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Interventions for hyperhidrosis (Protocol)

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Interventions for hyperhidrosis

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ABSTRACT

Objectives

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

To assess the effectiveness and safety of interventions for hyperhidrosis.

BACKGROUND

Please see Appendix 1 for a glossary of medical terms.

Description of the condition

Sweating is an important way to reduce the body's temperature, for example during strenuous physical activity or when exposed to a hot environment. Hyperhidrosis is defined as excessive sweating beyond what is physiologically required.

Hyperhidrosis can be categorised as primary (idiopathic), or secondary to other conditions such as infection, cancer, endocrine or neurological disorders, or as a side effect of some medications (Vorkamp 2010). Primary hyperhidrosis can affect people at any age, but often starts in childhood or at puberty (Shargall 2008; Solish 2007).

Hyperhidrosis can also be categorised by its location and whether it is focal or generalised. Focal locations of the body that are commonly affected include the axillae (underarms), palmoplantar (palms and soles of feet), craniofacial (scalp and face), and groin areas.

Hyperhidrosis is estimated to affect about 1% to 5% of the population, being present in a similar proportion of males and females (Shargall 2008; Strutton 2004). The condition occurs globally; however, there are some regional differences, for example about 4.8% of people in the USA have the condition, with around half of those having axillary hyperhidrosis (Doolittle 2016; Strutton 2004), whereas in China palmar hyperhidrosis is the most prevalent, with up to 5% of the population affected (Tu 2007). A higher prevalence of 12.8% has been reported in Japan (Fujimoto 2013).

The cause of primary hyperhidrosis is unknown, but is thought to be due to overreaction or hyperexcitability of the complex neurological pathways which control sweating. There is evidence of a hereditary predisposition for palmar hyperhidrosis; it is estimated that a child of a parent with the condition has a 1 in 4 chance of inheriting it (Higashimoto 2006).

The diagnosis of hyperhidrosis can be made initially based on clinical history, which can guide a determination of primary or secondary hyperhidrosis (Solish 2007). Hyperhidrosis is usually diagnosed where there is visible sweating, which interferes with daily activities, has lasted at least six months, and for which there is no known cause (NICE 2018). Where there is an underlying cause that can be treated, hyperhidrosis can be cured; otherwise the aim is to manage the condition. A study of people with primary hyperhidrosis found that 88% had no improvement in symptoms or severity over time, which did not vary by age group (Glaser 2016).

Hyperhidrosis can have a significant negative impact on a person's quality of life, both socially and in the workplace, and has been shown to have a greater impact on quality of life than other skin conditions such as atopic eczema, acne, psoriasis, or rosacea (Bechara 2007). The unpredictable and uncontrollable nature of the condition can make it very distressing for patients (Bechara 2007). Palmar hyperhidrosis can impair the ability to handle pens, paper, and electronic equipment (Wade 2018). However, the condition can go unreported due to social embarrassment and lead to loneliness and anxiety. Prolonged wet contact may also cause skin maceration and soreness as well as secondary skin infections (Solish 2007). Hyperhidrosis may be further complicated by bromhidrosis (unpleasant odour), which occurs from the by-products of bacteria that reside in these sweaty areas (Kanlayavattanakul 2011).

The severity of impact on an affected individual's life can be assessed by relevant questionnaires, such as the Hyperhidrosis Disease Severity Scale (HDSS; Solish 2007), Dermatology Life Quality Index (DLQI; Finlay 1994), or Hyperhidrosis Quality of Life Index (HidroQoL; Gabes 2021). These assessment tools can help overcome a patient's subjective perceptions of the severity of their condition and the effectiveness of treatment. To quantify the amount of sweat produced over a specific period of time, gravimetry can be used, or the starch-iodine (Minor's) test can also help to provide an objective measurement (Swinehart 2000). However, these two objective assessments are not usually performed in a clinical setting due to the time and complexity involved.

Description of the intervention

A wide variety of interventions are used in the management of hyperhidrosis, ranging from topical applications, iontophoresis, injectable therapies, oral anticholinergics, energy-based devices, and surgery. The availability of treatments varies in different countries as well as whether they are available through public or private healthcare systems. The chosen treatment depends upon the localised or generalised nature of the excessive sweating, its anatomical location, the availability of the intervention, side effects and tolerability (Hoorens 2012). In addition to active therapeutic interventions, patients are advised to make lifestyle modifications to avoid any triggers for their hyperhidrosis such as environmental, emotional, and dietary factors. Treatments are then usually trialled in a sequential manner, beginning with conservative options and progressing to more aggressive therapies as necessary until symptom control is achieved.

Topical pharmacological interventions

Topical antiperspirants

Topical antiperspirants are considered first-line treatments by patients as they are safe, cost-effective, and readily accessible (Grabell 2017). Aluminium chloride is the most commonly used antiperspirant and is most effective for primary focal hyperhidrosis affecting axillary areas, but may also be helpful for palmo-plantar sites (Pariser 2014; Walling 2011). ACH (aluminium chloride hexahydrate) preparations vary in strength from 6.25% to 40%. Over-the-counter aluminium chloride antiperspirants are widely available but contain a maximum strength of 12.5% ACH. Prescription antiperspirants are often required, and can be uptitrated and also delivered in different vehicles, such as ethyl alcohol or salicylic acid gel, to enhance efficacy (Nawrocki 2019; Solish 2007). Preparations should be applied to dry skin overnight when sweat rates are reduced, remain in place for six to eight hours before being washed off, and continued nightly until therapeutic benefit is achieved (usually within two weeks) before reducing frequency of application (Pariser 2014). Skin irritation can occur and may be helped by reducing the strength of preparation or frequency of use or adding emollient and/or topical corticosteroid regimens (Nawrocki 2019; Pariser 2014).

