grouped by product class, including: heated tobacco products; e-cigarettes; and non-heated/non-combustible products containing tobacco leaf (e.g. snus, chewing tobacco). Where studies provide multiple definitions of abstinence, we will prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We will use intention-to-treat analyses assuming participants with missing data at follow-up are non-abstainers.
- Abstinence from all commercial (non-pharmaceutical) tobacco/nicotine products at the longest follow-up point available, at four-week follow-up or longer. Where studies provide multiple definitions of abstinence, we will prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We will use intention-to-treat analyses assuming participants with missing data at follow-up are non-abstainers.
- Abstinence from all nicotine products (including pharmaceutical products) at the longest follow-up point available, at four-week follow-up or longer. Where studies provide multiple definitions of abstinence, we will prefer the strictest one (e.g. continuous abstinence over point prevalence; biochemically validated over self-report). We will use intention-to-treat analyses assuming participants with missing data at follow-up are non-abstainers.

Prevalence

- Change in the prevalence of other forms of tobacco/commercial nicotine use, measured as the proportion of people in a given locality that report use of these products, over a defined time period. Where multiple time periods are provided, we will use the outcome at the longest follow-up. If relevant, we will include sales as a proxy for prevalence, but it should be considered an indirect measure of prevalence, because people can reduce their tobacco consumption without quitting.

Search methods for identification of studies

Electronic searches

We will search the following databases from 2000 for relevant studies, using free text and controlled vocabulary relating to ONPs.

- MEDLINE (via Ovid)
- Embase (via Ovid)
- PsycINFO (via Ovid)
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (crsweb.cochrane.org)

Through our search of CENTRAL, we will also cover two online trial registries for the identification of unpublished studies.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
- World Health Organization (WHO) International Clinical Trials Registry Platform (apps.who.int/trialsearch)

We will not limit any of our searches by language or publication format. We will limit searches from 2000 onwards as ONPs were not available before then. Search terms can be found in Supplementary material 1.

Searching other resources

To help identify unpublished research and studies that may have been missed by our electronic searches, we will contact other experts in the field and check the reference lists of included studies for potentially relevant literature.

Data collection and analysis

Any review authors who have direct involvement in the conduct, analysis, or publication of a study that could be included in the review will not make study eligibility decisions about, extract data from, carry out the risk of bias assessment for, or perform GRADE assessments for outcomes including that study.

Selection of studies

We will adhere to the guidance in Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* [20].

Search results will be deduplicated and screened in Covidence [21]. Where multiple publications report a single study, we will combine them, paying particular attention to postpublication amendments, including expressions of concern, errata, corrigenda and retractions.

Two review authors will independently check the titles and abstracts for relevance against the eligibility criteria. Any disagreements will be resolved through discussion with a third review author. We will obtain the full-text versions of papers considered to be potentially relevant. Two review authors will independently assess the full-text reports for inclusion in the review. Any disagreements will be resolved through discussion with a third review author. Where necessary, we will contact study investigators for further information to aid our decision-making. We will record and report reasons for excluding studies at the full-text stage.

We will screen and include studies reported in any language. Should it be necessary, we will arrange for the translation of non-English language papers, first via software and if that proves insufficient, via help from someone fluent in the language. If we find multiple citations relating to the same study, we will group them into one study record with a single study ID.

Studies authored by review authors will not be screened by that review author, and they will not be involved in any other way in decisions regarding the inclusion of studies they have authored.

Data extraction and management

For each included study, two review authors will independently extract data to be used in analyses (including covariates) and for risk of bias assessment. Study characteristics will be extracted by a single review author. We will pilot our data extraction form, extracting data from two studies, and involving everyone responsible for data extraction, before proceeding to extract data from all eligible studies. We anticipate extracting data on the following variables.

- Methods (study design, study dates, recruitment methods, location, setting)
- Participants (n per group, age, sex/gender, race/ethnicity, tobacco/nicotine use history, inclusion/exclusion criteria)
- Interventions (product, nicotine content, flavouring, brand, any instructions regarding duration or frequency of use, behavioural support including any instructions for switching or ceasing use of tobacco/nicotine product(s))
- Comparators (as per interventions, but also with the possibility of no intervention/treatment)
- Outcomes (details on which eligible outcomes were reported and outcome data for each, details on how each were measured – including whether analyses were conducted per-protocol and/or intention-to-treat, in how many participants, over what period of time, and by whom)
- Funding sources and author conflicts of interest (extracted verbatim from manuscripts)

We will cross-check dual extraction, with any disagreements between review authors resolved through discussion or by involving a third review author. Data extraction processes will be carried out using Covidence and piloted before use [21]. We will import extracted and checked data into RevMan software [22]. If necessary, we will contact study authors to obtain additional information.

