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# Interventions for the treatment of persistent post-viral olfactory dysfunction (Protocol)

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# TABLE OF CONTENTS

[Intervention Protocol]

# Interventions for the treatment of persistent post-viral olfactory dysfunction

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## ABSTRACT

### Objectives

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

To assess the effects (benefits and harms) of interventions that have been used to treat post-viral olfactory dysfunction.

# BACKGROUND

## Description of the condition

Olfactory dysfunction refers to disorders of the sense of smell. This may include loss of (or reduction in) the sense of smell (anosmia, hyposmia), changes in the perception of odours (parosmia), or odour hallucinations (phantosmia). The sense of smell is often neglected, however the awareness of odours that may signal danger - smoke, gas or spoilt food - is critical for personal safety. The ability to detect and appreciate everyday odours, of food, fragrances and loved ones, is also key to a sense of enjoyment of life. Individuals with olfactory dysfunction report significant impairment of their quality of life (Croy 2014). Furthermore, there is growing evidence that neurodegenerative disease, depression and death are all associated with olfactory dysfunction, particularly in the elderly, although causality has not been established (Hummel 2017a; van Regemorter 2020).

Disorders of the sense of smell are common, but often under-reported (Murphy 2002; Wehling 2011). Reduced olfaction to the extent that gives no useful function in daily life (functional anosmia) is thought to affect around 5% of people (Hummel 2017a). The prevalence of hyposmia varies depending on the tool used to measure it, but is likely to affect around 20% of individuals.

The causes of olfactory dysfunction are varied and include nasal disorders, congenital abnormalities and trauma. However, one of the most frequent causes of olfactory disturbance are viruses; culprit pathogens include rhinovirus, coronavirus, parainfluenza and Epstein Barr virus (Suzuki 2007). Since early 2020, the SARS-CoV-2 coronavirus pandemic has also resulted in an unprecedented rise in post-viral olfactory dysfunction. Most people are aware of the short-term effect that common viruses, such as colds and influenza, have on the olfactory system - typically causing temporary olfactory impairment, often in association with symptoms of a blocked, stuffy or runny nose. This short-term disturbance is mainly due to a conductive loss of olfactory function, secondary to inflammation. However, in some individuals the olfactory disturbance persists, leading to a long-lasting reduction in olfactory function - sometimes complete anosmia, or other types of olfactory disturbance.

It is not clear whether post-viral olfactory disturbance is due to direct damage to the olfactory neuroepithelium or damage to olfactory processing pathways. Histological study of the olfactory epithelium has shown a reduction in the number of cilia on olfactory neurons, and a reduced number of olfactory vesicles in those with post-viral olfactory impairment (Jafek 1990; Moran 1992). However, viral transport may also occur from olfactory neurons towards the olfactory bulb and olfactory processing centres, causing a central olfactory loss.

Typically women are affected more frequently than men and incidence is thought to increase with age (Jafek 1990). While most individuals recall the antecedent infection, perhaps noting its severity, others will not attribute the change in olfaction to a specific event. In contrast to patients with chronic sinusitis, olfactory loss in this group tends to be more sudden and abrupt (Damm 2004). For many, post-infectious olfactory dysfunction is self-limiting. However, this review considers the interventions available for those who suffer persistent disturbance of the sense of smell after a viral infection.

## Description of the intervention

A number of interventions have been used for post-viral causes of anosmia. Steroids are commonly prescribed for olfactory dysfunction - these are typically administered locally as a nasal spray, drops or rinse, but may also be given as oral tablets.

Olfactory training is also frequently suggested for reduced or absent sense of smell - this involves regular exposure to a number of specific odours. It can be performed in a variety of different ways, using household items or essential oils. Several different regimens exist with no clear consensus regarding optimal duration and odours used.

A large number of other interventions have been used for post-viral olfactory loss (Addison 2021). A variety of vitamins, minerals and nutritional supplements have been proposed to be of benefit - either taken as an oral supplement, or in some instances used intranasally (such as intranasal vitamin A drops). Glutamate antagonists and xanthine derivatives (such as theophylline) are used occasionally in the treatment of post-viral olfactory dysfunction. Trials of acupuncture have also taken place.

Olfactory dysfunction has a considerable impact on quality of life, and may be a long-lasting or even permanent condition. Therefore, psychological therapies, such as counselling or cognitive behavioural therapy, may help to develop coping mechanisms and improve quality of life, even in the absence of objective improvement in the sense of smell.

For many individuals, smell loss is anticipated to improve with time and spontaneous recovery rates as high as 30% at one year have been described (Reden 2006). There is no intervention that could currently be regarded as standard care for individuals with post-viral anosmia. Therefore, interventions may simply be compared to no treatment, or to placebo treatments. However, olfactory training is often suggested as an intervention with few adverse effects, which may be used alongside other treatments; we therefore anticipate that this may be offered as a concurrent treatment in some studies.