Topical anticholinergics

Topical anticholinergic medications such as propantheline, scopolamine, and diphemanil methylsulfate have been used in hyperhidrosis. Topical glycopyrrolate with strength ranging from 0.5% to 4% in the form of gel, cream, or pads and 3% oxybutynin are most commonly used for focal hyperhidrosis and in some studies for larger areas of sweating, but their use may be limited by skin irritation, anticholinergic side effects, and lack of universally available commercial preparations (Nawrocki 2019). A topical glycopyrronium tosylate cloth approved by the US Food and Drug Administration in recent years for primary axillary hyperhidrosis in adults and children over nine years old has been reported as cost-effective relative to prescribed aluminium chloride (Bloudek 2021). Topical 1% glycopyrronium cream and sofpironnium gel are both currently undergoing clinical trials and may offer a future topical option for primary axillary hyperhidrosis (Abels 2021; Kirsch 2020). Most of these are prepared individually by pharmacists, and therefore may or may not be of consistent formulation.

Other topical agents

Historically other astringent preparations, such as formalin, glutaraldehyde, and tannic acid amongst others, were used in hyperhidrosis as keratinolytic effects in the stratum corneum temporarily blocked eccrine sweat ducts, but their use has been limited by numerous side effects including skin irritation, staining, lack of long-term efficacy, and toxicity (Nawrocki 2019).

Oral pharmacological therapies

Oral systemic treatments can be used for both focal and generalised hyperhidrosis, with oral anticholinergic medications being the most commonly prescribed (Grabell 2017; Nawrocki 2019). However, their use is often limited by side effects and poor tolerability.

Oral anticholinergic medications

Propantheline bromide, glycopyrrolate, oxybutynin, and methantheline bromide have been used largely off-label to treat mainly generalised primary hyperhidrosis (Nawrocki 2019). Oral propantheline bromide is the only anticholinergic currently licensed for hyperhidrosis in the UK (EMC 2018). These medications are usually taken in a daily dosing regimen, and treatment discontinuation is common due to adverse effects including most commonly dry mouth, dry eyes, blurred vision, urinary retention, constipation, drowsiness, tachycardia, gastrointestinal upset and reflux. They are contraindicated in individuals with pyloric stenosis, paralytic ileus, and myasthenia gravis and have numerous relative contraindications and potential drug interactions (Cruddas 2017; Nawrocki 2019).

Other systemic agents

Other oral agents used include beta-blockers such as propranolol, and short-term use of benzodiazepines to treat anxiety where it is a trigger for focal and generalised hyperhidrosis (Grabell 2017).

Iontophoresis

Iontophoresis is a first-line treatment mainly for palmo-plantar hyperhidrosis and can be used for axillary regions with the addition of electrode pads. Treatment is usually initiated in hospital 3 to 4 times per week for up to 30 minutes per treatment. A maintenance regimen is then required; home devices are also available. An ionised substance is passed through intact skin by applying a direct electrical current. In most cases tap water is used, but the effect can be amplified by adding aluminium chloride, anticholinergics, or botulinum toxin (Davarian 2008; Nawrocki 2019; Pariser 2014). Side effects are usually mild and include erythema, vesiculation, discomfort or cracking of skin, but these are usually easily treated. It is contraindicated in pregnancy, individuals with pacemakers, metal implants, epilepsy, and cardiac conditions (Pariser 2014). A 'dry-type' iontophoresis device that uses the patient's own sweat for conduction has also been evaluated in small studies for use in palmar hyperhidrosis (Choi 2013; Na 2007).

Injectable therapies

Botulinum toxin injections are well-established as a second-line therapy for hyperhidrosis, predominantly using botulinum toxin type A (BTX-A), of which there are serotypes including abobotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA. It is used for primary axillary hyperhidrosis and to a lesser extent palmo-plantar and cranio-facial sites (Solish 2007; Wade 2018). BTX-A is a neurotoxin produced by the bacterium *Clostridium botulinum* which helps to reduce sweating on a temporary basis, and two to three treatments per year are needed to maintain therapeutic benefit (Naumann 2003; Nawrocki 2020).

BTX is administered as an intradermal injection to target sweat glands located at the dermal-subcutaneous junction. The depth of injection and dosing regimen will vary depending on body site (Benson 2013). Higher doses and often anaesthetic measures are needed for palmo-plantar areas due to diffusion susceptibility and greater pain during administration at these sites (Nawrocki 2020). Whilst treatments are usually well-tolerated, adverse effects include pain, burning and pruritus, bruising, haematoma, localised pruritus, headaches, muscle pain, urticaria, compensatory sweating, and for palmo-plantar sites paraesthesia and weakness (Lowe 2007; Naumann 2004; Nawrocki 2020). Therapy is contraindicated in pregnant and breastfeeding women and individuals with sensitivity to formulation ingredients, injection-site infection, or previous sweat gland removal. Careful monitoring is also needed for patients with certain neurological disorders and concurrent medication use that might alter the metabolism of botulinum toxin (Campanati 2020; Nawrocki 2020).

Laser and energy-based device therapies

A number of destructive therapies have been used with the aim of reducing sweating in hyperhidrosis.