Should it be necessary, we will arrange for the translation of non-English language papers, first via Google Translate [23], and if that proves insufficient, via help from someone fluent in the language. We will then extract this information following the above process.

Review authors will not extract data from any studies of which they are authors.

Risk of bias assessment in included studies

We will assess risk of bias based on our critical outcomes only. Review authors will not appraise the risk of bias for any studies of which they are authors. For all studies, and regardless of the tool used, two review authors will independently assess the risk of bias, with any discrepancies resolved via discussion or referral to another reviewer.

Benefits and harms

We will follow Cochrane guidance for assessing risk of bias [24, 25]. For cross-over trials, we will follow the guidance set out in Chapter 23 [26]. As per the Cochrane Review of heated tobacco products [3], and the Cochrane Tobacco Addiction Group guidance on assessing risk of bias [27], we will use the Cochrane risk of bias tool v1 (RoB 1). We will assess the following domains.

- Selection bias (via random sequence generation and allocation concealment)
- Performance bias
- Detection bias
- Attrition bias
- Selective reporting bias
- Other risk of bias

For each study, we will make an overall judgement to summarise the risk of bias across domains. Following the guidance from the Cochrane Tobacco Addiction Group on assessing risk of bias [27], we will consider a study at high risk of bias overall if at least one domain is judged to be at high risk, of low risk of bias overall if all domains are judged to be of low risk, and of unclear risk for all other scenarios.

Prevalence

We will use ROBINS-I to assess risk of bias in non-randomised studies which report the critical outcome of smoking prevalence, following the approach taken in the Cochrane Review of heated tobacco products [3]. We will use the most recent version available at the time of assessment and will assess the following domains, judging each as low, moderate, serious or critical risk.

- Bias due to confounding (considering important confounders to be: tobacco/nicotine use prevalence at study start, if comparisons are being made between groups; other tobacco control interventions or developments)
- Bias in the selection of participants into the study
- Bias in the classification of the intervention (here we will consider definitions and measurements of ONP use)
- Bias due to missing outcome data

- Bias in measurement of the outcome (here we will consider definitions and measurement of smoking)
- Bias in selection of the reported result (which will be informed by whether or not authors have preregistered their analysis plans, and whether these have been followed)

We will not assess 'bias due to deviations from intended interventions' as our non-randomised studies of interest are not testing interventions as they are typically defined.

Overall risk of bias will be assessed in the same way as the RCTs, but with the judgement categories aligning to those of ROBINS-I, namely: low; moderate; serious; critical.

Measures of treatment effect

Benefits and harms

We will calculate risk ratios (RRs) and 95% confidence intervals (CIs) for dichotomous outcomes.

For continuous harms data, we will calculate mean differences on the raw (MD) or log-transformed (LMD) scale and the corresponding 95% CIs between the ONP and control groups at follow-up. If studies report geometric means, we will convert these onto the (natural) log scale, and if studies being pooled report mixtures of geometric and arithmetic means, we will convert them all onto the log scale, using Method 1 described in Higgins (2008) where appropriate [28].

We will use the longest follow-up data reported for outcomes assessing potential benefits. For outcomes assessing potential harms, we will use data at the closest follow-up after the end of treatment. Where possible, we will calculate treatment effects on an intention-to-treat basis.

Prevalence

For interrupted time-series studies, the treatment effect could be reflected by the step change and change in trends in prevalence or sales following the introduction of ONPs to the market (or the time point where they started gaining popularity) in the relevant locality, after adjusting for confounding variables.

For multiple time-series studies, the treatment effect of interest will be the association between ONP prevalence and prevalence or sales of the other tobacco/nicotine product in question, after adjusting for confounding variables. Where variables are log-transformed, the resulting coefficient describes the percentage change in other product prevalence associated with a 1% change in ONP prevalence.

