

Medical Policy



Title: Treatment of Hyperhidrosis

Related Policies:	▪ <i>Botulinum Toxin (BT)</i>
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Professional / Institutional
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Populations	Interventions	Comparators	Outcomes
Individuals: • With primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial)	Interventions of interest are: • Iontophoresis	Comparators of interest are: • Oral and topical medications • Botulinum toxin • Microwave treatment • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary axillary hyperhidrosis	Interventions of interest are: • Botulinum toxin type A or B	Comparators of interest are: • Oral and topical medications • Microwave treatment • Iontophoresis • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With primary palmar hyperhidrosis	Interventions of interest are: • Botulinum toxin type A	Comparators of interest are: • Oral and topical medications • Iontophoresis • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary palmar hyperhidrosis	Interventions of interest are: • Botulinum toxin type B	Comparators of interest are: • Oral and topical medications • Iontophoresis • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary plantar hyperhidrosis	Interventions of interest are: • Botulinum toxin type A or B	Comparators of interest are: • Oral and topical medications • Iontophoresis	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial)	Interventions of interest are: • Microwave treatment	Comparators of interest are: • Oral and topical medications • Botulinum toxin • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial)	Interventions of interest are: • Radiofrequency ablation	Comparators of interest are: • Oral and topical medications • Botulinum toxin • Microwave treatment • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary axillary hyperhidrosis	Interventions of interest are: • Surgical excision of axillary sweat glands	Comparators of interest are: • Oral and topical medications • Botulinum toxin	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary axillary and palmar hyperhidrosis	Interventions of interest are: • Endoscopic transthoracic sympathectomy	Comparators of interest are: • Oral and topical medications • Botulinum toxin • Microwave treatment • Iontophoresis • Surgical procedures	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals: • With primary plantar hyperhidrosis	Interventions of interest are: • Lumbar sympathectomy	Comparators of interest are: • Oral and topical medications • Botulinum toxin • Iontophoresis	Relevant outcomes include: • Symptoms • Quality of life • Treatment-related morbidity
Individuals:	Interventions of interest are:	Comparators of interest are:	Relevant outcomes include: • Symptoms

Populations	Interventions	Comparators	Outcomes
<ul style="list-style-type: none"> • With severe secondary gustatory hyperhidrosis 	<ul style="list-style-type: none"> • Iontophoresis • Botulinum toxin 	<ul style="list-style-type: none"> • Diet • Topical medications 	<ul style="list-style-type: none"> • Quality of life • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With severe secondary gustatory hyperhidrosis 	Interventions of interest are: <ul style="list-style-type: none"> • Tympanic neurectomy 	Comparators of interest are: <ul style="list-style-type: none"> • Diet • Topical medications 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Quality of life • Treatment-related morbidity

DESCRIPTION

Hyperhidrosis, or excessive sweating, can lead to impairments in psychologic and social functioning. Various treatments for hyperhidrosis are available, such as topical antiperspirant agents (eg, aluminum chloride 20% solution), oral medications, botulinum toxin, and surgical procedures.

OBJECTIVE

The objective of this evidence review is to determine whether the use of iontophoresis, botulinum toxin, microwave therapy, radiofrequency ablation, or surgical procedures improve the net health outcome for individuals who have any primary focal or secondary gustatory hyperhidrosis.

BACKGROUND

Hyperhidrosis

Hyperhidrosis has been defined as excessive sweating, beyond a level required to maintain normal body temperature, in response to heat exposure or exercise. It can be classified as primary or secondary. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), feet (plantar), or axillae (underarms). Secondary hyperhidrosis can result from a variety of drugs (eg, tricyclic antidepressants, selective serotonin reuptake inhibitors) or underlying diseases/conditions (eg, febrile diseases, diabetes, menopause). Secondary hyperhidrosis is usually generalized or craniofacial sweating.

Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. This trigeminovascular reflex typically occurs symmetrically on the scalp or face and predominately over the forehead, lips, and nose. Secondary facial gustatory hyperhidrosis occurs independently of the nature of the ingested food. This phenomenon frequently occurs after injury or surgery in the region of the parotid gland. Frey syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve. After the injury, these fibers regenerate, and miscommunication occurs between them and the severed postganglionic sympathetic fibers that supply the cutaneous sweat glands and blood vessels. The aberrant connection results in gustatory sweating and facial flushing with mastication. Aberrant secondary gustatory sweating follows up to 73% of surgical sympathectomies and is particularly common after bilateral procedures.

The consequences of hyperhidrosis are primarily psychosocial. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat

production can be assessed with the Minor starch-iodine test, which is a simple qualitative measure to identify specific sites of involvement.

Treatment

A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride, topical anticholinergic medications, oral anticholinergic medications, iontophoresis, intradermal injections of botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands. Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment for menopausal symptoms.

Iontophoresis uses electrical current to deliver medication transdermally. A charged ionic drug is placed on the skin with an electrode of the same charge, which drives the drug into the skin, with the purpose of achieving better penetration of the drug into underlying tissue. The benefits of this method would be an enhancement of treatment effects and a reduction in adverse events associated with systemic administration of the drug.

Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals, which prevents hyperstimulation of eccrine sweat glands that lead to excessive sweating. Therefore, intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and focal primary hyperhidrosis, most frequently involving the axillae or palms. The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches.

Surgical treatment options include removal of the eccrine glands and/or interruption of the sympathetic nerves. Eccrine sweat glands produce an aqueous secretion, the overproduction of which is primarily responsible for hyperhidrosis. These glands are innervated by the sympathetic nervous system. Surgical removal has been performed in patients with severe isolated axillary hyperhidrosis.

Various surgical techniques of sympathectomy have been tested. The second (T2) and third (T3) thoracic ganglia are responsible for palmar hyperhidrosis, the fourth (T4) thoracic ganglion controls axillary hyperhidrosis, and the first (T1) thoracic ganglion controls craniofacial hyperhidrosis. Thoracic sympathectomy has been investigated as a potentially curative procedure, primarily for combined palmar and axillary hyperhidrosis unresponsive to nonsurgical treatments. While accepted as an effective treatment, sympathectomy is not without complications. In addition to the immediate surgical complications of pneumothorax or temporary Horner syndrome, compensatory sweating on the trunk generally occurs in most patients, with different degrees of severity. Medical researchers have investigated whether certain approaches (eg, T3 sympathectomy vs. T4 sympathectomy) result in less compensatory sweating, but there remains a lack of consensus about which approach best minimizes the risk of this adverse event. Also, with lumbar sympathectomy for plantar hyperhidrosis, there has been concern about the risk of postoperative sexual dysfunction in both men and women.

Outcome Measures

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific

surveys. Of these, the Hyperhidrosis Disease Severity Scale (Appendix Table 1) has had a good correlation to other assessment tools and is practical in the clinical setting.

REGULATORY STATUS

In 2004, botulinum toxin type A (Botox®; Allergan Pharmaceuticals Ireland) was approved by the Food and Drug Administration (FDA) through the biologic license application process for use to treat primary axillary hyperhidrosis (severe underarm sweating) that cannot be managed by topical agents. In 2009, this product was renamed onabotulinumtoxinA. Other botulinum toxin products approved by FDA for non-cosmetic indications, but not specifically approved for treatment of hyperhidrosis, include:

2000: RimabotulinumtoxinB (Myobloc®; Solstice Neurosciences)

2009: AbobotulinumtoxinA (Dysport®; Medicis Pharmaceutical)

2010: IncobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals)

2022: DaxibotulinumtoxinA (Daxxify®; Revance Therapeutics).

In 2009, the FDA approved the following revisions to the prescribing information of botulinum toxin products:

- "A *Boxed Warning* highlighting the possibility of experiencing potentially life-threatening distant spread of toxin effect from injection site after local injection.
- A Risk Evaluation and Mitigation Strategy (REMS) that includes a *Medication Guide* to help patients understand the risk and benefits of botulinum toxin products.
- Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from 1 product to another botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products."