MiraDry

A device known as miraDry (Miramar Labs, Sunnyvale, CA) is an approved treatment that has demonstrated efficacy for treatment of axillary hyperhidrosis (Hong 2012). The procedure can be performed under local anaesthesia, and treatment of each axilla lasts up to an hour, with two treatments usually required three months apart. Typical side effects include swelling, redness and pain, whilst less commonly blistering or burning, rash, bumps, patchy alopecia at treatment sites, and compensatory sweating can occur (Glaser 2012; Hong 2012).

Ultrasound therapy

Microfocussed ultrasound device therapy is used to reduce sweating in axillary hyperhidrosis. Reported short-term side

effects include swelling, discomfort, redness and bruising; more prolonged adverse effects include altered sensation and axillary bumps (Nawrocki 2019; Nestor 2014).

Fractional microneedle radiofrequency

The procedure of fractional microneedle radiofrequency causes thermal destruction of eccrine sweat glands via bipolar energy emitted via microneedles inserted into the skin. It is a minimally invasive technique; side effects include pain, swelling, and redness. Repeat treatments are recommended (Abtahi-Naeini 2016; Fatemi 2015; Kim 2013).

Laser therapy

A number of laser modalities of varying penetration depths have been used for axillary hyperhidrosis. Lasers such as the neodymium-doped aluminium garnet (Nd:Yag) laser at wavelengths of 1064 nm and 1320 nm, as well as the 924- and 975-nanometre diode laser, can penetrate skin deeply enough to impact on eccrine sweat glands. Reported side effects include discomfort in the area, temporary reduced sensation, swelling, burns, erosion, haematoma, pigmentary change, hair reduction, and compensatory hyperhidrosis (Cervantes 2018; Nawrocki 2019). Recent reviews have noted that, whilst laser epilation may be of benefit in hyperhidrosis, there are limitations such as variability in device parameters and treatment protocols (Cervantes 2018; Wade 2018).

Surgical interventions

Surgical interventional procedures are usually reserved for cases in which other less invasive and more conservative measures have failed. Numerous techniques have been developed and evolved over the years with the aim of reducing sweat production in the affected areas, with varying levels of invasiveness and potential morbidity.

Excision of sweat glands

Excisional procedural approaches have been used to excise the subcutaneous tissue of axillary skin, removing the sweat glands and thus ameliorating axillary hyperhidrosis. Historically, a radical skin excision was performed via various techniques, but this confers a high risk of complication including haematoma, paraesthesia, focal alopecia, infection, scarring, retraction and restricted movement and is thus rarely performed today (Glaser 2014). A more selective and limited excision approach with a skin-paring technique known as Shelley's procedure can be used under local anaesthesia, with the aim of achieving therapeutic benefit and with a reduced side effect profile and scarring risk compared to the radical approach (Bechara 2008; Lawrence 2006; Wollina 2008).

Curettage

The technique of curettage for axillary hyperhidrosis was first developed many years ago (Jemec 1978), and involves using a curette device to remove the subcutaneous tissue via incisions made in the axillae. Numerous techniques exist and can be performed under local tumescent anaesthesia with reported improvement in sweat reduction. Reported side effects include infection, necrosis, haematoma, scarring, alopecia, hyperpigmentation, and ulceration (Glaser 2014).

Liposuction and suction-curettage

The procedure of liposuction in treating axillary hyperhidrosis can be performed under local anaesthesia and involves using small suction cannula incisions made in the axillary skin to remove subcutaneous fat and effectively remove eccrine sweat glands (Lillis 1990). Whilst this procedure confers less risk of scarring compared with excisional procedures, it does have a risk of relapse. Side effects described can include bruising, haematoma, infection, bleeding, bridle formation, paraesthesia, alopecia and seroma (Bechara 2006; Glaser 2014; Lee 2005).

In addition to the separate techniques of liposuction and curettage, a combination technique known as suction-curettage has more recently been developed for axillary hyperhidrosis. This involves removal of eccrine and apocrine sweat glands under local tumescent anaesthesia using a liposuction and an arthroscopic shaver device through a small incision (Glaser 2014). Specific techniques can vary between operators. It is described as a minimally invasive procedure with minimal complications; however, reported adverse effects include recurrence, haematoma, bruising, seroma, erosion, infection, hair loss, adhesions, paraesthesia, scarring, and brachial plexus damage (Glaser 2014; Nawrocki 2019; Rezende 2014).

Sympathetic denervation procedures

Endoscopic thoracopic sympathectomy (ETS) was first performed in 1989 and is now an established permanent surgical intervention for treatment-refractory hyperhidrosis of palmar, craniofacial, and axillary sites. The ideal candidate for ETS is considered to have had onset of hyperhidrosis prior to age 16, is younger than 25 years at the time of surgery, with a body mass index (BMI) less than 28, no sweating during sleep, without significant comorbidities, and with a resting heart rate greater than 55 beats per minute (Cerfolio 2011). Compensatory sweating is the most common side effect, and has been reported to occur in up to 98% of cases; risk can depend on the anatomical level targeted during the procedure. Other known risks include development of Horner's syndrome, pneumothorax, haemothorax, paraesthesia, hyperthermia, and bradycardia (Moraites 2014). Given the significant and serious risks involved, careful patient selection and counselling is key before undertaking this intervention.

How the intervention might work

Topical treatments

Aluminium salts work in hyperhidrosis by forming precipitates with sweat mucopolysaccharides that temporarily block eccrine sweat ducts (Hölzle 1984). Aluminium zirconium trichlorohydrex is used as the active ingredient in more recently developed topical over-the-counter antiperspirants and creates superficial duct blockages with less skin irritation. Previous concerns have been raised about the possible associations of topical aluminium use and the development of Alzheimer's disease and breast cancer, but these associations have not been supported by research (Nawrocki 2019; Pariser 2014).