Unit of analysis issues

Effectiveness and safety

For RCTs with more than two intervention arms, we will combine data from all relevant intervention conditions where ONPs were offered. For RCTs with more than two control arms, we will either combine data from each of these arms, or choose the most appropriate comparator. If it is not appropriate to pool intervention arms, we will split the control arm to act as a comparator to each separate intervention arm. If we identify cluster-RCTs, we will attempt to extract an estimate of the effect that accounts for the cluster design of the study (the intraclass correlation coefficient; ICC) and adjust for this. Where this is not reported, we will attempt to identify an ICC from a similar study to use in our adjusted analysis. Where an ICC can not be identified, we will not adjust for clustering but will remove the study in a sensitivity analysis.

Dealing with missing data

Benefits

For studies measuring other forms of tobacco/commercial nicotine product use as an outcome, we will assume that people with missing data at follow-up have not achieved abstinence, as is common in the field [29].

Harms

When assessing SAEs and AEs, we will calculate the proportion of those available at follow-up who experienced an event (when such data are available) rather than the proportion of people who were randomised. When assessing biomarkers, we will remove participants with missing follow-up data from the analysis (complete case).

Smoking prevalence

We do not expect issues with missing data in time-series studies.

Reporting bias assessment

Should a meta-analysis contain 10 or more studies, we will assess reporting bias using funnel plots. The greater the asymmetry in the plots, the higher the risk of reporting bias.

We will email study authors for any missing information of relevance to our review.

Synthesis methods

We will only pool data where studies fall into the same comparator group and report the same outcomes and where the synthesis would provide clinically meaningful results. Studies will be listed alphabetically by study ID. For any studies where we cannot statistically synthesise data, we will follow the guidance set out in the Synthesis Without Meta-analysis (SWiM) guidelines [30]. In particular, we will plan to create effect/association direction plots, grouped by comparison and outcome. Meta-analyses will be conducted in RevMan [22]. We will use the I^2 statistic to quantify the extent of statistical heterogeneity [31], considering I^2 values > 50% to indicate potential substantial statistical heterogeneity. When interpreting heterogeneity, we will consider both the direction and magnitude of the effects. If studies vary in effect direction, and I^2 is > 75%, we will not present pooled results.

Benefits and harms

For dichotomous data, following the standard methods of the Cochrane Tobacco Addiction Group, we plan to combine RRs and 95% CIs from individual studies using a Mantel-Haenszel random-effects model, to calculate pooled overall RRs with 95% CIs.

For continuous safety outcomes measuring biomarkers, we will pool the MDs or LMDs and measures of variance of individual studies using a generic inverse variance random-effects model.

Prevalence

We aim to calculate pooled estimates and their standard errors using a random-effects model for each of three coefficients, when reported: step change in prevalence or sales following the

introduction of ONPs (date as defined by study authors); change in these trends after the introduction; and changes associated with changes in prevalence or sale of ONPs. We will not pool time-series studies with notably different time periods (e.g. weekly versus annual).

Investigation of heterogeneity and subgroup analysis

Should sufficient studies be identified (i.e. 10 in a given meta-analysis), we will undertake the following subgroup analyses.

- Intensity of behavioural support provided for tobacco/other commercial nicotine product use outcomes, as this could be an effect modifier. This will be grouped as: no behavioural support; one-off behavioural support or written support only; multiple sessions of in-person behavioural support.
- For biomarker outcomes, we will undertake additional subgroup analyses to investigate differences by whether analyses were per-protocol or intention-to-treat, as we might expect effects to be more pronounced in per-protocol analyses. We define per-protocol analyses as those that only included participants who exclusively (or almost exclusively) used the product they were assigned, whereas intention-to-treat analyses include all participants regardless of actual product use.
- For continuous outcomes, whether data are change from baseline (preferred) or absolute value at follow-up.
- For prevalence, whether the outcome or exposure is actual prevalence of use, or sales data as a proxy measure.
- For benefits and harms, ONP characteristics including flavour and nicotine dose

All of the above are study-level variables. We will compare subgroup differences using the Chi^2 statistic and I^2 test for subgroup differences, considering $P < 0.05$ or $I^2 > 50\%$ to indicate potentially significant subgroup differences for each test, respectively. We note that lack of a 'significant' moderation effect could simply be due to low power.

Equity-related assessment

We will not investigate health inequity in this review, as based on our scoping searches there is not currently sufficient data to investigate using this lens.

Sensitivity analysis

We aim to carry out sensitivity analyses removing studies with the following characteristics.