## How the intervention might work

Steroids are frequently prescribed with the intention that they will have an anti-inflammatory effect on the nasal cavity, restoring the respiratory mucosa as well as the olfactory epithelium to its usual state and consequently promoting the return of olfactory function. The effect is anticipated to occur within days to weeks, and is likely to last for the duration of treatment and beyond. Whether steroids have a persisting effect after discontinuation is unclear. Intranasal steroids are used for a number of other conditions, and serious side effects are rare, but they may cause nasal irritation, nosebleeds or other localised complications. Steroids may also be administered systemically - typically as oral tablets, or sometimes parenterally.

Olfactory retraining aims to stimulate the olfactory neurons with a variety of odours in order to enhance smell detection. It is unclear whether any changes occur within the olfactory epithelium itself, or in the olfactory bulb. A recent systematic review suggested that olfactory retraining may give some benefit to those with olfactory disorders (Pekala 2016). However, the majority of included studies were prospective cohorts, with only one randomised controlled trial included.

A number of vitamins and minerals have been suggested to have a beneficial effect on the olfactory epithelium, including vitamins A, B12 and D, and zinc. It is thought that metabolites of vitamin A may play a role in regeneration of tissue in the olfactory epithelium or olfactory bulb, and this has been used intranasally to treat individuals with post-viral olfactory loss (Hummel 2017b). Vitamin B12 is known to be important in the maintenance of central and peripheral nervous function, and deficiency of vitamin B12 has been associated with olfactory impairment (Derin 2016). Vitamin D deficiency has also been linked to olfactory impairment (Bigman 2020). Zinc deficiency has also been shown to have an association with olfactory dysfunction.

Antioxidants, such as alpha lipoic acid and omega 3 fatty acids, have also been suggested as possible interventions to treat anosmia (Hummel 2002). They are thought to have neuroprotective properties that may help restore function within olfactory neurons or the olfactory bulb. Minocycline has also been trialled in post-viral olfactory loss - due to its neuroprotective properties, rather than its traditional role as an antibiotic (Reden 2011).

The impact of olfactory dysfunction on quality of life is substantial. Adjusting to, and learning to cope with, this life-changing symptom may be helped through psychological therapies, counselling or cognitive behavioural therapy.

There have also been small studies to assess the possible benefit of acupuncture in olfactory loss (Dai 2016; Vent 2010).

Glutamate plays an important role in neurotransmission for olfactory neurons and within the olfactory bulb. Glutamate antagonists, such as caroverine, have been proposed to help protect against neurotoxicity, and consequently improve olfactory function (Quint 2002). Finally, xanthine derivatives such as theophylline and pentoxifylline have been proposed to stimulate olfactory neuron activity, and may therefore have an effect on olfactory function.

It is possible that multiple premorbid health determinants will have an impact on the efficacy of treatment within each group; for example, those of advanced age with a relatively impaired immune response to infection. Consequently, we will take this into account when assessing the response to treatment.

### Why it is important to do this review

Olfaction is one of the five principal senses; its functions are wide-ranging - from detecting critical and life-threatening danger through detection of noxious stimuli to enhancing taste and appetite stimulation. Not only does smell function as its own distinct entity but also through its intimate relationship with gustation and the limbic system. A normal sense of smell is undervalued despite its integral role in daily life and impairment in olfactory function does not receive the same medical attention in comparison to that of sight and hearing.

A UK-based national survey of otorhinolaryngology consultants found that whilst 97% evaluated patients with olfactory dysfunction only 12% performed routine chemosensory testing for impairment; in this series post-infectious dysfunction made up nearly a fifth of presentations (McNeill 2007). It has been hypothesised that this relative neglect originates from frustration at a perceived lack of treatment options and a paucity of evidence in relation to those that do exist. A need for new treatment modalities and further guidelines in the area has been previously highlighted through patient surveys, which identified failure of clinicians to recognise the problem, a lack of treatment options and limited access to specialist services as some of the concerns raised (Ball 2021; Philpott 2021).

Many interventions described in the treatment of post-viral olfactory dysfunction carry risks associated with use. Perhaps one of the most notable examples is the use of steroids, particularly systemically. Others such as olfactory training require high levels of patient compliance and motivation to optimise outcomes. With this review we aim to comprehensively assess the benefits and harms of interventions to treat post-infectious olfactory dysfunction, to ensure that patients and caregivers can make an informed choice regarding the management of this complex condition.