The REMS requirement, provision of the medication guide, has since been removed and there are no current REMS requirements for botulinum toxin products.¹

In 2011, the miraDry® System (Miramar Labs) was cleared for marketing by FDA through the 510(k) process for treating primary axillary hyperhidrosis. This microwave device is designed to heat tissue at the dermal-hypodermal interface, the location of the sweat glands. Treatment consists of 2 sessions for a total duration of approximately 1 hour. Sessions occur in a physician's office, and a local anesthetic is used. The device is currently not approved for the treatment of palmar or plantar hyperhidrosis.

In 2023, the Brella® Sweat Control Patch (Candesant Biomedical, Inc.) was approved by the FDA through the 513(f)(2) de novo pathway for the treatment of primary axillary hyperhidrosis in adults. The patch is applied by a clinician and kept in place for up to 3 minutes, during which the patch's sodium layer creates heat after coming into contact with sweat, which leads to temporary inactivation of sweat glands.

POLICY**A. Primary Focal Hyperhidrosis**

1. Treatment of primary focal hyperhidrosis using the following therapies (see Table P1) may be considered **medically necessary** with any of the following medical complications:
 - a. acrocyanosis of the hands
OR
 - b. history of recurrent skin maceration with bacterial or fungal infections
OR
 - c. history of recurrent secondary infections
OR
 - d. history of persistent eczematous dermatitis despite medical treatments with topical dermatologic or systemic anticholinergic agents

Table P1 Treatments Considered Medically Necessary

Focal Regions	Treatments Considered Medically Necessary
Axillary	<ul style="list-style-type: none"> ▪ Aluminum chloride 20% solution ▪ Botulinum toxin for severe primary axillary hyperhidrosis inadequately managed with topical agents, in individuals ≥ 18 years ▪ Endoscopic Transthoracic Sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (ie, aluminum chloride or botulinum toxin, individually and in combination) has failed
Palmar	<ul style="list-style-type: none"> ▪ Aluminum chloride 20% solution* ▪ Botulinum toxin A products for severe primary palmar hyperhidrosis inadequately managed with topical agents, in individuals ≥ 18 years ▪ ETS, if conservative treatment (ie, aluminum chloride or botulinum toxin type A, individually and in combination) has failed
Plantar	<ul style="list-style-type: none"> ▪ Aluminum chloride 20% solution
Craniofacial	<ul style="list-style-type: none"> ▪ Aluminum chloride 20% solution ▪ ETS, if conservative treatment (ie, aluminum chloride) has failed

Aluminum chloride solution is approved by FDA for treatment of primary hyperhidrosis. At least 1 botulinum toxin product is FDA-approved for treatment in adults of severe axillary hyperhidrosis inadequately managed by topical agents.

ETS: endoscopic transthoracic sympathectomy; FDA: Food and Drug Administration.

2. Treatment of primary focal hyperhidrosis using the following therapies (see Table P2) are considered **experimental / investigational**:

Table P2 Treatments Considered Experimental / Investigational

Focal Regions	Treatments Considered Experimental / Investigational
Axillary	<ul style="list-style-type: none"> ▪ Axillary liposuction ▪ Iontophoresis ▪ Microwave treatment ▪ Radiofrequency ablation
Palmar	<ul style="list-style-type: none"> ▪ RimabotulinumtoxinB ▪ Iontophoresis ▪ Microwave treatment ▪ Radiofrequency ablation
Plantar	<ul style="list-style-type: none"> ▪ Botulinum toxin

Focal Regions	Treatments Considered Experimental / Investigational
	<ul style="list-style-type: none"> ▪ Iontophoresis ▪ Lumbar sympathectomy ▪ Microwave treatment ▪ Radiofrequency ablation
Craniofacial	<ul style="list-style-type: none"> ▪ Botulinum toxin ▪ Iontophoresis ▪ Microwave treatment ▪ Radiofrequency ablation

B. Secondary Hyperhidrosis

Secondary Gustatory Hyperhidrosis

1. The following treatments may be considered **medically necessary** for the treatment of severe secondary gustatory hyperhidrosis. (A list of gustatory hyperhidrosis conditions are: Frey syndrome, encephalitis, syringomyelia, diabetic neuropathies, herpes zoster parotitis, parotid abscess)
 - a. aluminum chloride 20% solution
 - b. surgical options (ie, tympanic neurectomy), if conservative treatment has failed.
2. Other treatments are considered **experimental / investigational** as a treatment for severe secondary gustatory hyperhidrosis including, but not limited to:
 - A. botulinum toxin
 - B. iontophoresis

- C. Treatment of hyperhidrosis is considered **not medically necessary** in the absence of functional impairment or medical complications.

POLICY GUIDELINES

- A. Absent evidence to the contrary, botulinum toxin products are considered to have a class effect.
- B. A multispecialty working group has defined primary focal hyperhidrosis as a condition characterized by visible, excessive sweating of at least 6 months in duration without apparent cause and with at least 2 of the following features:
 1. bilateral and relatively symmetric sweating
 2. impairment of daily activities
 3. frequency of at least once per week
 4. age at onset younger than 25 years
 5. positive family history, and
 6. cessation of focal sweating during sleep

- C. The Hyperhidrosis Disease Severity Scale (HDSS) is used by individuals to rate the severity of their symptoms on a scale of 1 to 4 (see Table PG1):

Table PG1. The Hyperhidrosis Disease Severity Scale

Score	Definition
1	My underarm sweating is never noticeable and never interferes with my daily activities
2	My underarm sweating is tolerable but sometimes interferes with my daily activities
3	My underarm sweating is barely tolerable and frequently interferes with my daily activities
4	My underarm sweating is intolerable and always interferes with my daily activities

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through May 1, 2025.

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

IONTOPHORESIS FOR PRIMARY FOCAL HYPERHIDROSIS (IE, AXILLARY, PALMAR, PLANTAR, CRANIOFACIAL)

Clinical Context and Therapy Purpose

The purpose of iontophoresis of sweat glands in individuals who have primary focal hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary focal hyperhidrosis. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), feet (plantar), or axillae (underarms). Topical antiperspirant treatment is typically tried first.

Interventions

The therapy being considered is iontophoresis of sweat glands.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, intradermal injections of botulinum toxin, microwave treatment, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the Hyperhidrosis Disease Severity Scale (HDSS, see Appendix Table 1) has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Systematic Reviews**

Wade et al (2017) published a comprehensive systematic review and meta-analysis, sponsored by the National Institute for Health Research, evaluating the following therapies for hyperhidrosis: iontophoresis, topical botulinum and botulinum injections, anticholinergic medications, curettage, and energy-based technologies that damage sweat glands (laser, microwave).² Because endoscopic thoracic sympathectomy is accepted as a last-line treatment, it was not evaluated. The literature search, conducted through July 2016, identified 50 studies for inclusion: 32 RCTs, 17 nonrandomized comparative studies, and a large prospective case series. Study quality was assessed using the Cochrane risk of bias tool. Reviewers concluded that the evidence for the clinical effectiveness and safety of second-line treatment for primary hyperhidrosis was limited due to a large number of studies with a high risk of bias, mostly due to

poorly reported methods. Assessments from this review for botulinum injections and microwave treatment appear in their respective sections below.

The Wade et al (2017) systematic review identified 10 studies using iontophoresis: 4 RCTs, 5 nonrandomized comparative studies, and a case series.² All studies were rated as having a high or unclear risk of bias. Comparators differed across studies: placebo (3 studies), botulinum (2 studies), no treatment (2 studies), and iontophoresis plus anticholinergic therapy (2 studies). Sample sizes ranged from 10 to 112, with the case series having the sample size of 112. Most studies treated hands, with some studies treating hands and feet. A meta-analysis could not be conducted due to the heterogeneity across studies. Reviewers concluded that the evidence was low quality but consistent, showing a potential benefit of iontophoresis compared with no treatment or placebo; however, when compared with botulinum injections, iontophoresis appeared less effective and had a short duration of effect.