- Judged to be at high risk of bias for at least one domain (according to ROB 1), or having serious concerns (according to ROBINS-I)
- With a minimum length of follow-up of less than four weeks (safety outcomes only)
- Funded by (or authors have received funding from) the tobacco or commercial nicotine industry
- Only classifying participants as ONP users if they use their product daily (prevalence only)
- Not all of the participants met our inclusion criteria, and this subgroup of participants could not be separated out
- Cluster-RCTs where adjustment for clustering could not be carried out
- Only used lower-nicotine dose ONPs (i.e. less than 4mg)
- Did not collect data beyond 4 weeks (biomarker outcomes only)

We will consider whether the point estimates in the sensitivity analyses are consistent in interpretation with those of the main analyses, as well as the extent to which CIs overlap between both analyses.

Certainty of the evidence assessment

We will create summary of findings tables using GRADEpro GDT for all critical outcomes, for biomarkers of exposure (NNAL, COHb, and metals), and for inflammatory markers, by following the guidelines in the *Cochrane Handbook of Systematic Reviews of Interventions* [32, 33, 34]. We will use the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each of these outcomes.

We will focus on the following comparisons for studies of benefits and harms.

- ONPs versus electronic cigarettes
- ONPs versus minimal intervention/no intervention
- ONPs versus nicotine replacement therapy

Two review authors (JHB and NL) will independently assess the certainty of evidence, with any disagreements resolved via discussion or referral to a third review author. Should a review author be involved in an included study, they will not be involved in any discussions or referrals relating to certainty of the evidence for any comparison where their study provided data.

Consumer involvement

This review has been commissioned as a part of the Center for the Assessment of Tobacco Regulation (CAsToR) 3.0, a NIH-FDA Tobacco Center of Regulatory Science (TCORS). All members of the CAsToR 3.0 steering committee, which includes diverse stakeholders, had the opportunity to input on the scope and design of this review via an online meeting and by commenting on a proposal. They will also have the opportunity to input into dissemination plans, once the analyses are complete. They are not able to dictate whether the review is published, or what it finds.

In addition to the CAsToR steering committee (predominantly based in the USA), two members of the public (PPI, based in the UK) with experience of tobacco and nicotine products will comment on the review, paying particular attention to the plain language summary. We are taking this approach such that our PPI is not confined to a single country.

We will meet with the CAsToR steering committee and with our PPI representatives after completion of analyses but before write-up to discuss the implications of our results and best routes for dissemination.

SUPPLEMENTARY MATERIALS

Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016220.

Supplementary material 1 Search strategies

Supplementary material 2 Template supplementary material: Summary of the characteristics of participants we would expect to see in the evidence and the actual participant characteristics extracted from the included studies

ADDITIONAL INFORMATION

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The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Tari Turner, Cochrane Australia; Cochrane Editorial Board
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Liz Bickerdike, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Andrea Takeda, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Clare Miles, Evidence Production and Methods Directorate (methods), Jo Platt, Central Editorial Information Specialist (search), and Humberto Choi (clinical reviewer)

Contributions of authors

JHB: conception of the review; funding acquisition; project administration; supervision; writing – original draft

NL: conception of the review; funding acquisition

HJ: conception of the review; funding acquisition

JLB: conception of the review; funding acquisition

CLM: writing – original draft

HTB: methodology; writing – review and editing

LS: methodology; writing – review and editing

JB: methodology; writing – review and editing

NT: methodology; writing – review and editing

ADW: methodology; writing – review and editing

MLG: methodology; writing – review and editing

Declarations of interest

JHB is an editor for Cochrane. She has received payments from the Truth Initiative and the US Food and Drug Administration for tobacco-related work. She has received grant funding (to her institution) from the National Institutes of Health, US Food and Drug Administration, World Health Organization, British Heart Foundation, Cancer Research UK, University of Oxford, and the British National Institute for Health Research. None of these are deemed conflicts of interest.

JLB is an editor for Cochrane. He has no conflicts.

HTB has no conflicts.

LS has received honoraria for talks, an unrestricted research grant and travel expenses to attend meetings and workshops from Pfizer and an honorarium to sit on an advisory panel from Johnson&Johnson, both pharmaceutical companies that make smoking cessation products. He has acted as paid reviewer for grant awarding bodies and as a paid consultant for health care companies. Other research has been funded by the Department of Health, UKRI, a community-interested company (National Centre for Smoking Cessation) and charitable sources (Cancer Research UK, Yorkshire Cancer Research). He has never received personal fees or research funding of any kind from alcohol, electronic cigarette or tobacco companies.