The ongoing COVID-19 pandemic has sparked a renewed interest in post-viral olfactory dysfunction as a significant proportion of those infected suffer at least a temporary alteration in sense of smell (Lechien 2020). Given the massive numbers infected and the high transmissibility of the virus, this is predicted to significantly impact the number of patients suffering from olfactory dysfunction. As this is a new phenomenon, research in this field is in its nascence, and is considered in separate living systematic reviews (O'Byrne 2021; Webster 2021).

The purpose of this present review is to outline what evidence exists with regard to post-viral olfactory dysfunction (excluding SARS-CoV-2 infection) and to comment on the benefits, risks and outcomes of these interventions.

## OBJECTIVES

To assess the effects (benefits and harms) of interventions that have been used to treat post-viral olfactory dysfunction.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomised controlled trials and quasi-randomised trials (where trials were designed as RCTs, but the sequence generation for allocation of treatment used methods such as alternative allocation, birth dates, alphabetical order etc.).

Olfactory dysfunction is unlikely to be stable over long periods of time, and individuals may experience considerable fluctuation of symptoms over a given time period. Cross-over trials are therefore unlikely to be identified in this area. If we do identify any cross-over studies, we will include data from the first phase only in the review.

We will only include studies where patients were followed up for at least four weeks.

#### Types of participants

Adult participants (aged 18 years or older) with abnormalities of their sense of smell following viral infection or presumed viral infection.

For a study to be included in this review, at least 95% of participants must have a proven or presumed post-viral cause of olfactory loss,

unless relevant data can be extracted specifically for the subgroup of individuals with post-viral olfactory dysfunction.

We will include trials that recruited participants with anosmia or hyposmia for at least four weeks. We will only include trials where individuals were identified as having olfactory dysfunction by psychophysical testing, rather than by self-report.

A separate Cochrane Review considers interventions used in the treatment of post-viral olfactory dysfunction that is specifically related to COVID-19 infection. Therefore trials that specifically include individuals with COVID-19 infection will be excluded from this review. If the study includes a mixed population of COVID and non-COVID participants we will include the study if the majority (> 50%) of participants do not have COVID-19 as a trigger for their olfactory dysfunction, or if subgroup data for those without COVID-19 can be identified.

Other (non-viral) infectious causes of olfactory dysfunction, such as bacteria, fungi or microfilaria, will be excluded from this review.

### Types of interventions

#### *Interventions*

We will include the following interventions, which have been proposed to specifically treat smell disturbance:

- Intranasal steroids
- Systemic steroids
- Olfactory training
- Intranasal vitamin A
- Zinc
- Omega 3 fatty acids, alpha lipoic acid
- Minocycline
- Caroverine
- Sodium citrate
- Theophylline, pentoxifylline
- Counselling
- Acupuncture

All routes of administration, doses and durations of treatment will be included.

We will exclude studies that consider surgery, as this is not currently an intervention of interest for post-viral olfactory loss. We will exclude studies where more than one intervention has been used.

Olfactory training is considered to be a complex intervention, as the method of delivery may vary considerably in different studies. This will be assessed using subgroup analyses (see below).

The main comparators will be:

- placebo or no treatment.

#### *Concurrent treatments*

We anticipate that some trials may include olfactory training (or other interventions) as concurrent therapy in both arms. There will be no limits on the type of concurrent treatments used. We will pool these trials with studies where no concurrent treatment was used and use sensitivity analyses to determine whether the effect estimates are changed because of this.

### Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies. All outcomes will be assessed at three possible time points:

- 1 to 3 months (this is the main time point of interest);
- > 3 months to 12 months;
- > 12 months to 3 years.

#### *Primary outcomes*

- Recovery of sense of smell:
  - as assessed by the participants;
  - as assessed by psychophysical testing, using Sniffin Sticks, UPSIT or another validated test.
- Disease-related quality of life, as assessed by the Olfactory Disorders Questionnaire, or other validated questionnaire (which specifically relates to olfactory dysfunction).
- Serious adverse effects (as defined by the trialists).

#### *Secondary outcomes*

- Change in sense of smell:
  - as assessed by the participants;
  - as assessed by psychophysical testing, using Sniffin' Sticks, UPSIT or other validated test.
- Generic quality of life, as assessed by validated methods (e.g. EQ-5D).
- Other adverse effects (including nosebleeds/bloody discharge).

## Search methods for identification of studies

### Electronic searches

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

### Searching other resources

The Cochrane ENT Information Specialist will search the following databases from their inception to identify published, unpublished and ongoing RCTs:

- the Cochrane ENT Register (search via the Cochrane Register of Studies to date);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (search via the Cochrane Register of Studies to date);
- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) (1946 to date);
- Ovid EMBASE (1974 to date);
- Web of Science, Web of Science (1945 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov:
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), https://apps.who.int/trialsearch/.