Topical anticholinergics work by inhibiting the action of acetylcholine at muscarinic receptors and reducing eccrine sweat gland production (Nawrocki 2019).

The astringent preparations, including formalin, glutaraldehyde, and tannic acid, have keratinolytic effects in the stratum corneum, which temporarily block eccrine sweat ducts (Nawrocki 2019).

Oral anticholinergic medications

Oral anticholinergics act systemically by inhibiting the effects of acetylcholine at muscarinic receptors, thereby reducing sweat gland secretion (Benson 2013).

Other systemic agents

Beta-blockers and benzodiazepines treat anxiety that may be a trigger for hyperhidrosis (Grabell 2017).

Iontophoresis

The exact mechanism of action of iontophoresis is not fully understood, but is postulated to involve sweat gland plugging, interference with nerve transmission, and reduced pH following hydrogen ion accumulation (Pariser 2014; Roustit 2014).

Injectable therapies

Botulinum toxin works by inhibiting acetylcholine release at the level of the neuromuscular junction, thus blocking cholinergic innervation of eccrine sweat glands and reducing sweating (Hambleton 1992; Hoorens 2012). This inhibitory effect can last for six to eight months, and two to three treatments per year are needed to maintain therapeutic benefit (Naumann 2003; Nawrocki 2020).

Laser and energy-based device therapies

Laser and energy-based device therapies are permanent solutions, although some may require more than one treatment. miraDry (Miramar Labs, Sunnyvale, CA) uses microwave energy to cause thermolysis and subsequent destruction of eccrine sweat glands (Glaser 2014). Microfocussed ultrasound device therapy works by causing thermal injury to eccrine glands (Nestor 2014). Fractional microneedle radiofrequency also causes thermal destruction of eccrine sweat glands, but via bipolar energy emitted via microneedles inserted into the skin (Kim 2013). Lasers can penetrate deeply enough to impact on germinal structures such as eccrine sweat glands through postulated mechanisms of direct thermal structural damage and photo-mechanical effects (Nawrocki 2019).

Surgical interventions

Surgical interventions are also permanent solutions. Several methods (excision, curettage) work by removing eccrine sweat glands (Nawrocki 2019). Endoscopic thorascopic sympathectomy works by removing the sympathetic innervation to eccrine sweat glands by a form of cutting or clipping the involved sympathetic nerves; no clear superior technique has been established (Moraites 2014).

Why it is important to do this review

There is currently no Cochrane Review for hyperhidrosis, despite it being a common condition that affects 1% to 5% of the population globally and can have a significant negative effect on the quality of life of those affected (Doolittle 2016; Shargall 2008; Strutton 2004). As such, it is important and timely to develop a Cochrane Review of interventions for hyperhidrosis so that healthcare professionals, patients, and the public can access the best available evidence. The provision of a 'consumer summary' will also be of particular benefit to patients and the public when making treatment decisions.

In 2020, Cochrane Skin undertook an extensive prioritisation exercise to identify a core portfolio of the most clinically important titles. This title was identified as a clinically important priority by the expert panel for development, maintenance, and investment of resources by the editorial base, and as in the top five reviews in the Cochrane Skin 2020 prioritisation process (Cochrane Skin 2020).

The Top 10 research priorities of the James Lind Alliance Priority Setting Partnership for hyperhidrosis included the following questions which could be identified by this Cochrane Review (JLA 2019).

Table 1: Research priorities from the James Lind Alliance Priority Setting Partnership for hyperhidrosis

Priority ranking	Research question
1	Are there any safe and effective permanent solutions for hyperhidrosis?
2	What is the most effective and safe oral treatment (drugs taken by mouth) for hyperhidrosis?
3	What are the most effective and safest ways to reduce sweating in particular areas of the body (e.g. hands, feet, underarms, face, head, etc.)?
6	What is the safest and most effective treatment for mild to moderate hyperhidrosis?
9	What is the safest and most effective surgery for hyperhidrosis?

A recent short survey carried out by the Hyperhidrosis Research Network (unpublished data), completed by patients (n = 39), showed support for this Cochrane Review. All respondents wanted more information about which treatments for hyperhidrosis are safe and effective, and 97% of respondents wanted a Cochrane Review of interventions for hyperhidrosis to be done.

We intend that our Cochrane Review of interventions for hyperhidrosis will contribute to clinical guidelines in the UK and

beyond. This systematic review aims to find and evaluate the best evidence regarding the effects of available interventions for hyperhidrosis. This review will provide key information on patient-important outcomes.

OBJECTIVES

To assess the effectiveness and safety of interventions for hyperhidrosis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all types of randomised controlled trials (RCTs), including cluster-RCTs and cross-over trials. We will also include quasi-RCTs (trials with allocation according to variables such as medical record number or date or birth).

Types of participants

We will include participants with the following.

- Participants of any age, gender, ethnicity.
- Mild, moderate, and severe primary hyperhidrosis.
- Generalised hyperhidrosis, or specific to areas of the body (e.g. palmar, plantar, axillary, face/head, etc.).
- Any healthcare setting.

Studies with a subset of relevant participants will only be included if data are presented separately. If separate data are not reported, we will contact the trial authors for this information.