JB has received unrestricted funding to study smoking cessation from Pfizer and J&J, who manufacture medicinal smoking cessation treatments.

NT has no conflicts of interest.

ADW has no conflicts of interest.

NL has received payment for lectures on systematic review methodology (Oxford University Hospitals NHS Foundation Trust), and has been an applicant and principal investigator on project funding to carry out research in the area of tobacco control from the NIHR Evidence Synthesis programme, Cancer Research UK (charity), Clarion Futures (charity), Oxfordshire County Council and the NIHR Oxfordshire and Thames Valley ARC, Greater Manchester NHS Integrated Care and the NIH. None of this is deemed a conflict of interest.

CLM has no conflicts of interest.

HJ has received grant funding (to her institution) from the National Institutes for Health, National Science Foundation, US Army Corps of Engineers' Engineer Research Development Center, the Robert Wood Johnson Foundation, the Kresge Foundation, the UK's Health Foundation and the UK Nuffield Trust, and has been a grant applicant for the NCI/Cancer Research UK Cancer Grand Challenge Rounds. She has served as a grant reviewer for the National Science Foundation and the UCSF Tobacco-Related Disease Research Program. She has acted as a consultant to the World Health Organization, and received travel and conference support from the WHO-affiliated European Observatory on Health Systems and Policies. None of this is deemed a conflict of interest.

MLG received a research grant from Pfizer and served as a member of the Scientific Advisory Board to Johnson & Johnson; he has also consulted with the US Food and Drug Administration, World Health Organization, and Campaign for Tobacco-Free Kids on the toxicity of tobacco products and tobacco control policies; MLG is also a Member of the IASLC Tobacco Control and Smoking Cessation Committee; and AACR Tobacco Product and Cancer Subcommittee.

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Registration and protocol

Cochrane approved the proposal for this review in August 2024.

Data, code and other materials

Data sharing is not applicable to this article as it is a protocol, so no datasets were generated or analysed.

REFERENCES

1. World Health Organization. Tobacco fact sheet; July 2023. Available at https://www.who.int/news-room/fact-sheets/detail/tobacco.

2. Lindson N, Butler AR, McRobbie H, Bullen C, Hajek P, Begh R, et al. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2024, Issue 1. Art. No: CD010216. [DOI: 10.1002/14651858.CD010216.pub8]

3. Tattan-Birch H, Hartmann-Boyce J, Kock L, Simonavicius E, Brose L, Jackson S, et al. Heated tobacco products for smoking cessation and reducing smoking prevalence. *Cochrane Database of Systematic Reviews* 2022, Issue 1. Art. No: CD013790. [DOI: 10.1002/14651858.CD013790.pub2]

4. Clarke E, Thompson K, Weaver S, Thompson J, O'Connell G. Snus: a compelling harm reduction alternative to cigarettes. *Harm Reduction Journal* 2019;**16**(1):62.

5. Inoue-Choi M, Shiels MS, McNeel TS, Graubard BI, Hatsukami D, Freedman ND. Contemporary associations of exclusive cigarette, cigar, pipe, and smokeless tobacco use with overall and cause-specific mortality in the United States. *JNCI Cancer Spectrum* 2019;**3**(3):pkz036.

6. Nutt DJ, Phillips LD, Balfour D, Curran HV, Dockrell M, Foulds J, et al. Estimating the harms of nicotine-containing products using the MCDA approach. *European Addiction Research* 2014;**20**(5):218-25.

7. Scientific Committee on Emerging and Newly Identified Health Risks. Health Effects of Smokeless Tobacco Products; 6 February 2008. Available at https://health.ec.europa.eu/publications/health-effects-smokeless-tobacco-products_en.