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL, Ovid MEDLINE and Ovid Embase (Appendix 1). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Technical Supplement to Chapter 4 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 6.1; Lefebvre 2020).

## Data collection and analysis

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist will also run non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

We will not perform a separate search for adverse effects. We will consider adverse effects described in included studies only.

We will contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

### Selection of studies

At least two review authors will independently screen titles and abstracts retrieved by the search to identify potentially relevant studies. Subsequently, at least two review authors will independently evaluate the full text of each potentially relevant study to determine whether it meets the inclusion/exclusions criteria for this review. Any differences will be resolved by discussion and consensus, with the involvement of a third author where necessary.

### Data extraction and management

At least two review authors will independently extract outcome data from each study using a standardised data collection form. Where a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Any discrepancies in the data extracted by the two authors will be checked against the original reports, and differences will be resolved through discussion and consensus, with recourse to a third author where necessary. If required, we will contact the study authors for clarification.

We will include key characteristics of the studies, such as the study design, setting, sample size, population and the methods for defining or collecting outcome data in the studies. We will also include details of the baseline characteristics of trial participants, with particular regard to prognostic features such as age, gender, duration of time since viral infection, persistence of rhinitis or sinusitis.

The primary effect of interest for this review will be the effect of treatment assignment (which reflects the outcomes of treatment for people who were assigned to the intervention) rather than a per protocol analysis (the outcomes of treatment only for those who completed the full course of treatment as planned). For the outcomes of interest in this review, we will extract the findings from the studies on an available case basis, i.e. all available data from all participants at each time point, based on the treatment to which they were randomised. This will be irrespective of compliance, or whether participants had received the intervention as planned.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias, we will extract the following summary statistics for each trial and outcome:

- For continuous data: the mean values, standard deviation and number of patients for each treatment group at the different time points for outcome measurement. Where endpoint data are not available, we will extract the values for change-from-baseline data instead. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. mean difference) from the studies.
- For binary data: we will extract information on the number of participants experiencing an event, and the number of participants assessed at that time point. If values for the individual treatment groups are not reported, where possible we will extract summary statistics (e.g. risk ratio) from the studies.
- For ordinal scale data: we do not anticipate identifying ordinal data which is of relevance for our outcomes. However, if this is identified and if the data appear to be normally distributed, or if the analysis performed by the investigators indicates that parametric tests are appropriate, then we will treat the outcome measure as continuous data. Alternatively, if data are available, we will convert these to binary data for analysis.

We have pre-specified time points of interest for the outcomes in this review. Where studies report data at multiple time points, we will take the longest available follow-up point within each of the specific time frames. For example, if a study reports an outcome at 4 weeks, 8 weeks and 12 weeks of follow-up then the 12-week data will be included for the time point 1 to 3 months.

### Assessment of risk of bias in included studies

Two authors will undertake assessment of the risk of bias of the included studies independently, with the following taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane risk of bias tool in RevMan 5.4 (RevMan 2020), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: 'low', 'high' or 'unclear' risk of bias.

### Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. recovery of sense of smell) as risk ratios (RR) with 95% confidence intervals (CIs). For the key outcomes that we will present in the summary of findings tables, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We may also calculate the number needed to

treat to benefit (NNTB) using the pooled results. The assumed baseline risk is typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies is used as the 'study population' (Handbook 2021). If a large number of studies are available, and where appropriate, we may also present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we will express treatment effects as a mean difference (MD) with standard deviation (SD) or as a standardised mean difference (SMD) if different scales have been used to measure the same outcome. We will provide a clinical interpretation of the SMD values using either Cohen's d or by conversion to a recognised scale if possible.

### Unit of analysis issues

Cross-over trials and cluster-randomised trials are not anticipated for this review topic. Post-viral anosmia is unlikely to be a stable condition, and interventions may not have a temporary effect. If cross-over trials are identified then we plan to use only the data from the first phase of the study. If cluster-randomised trials are identified then we will ensure that analysis methods are used to account for clustering in the data (Handbook 2021).

### Dealing with missing data

We will try to contact study authors via e-mail whenever the outcome of interest is not reported, if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis have been reported, unless the missing data are standard deviations. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2021). If it is impossible to estimate these, we will contact the study authors.

Apart from imputations for missing standard deviations, we will conduct no other imputations. We will extract and analyse all data using the available case analysis method.

### Assessment of heterogeneity

We will assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included studies for potential differences between them in the types of participants recruited, interventions or controls used and the outcomes measured.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the $Chi^2$ test (with a significance level set at P value < 0.10) and the $I^2$ statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance (Handbook 2021).

### Assessment of reporting biases

We will assess reporting bias as within-study outcome reporting bias and between-study publication bias.