Types of interventions

- Topical treatments
  - Aluminium chloride, formaldehyde, botulinum toxin, and anticholinergic/antimuscarinic solutions, sprays, creams, wipes, roll-ons, or gels.
  - Iontophoresis: tap water, with or without aluminium chloride or anticholinergic added, or 'dry type' device.
- Injectables
  - Botulinum toxin, delivered by subcutaneous injection at a dosage up to 250 units (BTX-A) or 5000 units (BTX-B).
- Oral anticholinergics
  - Oxybutynin, methantheline bromide, glycopyrrolate, and propantheline bromide (any dosage).
- Destructive treatments
  - Microwave (miraDry), fractionated microneedle radiofrequency, laser and ultrasound technologies.
  - Curettage, shaving and skin/sweat gland excision techniques.
  - Endoscopic thoracic sympathectomy, lumbar sympathectomy, and lower limb sympathectomy (including chemical sympathectomy).

We will compare interventions to no treatment, placebo, or other interventions where possible.

Types of outcome measures

We will assess both effectiveness and safety in this review. There is no core outcome set for hyperhidrosis on the Cochrane Skin Core Outcome Set Initiative (Cochrane Skin Core Outcome Set 2021); however, a core outcome set for hyperhidrosis is in development on Core Outcome Measures in Effectiveness Trials (COMET 2021). This outcome set is not due for completion until 2024.

We will include continuous and categorical data, but give preference to continuous measures where information is available.

As there is no agreed-upon standardised timing for assessing effectiveness outcomes, for consistency we will categorise duration/longevity of treatment effect as short term (less than 12 weeks) or longer term (12 weeks or more). For trials with multiple time points, trials may be included in both short- and long-term analyses. We will also report outcomes at baseline, end of treatment, and the end of follow-up regardless of the timing, and attempt to pool data with similar time points, where possible.

For safety data, we will report adverse events or withdrawal from treatment at any time point, but will present data separately during treatment and follow-up phases.

We will include studies regardless of whether or not they have reported on the outcomes of this review.

Primary outcomes

- Patient-reported symptom improvement, assessed using the Hyperhidrosis Disease Severity Scale (HDSS, Solish 2007), Likert scales, patient global assessment, or other patient-reported visual analogue scale.
- Withdrawal from treatment due to adverse effects.

Secondary outcomes

- Quality of life assessed using hyperhidrosis-specific tools such as the Hyperhidrosis Quality of Life Index (HidroQoL, Gabes 2021), Hyperhidrosis Quality of Life Questionnaire (HQLQ, de Campos 2003), and Hyperhidrosis Impact Questionnaire (HHIQ, Teale 2002) or non-disease-specific quality of life tools such as the Dermatology Life Quality Index (DLQI, Finlay 1994) and 36-item Short Form Health Survey (SF-36, Ware 1993).
- Sweat rate, assessed by gravimetric testing, evaporimetry, iodine starch test, or other reported methods.
- Major or minor adverse events.

Search methods for identification of studies

We aim to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist (Liz Doney) will search the following databases for relevant trials with no date restrictions:

- the Cochrane Skin Specialised Register 2021 via the Cochrane Register of Studies (CRS-Web);
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library;
- MEDLINE Ovid (from 1946 onwards); and

- Embase Ovid (from 1974 onwards).

Liz Doney has devised a draft search strategy for RCTs for MEDLINE (Ovid), which is displayed in Appendix 2. The draft MEDLINE strategy will be peer-reviewed by another Cochrane Information Specialist prior to execution using the Search methods and strategy peer review assessment form for Cochrane intervention protocols. This strategy will be used as the basis for search strategies for the other databases listed above.

Trial registers

Liz Doney will search the trial registers listed below using the following search terms: hyperhidrosis, hyperhydrosis, hyperidrosis, hyper perspiration, excessive sweating:

- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/);
- ClinicalTrials.gov (www.clinicaltrials.gov).

Searching other resources

Searching reference lists

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials.

Searching by contacting relevant individuals or organisations

We will contact experts/organisations in the field to obtain additional information on relevant trials.

Correspondence with triallists/experts/organisations

We will contact original authors for clarification and further data if trial reports are unclear.

Adverse effects

We will not perform a separate search for adverse effects of interventions used for the treatment of hyperhidrosis. We will consider adverse effects described in the included studies only.

Errata and retractions

The Cochrane Skin Information Specialist will run a specific search to identify errata or retractions related to our included studies, and we will examine any relevant retraction statements and errata that are retrieved.

Data collection and analysis

We will use Covidence software for the screening and managing of references (Covidence).

Selection of studies

Two review authors (LD, AC) will independently screen the titles and abstracts of studies identified by the search using Covidence (Covidence). Next, they will review the full texts of the studies selected as potentially relevant against the selection criteria. Any disagreements will be discussed; if consensus cannot be reached, a third review author (LF) will be consulted.

Data extraction and management

Two review authors (LD, AC) will extract the study characteristics and results from the included studies. Both review authors will use a standardised data collection form, which will be piloted with assistance from JS (statistician) and revised if necessary.

The data collection form will include the following information.

- Population characteristics, e.g. setting/country, age, gender, ethnicity, severity of hyperhidrosis, and area of the body affected.
- Interventions and comparators, including dosages and frequency.
- Primary and secondary outcomes.
- Study design and blinding methods.
- Funding and conflicts of interest.

We will contact the trial authors to obtain any missing data or information or for clarification (e.g. of randomisation method) as necessary. Any disagreements will be discussed; if consensus cannot be reached, a third review author (JS) will be consulted. Review authors will not extract data from their own trials.