8. Lindson N, Theodoulou A, Ordóñez-Mena JM, Fanshawe TR, Sutton AJ, Livingstone-Banks J, et al. Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses. *Cochrane Database of Systematic Reviews* 2023, Issue 9. Art. No: CD015226. [DOI: 10.1002/14651858.CD015226.pub2]

9. Hartmann-Boyce J, Livingstone-Banks J, Ordóñez-Mena JM, Fanshawe TR, Lindson N, Freeman SC, et al. Behavioural interventions for smoking cessation: an overview and network meta-analysis. *Cochrane Database of Systematic Reviews* 2021, Issue 1. Art. No: CD013229. [DOI: 10.1002/14651858.CD013229.pub2]

10. Travis N, Warner KE, Goniewicz ML, Oh H, Ranganathan R, Meza R, et al. The potential impact of oral nicotine pouches on public health: a scoping review. Nicotine & Tobacco Research 2024 Jun 17 [Epub ahead of print]. [DOI: 10.1093/ntr/ntae131]

11. Hartmann-Boyce J, Chepkin SC, Ye W, Bullen C, Lancaster T. Nicotine replacement therapy versus control for smoking cessation. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No: CD000146. [DOI: 10.1002/14651858.CD000146.pub5]

12. Hrywna M, Gonsalves NJ, Delnevo CD, Wackowski OA. Nicotine pouch product awareness, interest and ever use among US adults who smoke, 2021. *Tobacco Control* 2023;**32**(6):782-5.

13. Kramer RD, Park-Lee E, Marynak KL, Jones JT, Sawdey MD, Cullen KA. Nicotine pouch awareness and use among youth, national youth tobacco survey, 2021. *Nicotine & Tobacco Research* 2023;**25**(9):1610-3.

14. Royal College of Physicians. E-cigarettes and harm reduction: An evidence review; April 2024. Available at https://www.rcp.ac.uk/policy-and-campaigns/policy-documents/e-cigarettes-and-harm-reduction-an-evidence-review/.

15. Sun T, Tattan-Birch H. Sports, gigs, and tiktoks: multi-channel advertising of oral nicotine pouches. Nicotine & Tobacco Research 2024 Aug 27 [Epub ahead of print]. [DOI: 10.1093/ntr/ntae188]

16. Tattan-Birch H, Jackson SE, Dockrell M, Brown J. Tobacco-free nicotine pouch use in great britain: a representative population survey 2020-2021. *Nicotine & Tobacco Research: Official Journal of the Society for Research on Nicotine and Tobacco* 2022;**24**(9):1509-12.

17. Anuja M, Christian O, Ashley X, Samuel A, Priti B, Nigar N. Nicotine pouch sales trends in the US by volume and nicotine concentration levels from 2019 to 2022. *Substance Use and Addiction* 2022;**5**(11):e2242235.

18. Higgins JP, Lasserson T, Thomas J, Flemyng E, Churchill R. Methodological expectations of Cochrane intervention reviews. Cochrane: London, Version August 2023. Available from https://community.cochrane.org/mecir-manual.

19. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ (Clinical Research Ed.)* 2021;**372**:n71. [DOI: 10.1136/bmj.n71]

20. Lefebvre C, Glanville J, Briscoe S, Featherstone R, Littlewood A, Metzendorf M-I, et al. Chapter 4: Searching for and selecting studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated October 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

21. Covidence. Version accessed after 4 February 2025. Melbourne, Australia: Veritas Health Innovation, 2025. Available at https://www.covidence.org.

22. Review Manager (RevMan). Version 8.14.0. The Cochrane Collaboration, 2025. Available at https://revman.cochrane.org.

23. Google Translate. Google. Google, 2024.

24. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A. Chapter 7: Considering bias and conflicts of interest among the included studies. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions

Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

25. Higgins JP, Savović J, Page MJ, Elbers RG, Sterne JA. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

26. Higgins JP, Eldridge S, Li T editor(s). Chapter 23: Including variants on randomized trials. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.

27. Hartmann-Boyce J, Lindson N. Assessing and minimizing risk of bias in randomized controlled trials of tobacco cessation interventions: Guidance from the Cochrane Tobacco Addiction Group. *Addiction* 2023;**118**(9):1811-6.

28. Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. *Statistical Medicine* 2008;**27**(29):6072-92.

29. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction* 2005;**100**(3):299-303.

30. Campbell M, McKenzie JE, Sowden A, Katikireddi SV, Brennan SE, Ellis S, et al. Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ* 2020;**368**:l6890.

31. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research Ed.)* 2003;**327**(414):557-60.

32. Schünemann H, Brożek J, Guyatt G, Oxman A, editor(s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from https://gdt.gradepro.org/app/handbook/handbook.html.

33. GRADEpro GDT. Version accessed after 4 February 2025. Hamilton (ON): McMaster University (developed by Evidence Prime), 2025. Available at https://www.gradepro.org.

34. Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook.