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TABLE OF CONTENTS

ABSTRACT	1
BACKGROUND	2
OBJECTIVES	2
METHODS	2
ACKNOWLEDGEMENTS	5
REFERENCES	6
APPENDICES	8
CONTRIBUTIONS OF AUTHORS	9
DECLARATIONS OF INTEREST	9
SOURCES OF SUPPORT	9

[Intervention Protocol]

Interventions for smokeless tobacco use cessation

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ABSTRACT

Objectives

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

To assess the effects of behavioural and pharmacological interventions for smokeless tobacco use cessation.

BACKGROUND

Description of the condition

Smokeless tobacco products are consumed orally or nasally and do not involve combustion or heating at the time of use. Over 300 million people worldwide consume smokeless tobacco, but it is predominant in South and Southeast Asia ([Siddiqi 2020](#)).

There are significant differences between the various smokeless tobacco products: they take a variety of forms (e.g. plugs, loose-leaf, powders) and are often combined with a range of additional ingredients, such as betel leaf, areca nut, slaked lime, and various flavourings. These differences can have an impact on how addictive smokeless tobacco products are. Betel and areca can stimulate the same brain receptors as nicotine ([Horenstein 2017](#)), while slaked lime raises the pH of the product, making the nicotine in tobacco more bioavailable ([Bhisey 2012](#)).

Smokeless tobacco products also vary in their potential to harm human health, depending primarily on the amount of toxic chemicals (e.g. tobacco-specific nitrosamines) released during their use. Many smokeless tobacco products, particularly those consumed in Asia and Africa, lead to different types of head and neck cancers ([Zhou 2013](#)). The use of these products is associated with an increased risk of cardiovascular deaths ([Vidyasagaran 2016](#)), and use during pregnancy is linked to adverse reproductive outcomes, such as stillbirths and low birth weight ([Inamdar 2015](#)). However, some smokeless tobacco products, such as Swedish snus, are considered a less harmful alternative to combustible tobacco ([Clarke 2019](#); [Nutt 2014](#); [SCENIHR 2008](#)).

Description of the intervention

Interventions for the cessation of smokeless tobacco use may take similar forms to those interventions targeting combustible tobacco use. Examples are as follows.

- Pharmacotherapies
 - nicotine replacement therapy ([Hartmann-Boyce 2018](#); [Lindson 2019](#))
 - varenicline ([Cahill 2016](#))
 - bupropion ([Howes 2020](#))
- Various forms of behavioural support ([Hartmann-Boyce 2021a](#))
 - higher-intensity interventions
 - counselling ([Lancaster 2017](#); [Matkin 2019](#); [Stead 2017](#))
 - lower-intensity interventions
 - print-based self-help ([Livingstone-Banks 2019a](#))
 - mobile phone-based support ([Whittaker 2019](#))
 - internet support ([Taylor 2017](#))

Interventions may be delivered in the community or in clinical settings by clinicians ([Stead 2013](#)), nurses ([Rice 2017](#)), pharmacy staff ([Carson-Chahhoud 2019](#)), or dental professionals ([Holliday 2021](#)).

How the intervention might work

Pharmacotherapies work primarily by mitigating the craving and withdrawal symptoms associated with quitting and by reducing the rewarding sensations derived from tobacco consumption. Behavioural therapies can increase motivation for a quit attempt, for example, by highlighting the health consequences associated

with tobacco consumption ([Clair 2019](#)). Behavioural therapies can also provide support to make quit attempts more successful, for example, by discussing coping strategies and advising on how to overcome challenges, rewarding continued abstinence, or signposting further available support.

Why it is important to do this review

Tobacco is extremely damaging to health, and while combustible tobacco has been the subject of a very large amount of research, smokeless tobacco products receive less attention. Smokeless tobacco is also a driver of inequality. It has a disproportionate effect on some of the world's poorest: over 85% of the global burden of disease is associated with users in South and Southeast Asia ([Siddiqi 2020](#)). In South Asian countries, those with less education and income are more likely to use smokeless tobacco ([Zhao 2021](#)).

OBJECTIVES

To assess the effects of behavioural and pharmacological interventions for smokeless tobacco use cessation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster RCTs. We will not include quasi-randomised studies, in which the allocation sequence is not truly random, for example, studies where participant date of birth determines participant allocation.

Types of participants

We will include any users of any smokeless tobacco product, including products in which tobacco is the sole ingredient and products in which tobacco is mixed with other non-tobacco ingredients, such as betel leaf or areca nut. We will include studies that include dual users of smokeless and combustible tobacco.

We will exclude studies that include users of electronic cigarettes or heated tobacco products, which are covered in separate Cochrane Reviews ([Hartmann-Boyce 2021b](#); [Tattan-Birch 2022](#)), unless these participants are also users of smokeless tobacco products. We will also include studies of participants who have recently stopped their smokeless tobacco use, to evaluate relapse prevention interventions (as we did for combustible tobacco in [Livingstone-Banks 2019b](#)).

To be eligible, studies whose participants are not all smokeless tobacco users (including dual users) must either report cessation among smokeless tobacco users as a subgroup or include at least 50% of participants who are smokeless tobacco users.

Types of interventions

We will include any intervention intended to help people quit smokeless tobacco use. Interventions could take the form of any form of pharmacotherapy (e.g. nicotine replacement therapy (NRT), bupropion, varenicline, etc.), any behavioural support (e.g. brief advice, counselling, self-help, text messaging, etc.), or combination treatment. Eligible comparators include no intervention, usual care, placebo, or another intervention of lesser or similar intensity.

Interventions could be focussed specifically on smokeless tobacco use or tobacco use more generally.

Types of outcome measures

Primary outcomes

- Abstinence from all tobacco at longest follow-up, at least six months after baseline. In studies that do not report abstinence from all tobacco use, we will use abstinence from smokeless tobacco use. We will use the strictest definition of abstinence reported in each study (e.g. prolonged or continuous over point prevalence), and where available, we will favour biochemically validated abstinence over self-reported abstinence. We will not include studies that do not measure abstinence from all forms of tobacco or smokeless tobacco at six months or longer after baseline.

Harms outcomes

The safety and tolerability of electronic cigarettes and pharmacological interventions for individuals are better explored in other reviews (Cahill 2013; Cahill 2016; Hartmann-Boyce 2018; Hartmann-Boyce 2021b; Howes 2020; Lindson 2019). A new Cochrane Review will assess the potential impact of electronic cigarette use on tobacco uptake among young people (Hartmann-Boyce (unpublished)). Trials of behavioural interventions are very unlikely to record adverse events, and a recent overview of Cochrane Reviews of behavioural interventions found no evidence of harms (Hartmann-Boyce 2021a). However, in the event that any studies report harms from behavioural interventions, we will summarise these narratively.

Search methods for identification of studies

Electronic searches

We will search the following databases for relevant trials:

- Cochrane Tobacco Addiction Group Specialised Register via the Cochrane Register of Studies (crsweb.cochrane.org); and
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies (crsweb.cochrane.org).

The Cochrane Tobacco Addiction Group Specialised Register is populated by searches of CENTRAL, MEDLINE, Embase, and PsycINFO, together with handsearching of specialist journals, conference proceedings, and reference lists of previous trials and overviews. See the [Cochrane Tobacco Addiction Group's website](#) for full details of how the Register is compiled.

We will also conduct separate searches of the following databases for relevant trials:

- MEDLINE;
- Embase; and
- PsycINFO via Ovid.

We will search for terms related to smokeless tobacco use, forms of products (e.g. plug, quid, chew, etc.), the names of specific products (e.g. snus, paan, khaini, etc.), and commonly added ingredients (e.g. betel, areca). We list search strategies for each database in [Appendix 1](#).

We will also search two online trial registries to identify unpublished studies:

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

We will not limit any of our searches by language, year of publication, or publication format.

Searching other resources

We will check the reference lists of included studies and relevant systematic reviews for any relevant studies missed by the electronic searches.

Data collection and analysis

Selection of studies

We will screen the search results in two stages using the software [Covidence](#). Two review authors (of JL-B, AV, RC, or RM) will independently screen each identified title and abstract for eligibility. We will resolve any disagreement in judgement through discussion and if needed by referring to a third review author. We will obtain the full text of all reports that appear to be potentially eligible and repeat the duplicate screening process. We will note reasons for study exclusion and create a PRISMA diagram to document the flow of studies.

Data extraction and management

Two review authors (of JL-B, AV, FS, or RC) will independently extract the following information about each included study in duplicate, using a prepiloted data extraction form. We will resolve any disagreement through discussion and if needed by referring to a third review author.

- Study-level information, including study design, setting (whether community or healthcare and whether primary care in particular), dates, method of recruitment, and whether recruitment was limited solely to smokeless tobacco users.
- Type of smokeless tobacco products being used by participants, and rates of dual use with combustible tobacco, areca nut, or betel nut.
- Participant numbers and characteristics, including the level of motivation; pre-existing conditions; demographic information; and measures of tobacco dependence, such as the Fagerström Nicotine Dependence Scale-Smokeless Tobacco (FTND-ST) (Ebbert 2006).
- Description of the intervention(s), including the provider, mode of delivery, intervention components, whether focused on why or how to quit, and duration.
- Description of comparator(s), including the provider, mode of delivery, intervention components, and duration.
- Study outcome measures, including definition of abstinence, length of follow-up, and whether abstinence was biochemically validated.
- Outcome data for all tobacco abstinence and smokeless-only abstinence, and follow-up rates.
- Information relevant to the risk of bias assessment.
- Study funding source.

- Study authors' declarations of interest.

Assessment of risk of bias in included studies

We will assess each included study for risk of bias using Cochrane's RoB 1. We will assess the following domains of risk.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding/objectivity of outcome assessment (detection bias).
- Blinding of participants and study personnel (performance bias – we will only assess this domain in studies testing pharmacological interventions, as behavioural interventions cannot be blinded).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other potential risks of bias.

Two review authors (of JL-B, AV, FS, or RC) will independently judge each study as at low, unclear, or high risk of bias for each domain, with each judgement justified using information from the study report. We will resolve disagreements in judgement through discussion and if needed by referral to a third review author.

Measures of treatment effect

We will present estimates of effect using risk ratios (RRs), calculated as $((\text{number of events in intervention condition}/\text{intervention denominator})/(\text{number of events in control condition}/\text{control denominator}))$, with a 95% confidence interval (CI). An RR greater than one indicates a higher rate of tobacco abstinence in the intervention group compared with the control group.

Unit of analysis issues

As cluster-randomised trials are eligible for inclusion in this review, there is the potential for unit of analysis issues. We will evaluate whether each such study accounted for clustering in their reported analyses, and where required, we will adjust for clustering using an intraclass correlation, either from the study in question or from a similar study. Where studies have more than one eligible intervention arm compared with a non-intervention control, we will either pool intervention arms together (if they are sufficiently similar in intensity) or add them separately to the meta-analysis and split the control evenly between them, to avoid double-counting any participants in the analysis.

Dealing with missing data

We will conduct our analyses on an intention-to-treat basis, including all tobacco users in the study arms to which they were randomised, regardless of whether they received the intervention. We will count participants lost to follow-up as continuing tobacco users, which is standard in the field (West 2005). Where study reports lack information needed for the review, we will try to contact study authors to ask for this information. We will record attempts to contact study authors in the Characteristics of included studies tables.

Assessment of heterogeneity

To investigate heterogeneity, we will use the I^2 statistic, given by the formula $[(Q - df)/Q] \times 100\%$, where Q is the χ^2 statistic and df is its degrees of freedom (Higgins 2003). This describes the percentage

of variability in effect estimates that is due to heterogeneity rather than to sampling error (chance). We will interpret the I^2 result using the following overlapping bands.

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

If we find moderate to substantial heterogeneity, then we will investigate further with subgroup analyses based on study characteristics decided upon through review author consensus. If we find considerable unexplained statistical heterogeneity, then we will consider whether it is appropriate to report a pooled result (Higgins 2021).

Assessment of reporting biases

If 10 or more studies contribute to any comparison, then we will assess the risk of reporting bias using a funnel plot. Regardless of the number of studies included, we will consider and narratively discuss the possibility of reporting bias.

Data synthesis

We will provide a narrative summary of the included studies. Where appropriate, we will pool data from sufficiently similar studies in meta-analyses using a Mantel-Haenszel model to calculate the RR with a 95% confidence interval. We will use a random-effects model for studies of behavioural interventions and a fixed-effect model for studies of pharmacotherapy, in accordance with the standard methods of the Cochrane Tobacco Addiction Group for cessation studies.

Subgroup analysis and investigation of heterogeneity

There is huge variation in the geographical origin, constituents, and form of use among smokeless tobacco products. To investigate the potential heterogeneity this may bring to our results, we will conduct subgroup analyses and divide studies by:

- geographical/cultural origin of the product (e.g. South/Southeast Asian, Nordic countries, North American, etc.); and
- whether smokeless tobacco products were comprised solely of tobacco or contained additional ingredients, such as betel leaf, areca nut, or slaked lime, which may make cessation more difficult. If we find studies with enough variation of products and detail of reporting, then we will consider subgrouping according to the four categories of smokeless tobacco developed by the National Cancer Institute and Centers for Disease Control and Prevention (NCI and CDC 2014), which categorise products based on their key constituents besides tobacco.

We will assess heterogeneity between subgroups using the I^2 statistic, which gives the percentage of variability in effect estimates that is due to genuine subgroup differences rather than mere chance.

Sensitivity analysis

We will conduct sensitivity analyses to test whether results are impacted by the following:

- the removal of studies judged to be at high risk of bias;

- the use of smokeless-only abstinence rates; and
- the removal of studies reporting high levels of areca or betel use outside of smokeless tobacco products.

If we find studies that we deem to be meaningfully different from the other studies in an analysis (e.g. if the form of tobacco consumed is different in a way that may affect the effects of a cessation intervention), then we will consider removing them in a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

Following standard Cochrane methods, we will create summary of findings tables for all comparisons of our primary outcome (tobacco use cessation). Two review authors (JL-B and AV) will independently assess the certainty of the evidence using the five GRADE considerations (risk of bias, inconsistency, imprecision, indirectness, and publication bias) (Higgins 2021; Schünemann 2020).

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Editorial and peer-reviewer contributions:

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Lisa Bero, Public Health and Health Systems Network Senior Editor.
- Cochrane Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Helen Wakeford, Central Editorial Service.
- Cochrane Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Central Editorial Service.
- Cochrane Copy Editor (copy editing and production): Laura Prescott.
- Peer-reviewers (provided comments and recommended an editorial decision):
 - Professor Jon O Ebbert, MD, MSc, Primary Care Internal Medicine Research, Mayo Clinic, Rochester, USA (clinical/content review);
 - Dr Manu Raj Mathur, Head - Health Policy, Public Health Foundation of India & Professor of Dental Public Health, Queen Mary University of London, UK (clinical/content review);
 - Dr Hemantha Amarasinghe, Head of Training Unit, Institute of Oral Health, Maharagama, Sri Lanka (clinical/content review);
 - Neluwa-Liyanage R Indika, Department of Biochemistry, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda, Sri Lanka (consumer review);
 - Rachel Richardson, Cochrane Editorial and Methods Department (methods review);
 - Robin Featherstone, Central Editorial Service, Cochrane Editorial and Methods Department (search review).

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APPENDICES
Appendix 1. Search strategy
Cochrane Tobacco Addiction Group Specialised Register

1. (Plug or twist or leaf or powder* or pouch* or leaves or quid or dissolve* or dip* or smokeless or spit* or sniff* or nose or nasal):TI,AB,MH,EMT,KY,XKY
2. ((chew* or oral* or mouth) adj3 tobacco*):TI,AB,MH,EMT,KY,XKY
3. (afzal or alqat or ammari or ariva or bajar or bajjar or black bull or catechu or chada or chadha or chaw or chemma or cutch or dantamanjan or dediguss or dhora or dokta or gudakhu or gudaku or gudhaku or gul or guthka or gutka or gutkha or hidakphu or iq?mik or iqmik or kaini or kapoori or khaini or kharra or khimam or khiwam or kiwam or mainpuri or manjan or maras or masherri or mawa or mingkulpa or misheri or mishri or naffa or nass or nasswar nasvay or naswar or neffa or niswar or nufha or pan parag or pan masala or paan or pattiwala or pituri or qimam or qiwam or red tooth or sada pata or saffa or saood or saute or shama or shamma* or snuf* or snuif or snus or supari or surti or sute or taaba or tambakoo or tapkeer or tapkir or tawa or tenfeha or tombol or toombak or tuibur or tumbaku or vizapatta or zarda):TI,AB,MH,EMT,KY,XKY
4. ((rap? or chim?) adj3 tobacco*):TI,AB,MH,EMT,KY,XKY
5. (Betel or areca):TI,AB,MH,EMT,KY,XKY
6. MESH DESCRIPTOR tobacco, smokeless EXPLODE ALL
7. MESH DESCRIPTOR Areca
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