Assessment of risk of bias in included studies

Two review authors (LF, LD) will independently assess risk of bias using Cochrane's RoB 2 tool (Sterne 2019), which employs the following domains:

- randomisation process;
- deviations from the intended interventions;
- missing outcome data;
- measurement of the outcome;
- selective outcome reporting.

We will assess risk of bias of primary and secondary outcomes, as described in the summary of findings table, with a focus on the effect of the assignment to intervention (the 'intention-to-treat' (ITT) effect).

The review authors will answer a series of signalling questions that will inform judgement on the risk of bias in each domain for each outcome. The answers to the signalling questions will be made available in an online repository. Based on review author judgement and consideration of the RoB 2 Excel tool, which will be used to conduct the assessment (Sterne 2019), each domain will be assigned one of three levels: low risk of bias, some concerns, or high risk of bias. We will define overall bias for each outcome as follows.

- Low risk of bias: the outcome is judged to be at low risk of bias for all domains.
- Some concerns: the outcome is judged to raise some concerns in at least one domain, but is not at high risk of bias for any domain.
- High risk of bias: the outcome is judged to be at high risk of bias in at least one domain, or there are some concerns for multiple domains such that our confidence in the result is substantially lowered.

The overall risk of bias will be arrived at from the signalling questions for each domain (Sterne 2019). We will use the risk of bias judgements in our GRADE assessment (for the consideration

'study limitations'). See 'Summary of findings and assessment of the certainty of the evidence' section below.

We will assess risk of bias of cross-over and cluster trials using extensions to RoB 2 that are designed to address the additional considerations for these types of RCTs (Eldridge 2021; Higgins 2021a).

Any differences in opinion between the two review authors will be resolved through discussion; if an agreement cannot be reached, a third review author will be consulted (AC).

We will use RevMan Web to input the risk of bias results and to produce a risk of bias graph (RevMan Web 2020).

Measures of treatment effect

For continuous data, we will calculate unstandardised (weighted) mean differences (MD) plus associated 95% confidence intervals (CI), if all included studies used the same scale to measure a particular outcome. When pooling data from scoring schemes with continuous outcomes, we will use standardised mean differences (SMD) and associated 95% CI where different instruments or scales have been used to report outcomes.

For binary data, we will calculate risk ratios (RR) and associated 95% CI, and the number needed to treat for an additional harmful outcome (NNTH).

Unit of analysis issues

We will consider unit of analysis issues if any of the included studies are cluster trials, cross-over trials, or studies with multiple treatment groups.

We will account for clustering of data in cluster-randomised trials, and pooling with non-clustered parallel trials. Where raw data are available, we will use estimates derived from hierarchical (multilevel) modelling, with participants (level-1) clustered within units such as surgeries, etc. (level-2). This facilitates the assessment of the clustering effect in such trials using the variance partition coefficient. This statistic is the proportion of residual variance accounted for by variation between higher-level units. Otherwise we will attempt to estimate the intraclass correlation coefficient from similar studies and use this statistic in the method of Rao 1992 to calculate the design effect, which will be used to adjust the effective sample sizes. We will use the generic inverse variance method for analyses that include cluster trials.

We will re-calculate data from cross-over trials, if necessary, using appropriate methods for paired data, where these data are given.

Where studies include multiple treatment groups, we will combine groups to make a single pairwise comparison where possible and appropriate. Otherwise, we will follow one or more methods recommended by Cochrane (Higgins 2021): select one pair of interventions and exclude the others; split the shared group into two or more groups and include two or more comparisons; or include two or more correlated comparisons and allow for the correlation.

Dealing with missing data

We will attempt to contact the trial authors to request any missing information (e.g. about blinding or randomisation) or data (number of participants, means or standard deviations, etc.). Where necessary, we will impute summary statistics following the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). We will attempt to calculate missing data from other values given where necessary: for example, we may calculate missing standard deviation values from given CIs or standard errors.

We will extract data on an ITT basis, where those participants who leave the study early or who were lost to follow-up will be assumed to have the same rates of negative outcomes as those who completed the trial. For continuous data, we will consider firstly available-case analysis, that is including data only on those participants whose results are known. We will consider the potential impact of the missing data on the results in our interpretation of the results of the review. This will depend on the degree of 'missingness', the pooled estimate of the treatment effect, and the variability of the outcomes. Variation in the degree of missing data may also be considered as a potential source of heterogeneity. We will also consider ITT analysis using imputation, basing analyses on the total number of randomised participants, irrespective of how the original study authors analysed the data. This will involve imputing outcomes for the missing participants.

Assessment of heterogeneity

We will visually assess statistical heterogeneity by looking for any overlap of CIs on the forest plots, considering limited overlap as a possible indicator of heterogeneity. We will also assess evidence for heterogeneity using the Chi^2 test for heterogeneity and the I^2 statistic, employing the following threshold values provided in the *Cochrane Handbook* (Higgins 2021), acknowledging that the I^2 statistic depends on the magnitude and direction of effects and the strength of the evidence for heterogeneity, which will be determined via the Chi^2 test:

- 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.

In the case of outlier studies, we will conduct sensitivity analyses by removal of these studies and recalculation of results. We will only pool studies if they are clinically and methodologically similar.

We will also explore planned heterogeneity using subgroup and sensitivity analyses. If statistical heterogeneity cannot be explained, we will consider downgrading the evidence in our GRADE assessment.

Assessment of reporting biases

We will attempt to minimise reporting bias to the greatest degree possible by searching all possible sources to identify study reports and results, including those from unpublished trials (Higgins 2021).

If 10 or more studies are included in the meta-analysis, we will conduct a small-study effects analysis facilitated by construction of funnel plots, and will assess these using caution bearing in mind documented limitations in interpretation.

Data synthesis

We will only undertake a meta-analysis if the participants, interventions, comparisons, and outcomes are judged to be sufficiently similar to arrive at an answer that is clinically meaningful. Results will be pooled from trials using fixed-effect or random-effects models, considering issues of trial methodological and clinical heterogeneity, and reported diagrammatically using forest plots. However, we anticipate using random-effects analyses for all models, based on our expectation of the existence of clinical and methodological heterogeneity. Where issues of trial methodological and clinical heterogeneity appear to exist, we will also consider strategies including: not pooling data and conducting subgroup analyses or sensitivity analyses.

Where data cannot be pooled due to high heterogeneity, we will still provide descriptive analysis of trial results and report them in the text of the review.

Where meta-analyses are possible, for continuous outcomes, we will use the inverse variance method for fixed-effect models, and the DerSimonian and Laird variant of the inverse variance methods for random-effects models. For dichotomous outcomes, we will use the Mantel-Haenszel method for fixed-effect models, and the DerSimonian and Laird method for random-effects models. A 0.5 zero-cell correction will be applied in the event of zero frequencies.

For studies with multiple treatment groups, we will aim to combine treatment groups to facilitate a single pairwise comparison following methods recommended by Cochrane (Higgins 2021).

Where results from dichotomous outcomes are estimated for individual studies with low numbers of events (< 10 in total), or where the total sample size is less than 30 participants and a risk ratio is used, we will report the proportion of events in each group together with a P value from a Fisher's exact test.

We will use Stata statistical software or RevMan Web for all meta-analyses (RevMan Web 2020; Stata 2017). We will copy results, tables, and figures generated by Stata manually into RevMan Web.

Where we are unable to perform a meta-analysis, we will follow the Synthesis Without Meta-analysis (SWiM) reporting guideline to provide a narrative synthesis as recommended by Cochrane (Higgins 2021).

Subgroup analysis and investigation of heterogeneity

We will compare subgroups according to area of the body affected and to disease severity, subject to available data in the subgroups of interest. We will conduct within-groups testing (reporting estimate, 95% CIs, Z-test or Chi^2 test and corresponding P value) and between-groups testing (reporting Z-test or Chi^2 test and corresponding P value) in all cases.

Sensitivity analysis

If there are sufficient trials for any one intervention, we will perform sensitivity analyses to look at aspects such as excluding trials with high risk of bias or some concerns and trials where data have been imputed and calculated differently (e.g. extracted from a figure). We will analyse trials above and below an agreed cut-off point and see if the results are changed by excluding the lower-quality trials. Results will be plotted on influence plots. Any individual study suspected of excessive influence will be identified by the point estimate of

- its 'omitted' analysis lying outside the confidence interval of the 'combined' analysis; or
- its 'omitted' meta-analytic estimate differing in significance relative to the 'combined' analysis.

Summary of findings and assessment of the certainty of the evidence

We will create summary of findings tables for our main comparisons, which have been chosen following consultation with clinicians and patients.

- Oxybutynin versus placebo/no treatment.
- Botulinum toxin versus placebo/no treatment.
- Iontophoresis versus placebo/no treatment.
- Oxybutynin versus botulinum toxin.
- Oxybutynin versus iontophoresis.
- Botulinum toxin versus iontophoresis.
- Topical glycopyrrolate versus placebo/no treatment.

Each summary of findings table will include our primary and secondary outcomes, as follows.

- Patient-reported symptom improvement, assessed using the Hyperhidrosis Disease Severity Scale (HDSS), Likert scales, patient global assessment, or other patient-reported visual analogue scale.
- Withdrawal from treatment due to adverse effects.
- Quality of life assessed using hyperhidrosis-specific tools such as the Hyperhidrosis Quality of Life Index (HidroQoL), Hyperhidrosis Quality of Life Questionnaire (HQLQ), and Hyperhidrosis Impact Questionnaire (HHIQ) or non-disease-specific quality of life tools, such as the Dermatology Life Quality Index (DLQI) and 36-item Short Form Health Survey (SF-36).
- Major and minor events including dry mouth or compensatory sweating.

We will use the GRADE approach to determine the certainty of the evidence and magnitude of effects (Schünemann 2013). The GRADE approach takes into account the following considerations:

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

Two review authors (LD, AC) will perform the GRADE assessments. Any disagreements will be discussed; if consensus cannot be reached, a third review author (LF) will be consulted.

We will use GRADEpro GDT software to create the summary of findings tables and to conduct the GRADE assessments (GRADEpro GDT).

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APPENDICES

Appendix 1. Glossary

Acetylcholine: a chemical released by nerve cells to send messages to other cells

Anticholinergics: drugs that block the action of acetylcholine

Astringent: a chemical that causes the contraction of skin cells and other body tissues

Axillary: of the armpit

Brachial plexus damage: damage to the network of nerves that sends signals from your spinal cord to your shoulder, arm, and hand

Bradycardia: a slower-than-normal heart rate

Bridle formation: a band of fibrous material stretching across the surface of an ulcer or other lesion

Craniofacial: of the skull and face

Dermal-subcutaneous junction: the boundary between the dermis layer of the skin and the fat layer beneath

Eccrine sweat ducts: a tube that carries an odourless watery fluid (sweat) onto the surface of the skin

Focal hyperhidrosis: hyperhidrosis that is limited to certain areas of the body

Generalised hyperhidrosis: hyperhidrosis that affects the entire body

Gravimetry: a test used to assess the amount of sweat produced in a given period of time

Haematoma: an abnormal collection of blood outside of a blood vessel, for example after an injury

Haemothorax: accumulation of blood in the fluid-filled space around the lungs

Horner's syndrome: a combination of symptoms caused by the disruption of a nerve pathway from the brain to the face and eye on one side of the body

Hyperhidrosis: excessive sweating

Idiopathic: of unknown cause

Intradermal: between the layers of the skin

Ionised substance: a substance that is electrically charged

Iontophoresis: a treatment that uses a machine to pass a low-voltage electrical current through the skin of the hands or feet, which are immersed in shallow trays of water

Keratinolytic: breaks down keratin, a protein found in skin and hair

Maceration: the softening and breaking down of skin resulting from prolonged exposure to moisture

Muscarinic receptors: proteins in the brain that respond to the binding of acetylcholine

Myasthenia gravis: a rare, long-term condition that causes muscle weakness

Palmo-plantar: of the hands and feet

Paraesthesia: a feeling of abnormal sensation, such as pins and needles or tingling

Paralytic ileus: a condition where the motor activity of the bowel is impaired

Pneumothorax: a collapsed lung

Precipitates: solids separated out of a solution

Pruritus: itchy skin

Pyloric stenosis: a condition that blocks food from entering the small intestine

Seroma: a build-up of clear bodily fluids in a place on the body where tissue has been removed by surgery

Stratum corneum: the outer layer of the skin

Sweat mucopolysaccharides: long chains of sugar molecules found in sweat

Systemic treatments: treatments that work throughout the whole body

Tachycardia: a faster-than-normal heart rate

Thermolysis: chemical breakdown caused by heat

Uptitrated: starting therapy at a lower dose and increasing the dose over time

Urticarial: raised itchy rash

Vehicle: an inactive substance that is combined with an active medication to facilitate administration

Vesiculation: the formation of small, fluid-filled sacs on the skin

Appendix 2. Draft search strategy for MEDLINE (Ovid)

Ovid MEDLINE(R) ALL <1946 to November 03, 2021>

1 hyperhidrosis/ 3225
2 hyperhidros$.ti,ab. 3535
3 hyperhydros$.ti,ab. 195
4 hyperidros$.ti,ab. 27
5 hyperperspir$.ti,ab. 9
6 or/1-5 4540
7 perspir$.ti,ab. 1261
8 sweat$.ti,ab. 24472
9 Sweating/ 7013
10 7 or 8 or 9 28223
11 (idiopath$ or unknown).ti,ab. 656761

12 excess$.ti,ab. 323943
13 or/11-12 969392
14 10 and 13 2318
15 randomized controlled trial.pt. 549520
16 controlled clinical trial.pt. 94520
17 randomized.ab. 539284
18 placebo.ab. 222824
19 clinical trials as topic.sh. 197996
20 randomly.ab. 369139
21 trial.ti. 250476
22 15 or 16 or 17 or 18 or 19 or 20 or 21 1404747
23 exp animals/ not humans.sh. 4909955
24 22 not 23 1292558
25 6 or 14 6357
26 24 and 25 504

[Lines 15-24: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format, from section 3.6.1 in Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Technical Supplement to Chapter 4: Searching for and selecting studies. In: Higgins JPT, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, Welch VA (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 6. Cochrane, 2019. Available from: www.training.cochrane.org/handbook]

CONTRIBUTIONS OF AUTHORS

LD was the contact person with the editorial base.
LD co-ordinated contributions from the co-authors and wrote the final draft of the protocol.
LD, JS, AC, and LF worked on the Methods section.
LM, STC, RB, and KR drafted the clinical sections of the Background and responded to the clinical comments of the referees.
LD, AC, JS, and LF responded to the methodology and statistics comments of the referees.
All authors contributed to writing of the protocol.
LH was the consumer co-author and checked the protocol for readability and clarity. S/he also ensured that the outcomes are relevant to consumers.
LD is the guarantor of the final review.

Disclaimer

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DECLARATIONS OF INTEREST

Louise Dunford: declared that they have no conflict of interest.

Andrew V Clifton: declared that they have no conflict of interest.

John Stephenson: declared that they have no conflict of interest.

Kathy Radley: declared that they have no conflict of interest.

Louise McDonald: reports sponsorship for attendance at the virtual Annual British Association of Dermatology Meeting 2020 and 2021 from Novartis Pharmaceuticals (registration fee); and support for attendance at the virtual European Academy of Dermatology and Venereology conference in October 2020 from Novartis (registration fee); funding to attend the 'Skin Academy' teaching conference in Barcelona as a trainee in dermatology (2018 and 2019, travel and accommodation) from Almirall; personal payments.

Laurice Fretwell: declared that they have no conflict of interest.

Seau Tak Cheung: reports income from private practice from private hospitals for their work as a Consultant Dermatologist (the number of private patients with hyperhidrosis treated overall is small – less than 2%); personal payment.

Lynne Hague: declared that they have no conflict of interest.

Robert J Boyle: declared that they have no conflict of interest.

Clinical reviewer David M Pariser: reports having been an investigator, consultant, or both for several companies that are developing products not yet on the market and for others that have marketed products for the treatment of hyperhidrosis (and many other dermatologic conditions). He is not aware of any marketed product for the treatment of hyperhidrosis in the USA for which he has been either an investigator or consultant. There are studies that may be included in the review to which he has contributed or of which he is an author.

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