#### *Outcome reporting bias (within-study reporting bias)*

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol or trial registry, whenever this can be obtained. If the protocol or trial registry entry is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will seek further information from the study authors. If no further information can be found, we will note this as being a 'high' risk of bias when the risk of bias tool is used. If there is insufficient information to judge the risk of bias we will note this as an 'unclear' risk of bias (Handbook 2011).

#### *Publication bias (between-study reporting bias)*

We will assess funnel plots if sufficient studies (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we will conduct more formal investigation using the methods proposed by Egger 1997. We will also report on whether there were any studies identified through trial registries and other sources (Searching other resources), with unpublished reports.

### Data synthesis

Where possible and appropriate (if participants, interventions, comparisons and outcomes are sufficiently similar in the studies identified) we will conduct a quantitative synthesis of results. We will conduct all meta-analyses using RevMan 5 (RevMan 2020). We will use a random-effects method for meta-analysis.

For dichotomous data, we plan to analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods.

For continuous outcomes, if all data are from the same scale, we will pool mean follow-up values with change-from-baseline data and report this as a mean difference (MD). If there is a need to report standardised mean differences then endpoint and change-from-baseline data will not be pooled.

Sense of smell may be tested using a variety of methods, which consider different aspects of the sense of smell. These are:

- identification - the ability to identify and name a specific odour;
- threshold - the concentration of an odour which can be detected;
- discrimination - the ability to discriminate between odours.

We will include methods that consider any or all of the above aspects of sense of smell. Where meta-analysis is appropriate, we will only pool results that look at the same individual aspect (or aspects) of sense of smell.

### Subgroup analysis and investigation of heterogeneity

If statistical heterogeneity is identified for any comparisons, we will assess this considering the following subgroups:

- age of participants in the study (under 60 years versus those aged 60 or over);
- duration of time since viral infection (less than six months versus six months or longer);
- type of olfactory dysfunction in study participants (anosmia, hyposmia, parosmia or phantosmia).

We will identify studies as belonging to a particular subgroup if more than 2/3 participants (66%) belong to that category. If studies present data for subgroups of individuals within the study we will use this for subgroup analysis, where applicable, regardless of whether studies have stratified their randomisation according to those subgroups.

We anticipate that the varying methods used for olfactory training may be a source of heterogeneity in effects. If we identify heterogeneity in the comparison of olfactory training then we will explore this considering the following factors:

- classical versus modified olfactory training (using the same scents throughout, compared to changing the scents);
- the number of scents used;
- the delivery method (e.g. essential oils in a jar compared to natural scents, such as a peeled orange);
- the time spent for each training session;
- the frequency of training sessions;
- high concentration versus low concentration;
- duration of training (less than 12 weeks versus more than 12 weeks).

### Sensitivity analysis

We plan to carry out sensitivity analyses to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the studies. We plan to conduct sensitivity analysis for the following factors, whenever possible:

- impact of model chosen: to investigate whether the use of a fixed-effect model impacts on the effect estimates;
- inclusion of studies with concurrent treatments: to exclude these studies from the pooled estimates of effect for any intervention.

### Summary of findings and assessment of the certainty of the evidence

Two independent authors will use the GRADE approach to rate the overall certainty of evidence using GRADEpro GDT (https://gradepro.org/). The certainty of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high certainty of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low certainty implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high certainty. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a summary of findings table (constructed according to the Handbook 2021) for the following comparison(s):

- intranasal steroids versus no treatment/placebo;
- olfactory training versus no treatment/placebo;
- intranasal vitamin A versus no treatment/placebo.

We will include all outcomes in the summary of findings table, at the time point one to three months.

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# REFERENCES

## Additional references


### Addison 2021

Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C et al .Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. *Journal of Allergy and Clinical Immunology* 2021;**147**(5):1704-19.

### Ball 2021

Ball S, Boak D, Dixon J, Carrie S, Philpott CM.Barriers to effective health care for patients who have smell or taste disorders. Clinical Otolaryngology 2021 Jun 4 [Epub ahead of print]. [DOI: 10.1111/coa.13818]

### Bigman 2020

Bigman G.Age-related smell and taste impairments and vitamin D associations in the U.S. Adults National Health and Nutrition Examination Survey. *Nutrients* 2020;**12**(4):984.

### Croy 2014

Croy I, Nordin S, Hummel T.Olfactory disorders and quality of life--an updated review. *Chemical Senses* 2014;**39**(3):185-94.

### Dai 2016

Dai Q, Pang Z, Yu H.Recovery of olfactory function in postviral olfactory dysfunction patients after acupuncture treatment. *Evidence-based Complementary and Alternative Medicine: ECAM* 2016;**2016**:4986034. [DOI: 10.1155/2016/4986034] [PMID: 27034689]

### Damm 2004

Damm M, Temmel A, Welge-Lüssen A, Eckel HE, Kreft MP, Klussmann JP, et al.Olfactory dysfunctions. Epidemiology and therapy in Germany, Austria and Switzerland [Riechstörungen. Epidemiologie und Therapie in Deutschland, Osterreich und der Schweiz]. *HNO* 2004;**52**(2):112-20. [PMID: 14968312]

### Derin 2016

Derin S, Koseoglu S, Sahin C, Sahan M.Effect of vitamin B12 deficiency on olfactory function. *International Forum of Allergy & Rhinology* 2016;**6**(10):1051-5.

### Egger 1997

Egger M, Davey Smith G, Schneider M, Minder C.Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;**315**(7109):629.

### Handbook 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

### Handbook 2021

Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors).Cochrane Handbook for Systematic Reviews of Interventions Version 6.2 (updated February 2021). Cochrane, 2021. Available from www.training.cochrane.org/handbook.

### Hummel 2002

Hummel T, Heilmann S, Hüttenbriuk KB.Lipoic acid in the treatment of smell dysfunction following viral infection of the upper respiratory tract. *Laryngoscope* 2002;**112**(11):2076-80.

### Hummel 2017a

Hummel T, Whitcroft KL, Andrews P, Altundag A, Cinghi C, Costanzo RM, et al.Position paper on olfactory dysfunction. *Rhinology. Supplement* 2017;**54**(26):1-30. [PMID: 29528615]

### Hummel 2017b

Hummel T, Whitcroft KL, Rueter G, Haehner A.Intranasal vitamin A is beneficial in post-infectious olfactory loss. *European Archives of Oto-rhino-laryngology* 2017;**274**(7):2819-25.

### Jafek 1990

Jafek BW, Hartman D, Eller PM, Johnson EW, Strahan RC, Moran DT.Postviral olfactory dysfunction. *American Journal of Rhinology* 1990;**4**(3):91-100.

### Lechien 2020

Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al.Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *European Archives of Oto-rhino-laryngology* 2020;**277**(8):2251-61. [DOI: 10.1007/s00405-020-05965-1]

### McNeill 2007

McNeill E, Ramakrishnan Y, Carrie S.Diagnosis and management of olfactory disorders: survey of UK-based consultants and literature review. *Journal of Laryngology and Otology* 2007;**121**(8):713-20.

### Moran 1992

Moran DT, Jafek BW, Eller PM, Rowley III JC.Ultrastructural histopathology of human olfactory dysfunction. *Microscopy Research and Technique* 1992;**23**:103-10.

### Murphy 2002

Murphy C, Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM.Prevalence of olfactory impairment in older adults. *Journal of the American Medical Association* 2002;**288**(18):2307-12. [DOI: 10.1001/jama.288.18.2307]

### O'Byrne 2021

O'Byrne L, Webster KE, MacKeith S, Philpott C, Hopkins C, Burton MJ.Interventions for the treatment of persistent post-COVID-19 olfactory dysfunction. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No: CD013876. [DOI: 10.1002/14651858.CD013876.pub2]

### Pekala 2016

Pekala K, Chandra RK, Turner JH.Efficacy of olfactory training in patients with olfactory loss: a systematic review and meta-analysis. *International Forum of Allergy & Rhinology* 2016;**6**(3):299-307.

**Philpott 2021**

Philpott CM, Boardman J, Boak D.Patient experiences of postinfectious olfactory dysfunction. ORL: Journal for Oto-Rhino-Laryngology and its Related Specialties 2021 May 10 [Epub ahead of print]. [DOI: 10.1159/000516109]

**Quint 2002**

Quint C, Temmel AF, Hummel T, Ehrenberger K.The quinoxaline derivative caroverine in the treatment of sensorineural smell disorders: a proof-of-concept study. *Acta Oto-laryngologica* 2002;**122**(8):877-81. [PMID: 12542209]

**Reden 2006**

Reden J, Mueller A, Mueller C, Konstantinidis I, Frasnelli J, Landis BN, et al.Recovery of olfactory function following closed head injury or infections of the upper respiratory tract. *Archives of Otolaryngology--Head and Neck Surgery* 2006;**132**(3):265-9.

**Reden 2011**

Reden J, Herting B, Lill K, Kern R, Hummel T.Treatment of postinfectious olfactory disorders with minocycline: a double-blind, placebo-controlled study. *Laryngoscope* 2011;**121**(3):679-82.

**RevMan 2020 [Computer program]**

The Cochrane Collaboration Review Manager (RevMan).Version 5.4. Copenhagen: The Cochrane Collaboration, 2020.

**Suzuki 2007**

Suzuki M, Saito K, Min WP, Vladau C, Toida K, Itoh H, et al.Identification of viruses in patients with post-viral olfactory dysfunction. *Laryngoscope* 2007;**117**(2):272-7.

**van Regemorter 2020**

van Regemorter V, Hummel T, Rosenzweig F, Moraux A, Rombaux P, Huart C.Mechanisms linking olfactory impairment and risk of mortality. *Frontiers in Neuroscience* 2020;**14**:140.

**Vent 2010**

Vent J, Wang DW, Damm M.Effects of traditional Chinese acupuncture in post-viral olfactory dysfunction. *Otolaryngology - Head and Neck Surgery* 2010;**142**(4):505-9. [PMID: 20304268]

**Webster 2021**

Webster KE, O'Byrne L, MacKeith S, Philpott C, Hopkins C, Burton MJ.Interventions for the prevention of persistent post-COVID-19 olfactory dysfunction. *Cochrane Database of Systematic Reviews* 2021, Issue 7. Art. No: CD013877. [DOI: 10.1002/14651858.CD013877.pub2]

**Wehling 2011**

Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ.Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. *Archives of Clinical Neuropsychology* 2011;**26**(3):260-9. [DOI: 10.1093/arclin/acr019]

## APPENDICES

### Appendix 1. Draft search strategies

| CENTRAL (CRS) | MEDLINE (Ovid) | Embase (Ovid) |
|---|---|---|
| 1 MESH DESCRIPTOR Respiratory Tract Infections AND CENTRAL:TARGET 2410<br>2 MESH DESCRIPTOR Common Cold AND CENTRAL:TARGET 552<br>3 MESH DESCRIPTOR Influenza, Human AND CENTRAL:TARGET 2805<br>4 MESH DESCRIPTOR Rhinovirus AND CENTRAL:TARGET 5<br>5 MESH DESCRIPTOR Virus Diseases AND CENTRAL:TARGET 250<br>6 (follow* or post or after or previous*) adj6 (viral or URTI or cold or flu or infect* or virus* or influenza* or rhinovirus*) AND CENTRAL:TARGET 21471<br>7 postviral or pvol or postinfect* or PVOD or PIOD AND CENTRAL:TARGET 151 | MEDLINE (Ovid MEDLINE® Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) 1946 to present<br><br>1 Respiratory Tract Infections/ 40512<br>2 Common Cold/ 4308<br>3 Influenza, Human/ 53089<br>4 Rhinovirus/ 3940<br>5 Virus Diseases/ 40004<br>6 ((follow* or post or after or previous*) adj6 (viral or URTI or cold or flu or infect* or virus* or influenza* or rhinovirus*)).ab,ti. 274515<br>7 (postviral or pvol or postinfect* or PVOD).ab,ti. 10995<br>8 1 or 2 or 3 or 4 or 5 or 6 or 7 402258<br>9 exp Olfaction Disorders/ 5131 | Embase 1974 to present<br><br>1 respiratory tract infection/ or respiratory tract disease/ or influenza/ or upper respiratory tract infection/ or viral respiratory tract infection/ 212169<br>2 common cold/ or rhinovirus infection/ 11025<br>3 virus infection/ or viral upper respiratory tract infection/ 166172<br>4 ((follow* or post or after) adj6 (viral or URTI or cold or flu or infect* or virus* or influenza* or rhinovirus*)).ab,ti. 314296<br>5 (postviral or pvol or postinfect* or PVOD).ab,ti. 12348<br>6 1 or 2 or 3 or 4 or 5 660625<br>7 exp smelling disorder/ 14339<br>8 olfactory discrimination/ 5582<br>9 (Olfaction or olfactory or Dysosmia* or Parosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*).ab,ti. 62367<br>10 (smell* adj6 (disorder* or loss or distort* or alter* or dysfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)).ab,ti. 4376<br>11 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)).ab,ti. 335<br>12 7 or 8 or 9 or 10 or 11 71202<br>13 6 and 12 1967 |

*(Continued)*

8 #1 OR #2 OR #3 OR #4 OR #6 OR #7 AND CENTRAL:TARGET 26239
9 MESH DESCRIPTOR Olfaction Disorders EXPLODE ALL AND CENTRAL:TARGET 145
10 (Olfaction or olfactory or Dysosmia* or Parosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 1438
11 (smell* adj6 (disorder* or loss or distort* or alter* or dysfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 560
12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 174
13 #9 OR #10 OR #11 OR #12 AND CENTRAL:TARGET 1790
14 #8 AND #13 AND CENTRAL:TARGET 82
15 (idiopathic or unknown or sensorineural or unexplained) adj6 (Olfaction or olfactory or Dysosmia* or Parosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia* or smell*) AND CENTRAL:TARGET 15
16 #14 OR #15 AND CENTRAL:TARGET 92

10 (Olfaction or olfactory or Dysosmia* or Parosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia*).ab,ti. 52954
11 (smell* adj6 (disorder* or loss or distort* or alter* or dysfunction or impair* or abscen* or reduce* or different* or sensation* or abnormal* or perception* or change* or expected or decreas* or deficit*)).ab,ti. 3166
12 (smell* adj6 (prevent* or rehab* or recover* or therap* or train* or retrain*)).ab,ti. 255
13 9 or 10 or 11 or 12 55366
14 8 and 13 931
15 ((idiopathic or sensorineural or unknown or unexplained) adj6 (Olfaction or olfactory or Dysosmia* or Parosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia* or smell*)).ab,ti. 516
16 14 or 15 1417
17 randomized controlled trial.pt. 546328
18 controlled clinical trial.pt. 94455
19 randomized.ab. 537187
20 placebo.ab. 222265
21 drug therapy.fs. 2386189
22 randomly.ab. 367833
23 trial.ab. 571906
24 groups.ab. 2259214
25 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 5145290
26 exp animals/ not humans.sh. 4898545
27 25 not 26 4476054
28 16 and 27 218

14 ((idiopathic or sensorineural or unknown or unexplained) adj6 (Olfaction or olfactory or Dysosmia* or Paraosmia* or Anosmia* or hyposmia* or phantosmia* or Cacosmia* or microsmia* or smell*)).ab,ti. 698
15 13 or 14 2614
16 Randomized controlled trial/ 680082
17 Controlled clinical study/ 464185
18 Random$.ti,ab. 1715554
19 randomization/ 91984
20 intermethod comparison/ 276092
21 placebo.ti,ab. 330856
22 (compare or compared or comparison).ti. 548538
23 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 2382951
24 (open adj label).ti,ab. 91664
25 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 249372
26 double blind procedure/ 188736
27 parallel group$1.ti,ab. 28241
28 (crossover or cross over).ti,ab. 113066
29 ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 364854
30 (assigned or allocated).ti,ab. 429955
31 (controlled adj7 (study or design or trial)).ti,ab. 390284
32 (volunteer or volunteers).ti,ab. 261445
33 human experiment/ 556748
34 trial.ti. 341129
35 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 5545783
36 (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. 12309
37 comparative study/ or controlled study/ 9064705
38 randomi?ed controlled.ti,ab. 327369
39 randomly assigned.ti,ab. 145022
40 37 or 38 or 39 9250247
41 36 not 40 8737
42 Cross-sectional study/ 439974
43 randomized controlled trial/ or controlled clinical study/ or controlled study/ 8519742
44 (randomi?ed controlled or control group$1).ti,ab. 996120
45 43 or 44 8886001
46 42 not 45 285482
47 (((case adj control$) and random$) not randomi?ed controlled).ti,ab. 19033
48 (Systematic review not (trial or study)).ti. 188872
49 (nonrandom$ not random$).ti,ab. 17313
50 "Random field$".ti,ab. 2597
51 (random cluster adj3 sampl$).ti,ab. 1387
52 (review.ab. and review.pt.) not trial.ti. 931929
53 "we searched".ab. 62770
54 review.ti. or review.pt. 3139515
55 53 and 54 38663
56 "update review".ab. 118
57 (databases adj4 searched).ab. 45894
58 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 1125013
59 41 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 55 or 56 or 57 1393941
60 35 not 59 5259328

(Continued)

61 15 and 60 413

## CONTRIBUTIONS OF AUTHORS

Lisa O'Byrne: scoped, designed and drafted the protocol with the help of the other authors.

Katie E Webster: scoped, designed and drafted the protocol with the help of the other authors.

Samuel MacKeith: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Carl Philpott: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Claire Hopkins: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

Martin J Burton: clinical guidance at all stages of protocol development, commented on and edited the draft protocol and agreed the final version.

## DECLARATIONS OF INTEREST

Lisa O'Byrne: none known.

Katie E Webster: none known.

Samuel MacKeith: Sam MacKeith is Assistant Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol.

Carl Philpott: Professor Carl Philpott sees and treats patients with smell loss. He has written various online publications on the topic and conducted interviews and webinars internationally. He is a Trustee for the charity Fifth Sense. He is the senior author on the Clinical Olfactory Working Group consensus document on the management of post-infectious olfactory dysfunction and the consensus document on the use of systemic corticosteroids in COVID-19 related olfactory dysfunction.

Claire Hopkins: Professor Claire Hopkins sees and treats patients with smell loss. She has spoken on the association between COVID and smell loss in multiple media outlets. She is senior author of the British Rhinological Society position paper on management of COVID-19 related smell loss.

Martin J Burton: Professor Martin Burton is Co-ordinating Editor of Cochrane ENT, but had no role in the editorial process for this protocol.

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