CENTRAL

1. ((Plug or twist or leaf or powder* or pouch* or leaves or quid or dissolve* or dip* or smokeless or spit* or sniff* or nose or nasal or chew* or oral* or mouth) adj3 tobacco*):TI,AB,MH,EMT,KY,XKY
2. (afzal or alqat or ammari or ariva or bajar or bajjar or black bull or catechu or chada or chadha or chaw or chemma or cutch or dantamanjan or dediguss or dhora or dokta or gudakhu or gudaku or gudhaku or gul or guthka or gutka or gutkha or hidakphu or iq?mik or iqmik or kaini or kapoori or khaini or kharra or khimam or khiwam or kiwam or mainpuri or manjan or maras or masherri or mawa or mingkulpa or misheri or mishri or naffa or nass or nasswar nasvay or naswar or neffa or niswar or nufha or pan parag or pan masala or paan or pattiwala or pituri or qimam or qiwam or red tooth or sada pata or saffa or saood or saute or shama or shamma* or snuf* or snuif or snus or supari or surti or sute or taaba or tambakoo or tapkeer or tapkir or tawa or tenfeha or tombol or toombak or tuibur or tumbaku or vizapatta or zarda):TI,AB,MH,EMT,KY,XKY
3. ((rap? or chim?) adj3 tobacco*):TI,AB,MH,EMT,KY,XKY

Interventions for smokeless tobacco use cessation (Protocol)

4. (Betel or areca):TI,AB,MH,EMT,KY,XKY
5. MESH DESCRIPTOR tobacco, smokeless EXPLODE ALL
6. MESH DESCRIPTOR Areca
7. 1 or 2 or 3 or 4 or 5 or 6

MEDLINE, Embase, PsycINFO

1. ((Plug or twist or leaf or powder* or pouch* or leaves or quid or dissolve* or dip* or smokeless or spit* or sniff* or nose or nasal or chew* or oral* or mouth) adj3 tobacco*).mp.
2. (afzal or alqat or ammari or ariva or bajar or bazaar or black bull or catechu or chada or chadha or chaw or chemma or cutch or dantamanjan or dediguss or dhora or dokta or gudakhu or gudaku or gudhaku or gul or guthka or gutka or gutkha or hidakphu or iq?mik or iqmik or kaini or Kapoori or khaini or kharra or khimam or khiwam or kiwam or mainpuri or manjan or maras or masherri or mawa or mingkulpa or misheri or mishri or naffa or nass or nasswar nasvay or naswar or neffa or niswar or nufha pan parag or pan masala or paan or pattiwala or pituri or qimam or qiwan or red tooth or sada pata or saffa or saood or saute or shama or shamma* or snuf* or snuif or snus or supari or surti or sute or taaba or tambakoo or tapkeer or tapkir or tawa or tenfeha or tombol or toombak or tuibur or tumbaku or vizapatta or zarda).mp.
3. ((rap? or chim?) adj3 tobacco*).mp.
4. (Betel or areca).mp
5. exp Tobacco, Smokeless/
6. Areca/
7. 1 or 2 or 3 or 4 or 5 or 6
8. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.
9. exp animals/ not humans.sh.
10. 8 not 9
11. 7 and 10

CONTRIBUTIONS OF AUTHORS

JL-B drafted the protocol. All authors discussed the methods of the protocol and edited and commented on the manuscript.

DECLARATIONS OF INTEREST

JL-B is the Managing Editor of the Cochrane Tobacco Addiction Group. He was not involved in the editorial processes related to this review.

FS: none to declare.

AV: none to declare.

RM: none to declare.

RS and KS have been involved in conducting studies that may be eligible for inclusion in this review; they will not be involved in the screening, data extraction, or quality assessment of any studies in which they themselves were investigators.

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