Randomized Controlled Trials

A RCT by Rajagopal et al (2014) compared iontophoresis plus topical aluminum chloride hexahydrate with botulinum toxin injection but did not provide data on the efficacy of this therapy compared with placebo.³ The trial included 60 patients with a baseline HDSS score of 3 or 4.⁴ Patients were randomized to treatment with iontophoresis 3 times weekly or to 1 botulinum toxin injection in each hand, with 2 weeks between treatments. HDSS scores were recorded at 4 weeks; nonresponders were permitted to crossover to the other treatment arm. At the end of the initial 4 weeks, improvement (defined as a decrease of at least 1 point in HDSS score) was identified in 24 (80%) of 30 patients in the botulinum toxin group and 14 (47%) of 30 patients in the iontophoresis group ($p=.007$). Sixteen patients in the iontophoresis arm crossed over to the botulinum toxin arm, with 12 showing excellent improvement after an additional 4 weeks. In contrast, only 1 of the 6 patients who crossed over to the iontophoresis arm showed improvement after a second 4-week treatment period. In this relatively small sample with a relatively short intervention period, iontophoresis was less effective than botulinum toxin.

Case Series

Among the case series is a retrospective study, Dogruk Kacar et al (2014) from Turkey, which included 21 pediatric patients under age 18 years.⁵ Most patients ($n=16$) had palmoplantar hyperhidrosis. Nineteen patients completed the course of 21 tap water iontophoresis sessions. Among study completers, the mean self-report treatment effectiveness score, rated on a 0-to-10 visual analog scale, was 6.36 at the end of treatment. Seventeen (89.5%) of 19 patients reported a 50% or more decrease in sweating at the end of treatment. Another representative series is the McAleer and Collins (2014) study from Ireland, which included 28 patients.⁶ Patients received a minimum of 9 treatments over 21 days in a clinical setting. Twenty (80%) of the 25 patients for whom data were available after hospital administration of tap water iontophoresis reported a moderate or great amount of improvement in symptoms and a moderate or great improvement in quality of life.

Section Summary: Iontophoresis for Primary Focal Hyperhidrosis

There is insufficient evidence that iontophoresis is an effective treatment of primary focal hyperhidrosis. A systematic review of 10 studies suggested a potential benefit of iontophoresis; however, the studies had either low or unclear risk of bias. The single RCT among the 10 studies found iontophoresis less effective than botulinum toxin in the short-term treatment of palmar

hyperhidrosis. Randomized controlled trials are needed to show that iontophoresis is more effective than placebo treatment or at least as effective as alternative therapies.

PRIMARY AXILLARY HYPERHIDROSIS TREATED WITH BOTULINUM TOXIN TYPE A OR B

Clinical Context and Therapy Purpose

The purpose of intradermal injections of botulinum toxin type A or B into axillary sweat glands in individuals who have primary axillary hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary axillary hyperhidrosis. Primary axillary hyperhidrosis is idiopathic and involves the axillae (underarms).

Interventions

The therapy being considered is intradermal injections of botulinum toxin type A or B into axillary sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, iontophoresis, microwave treatment, and surgical excision of axillary sweat glands.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

The previously discussed Wade et al (2017) systematic review identified 23 studies evaluating botulinum injections for the treatment of primary hyperhidrosis; 13 were RCTs, and 10 were nonrandomized comparative studies.² Fourteen studies were considered high risk of bias, 8 studies unclear risk, and 1 study low risk. Twenty-one studies used botulinum type A (usually 50 units, though some studies used up to 250 units) and 2 studies used botulinum type B (2500 units or 5000 units). Comparators differed across studies: placebo (12 studies), no treatment (4 studies), curettage (4 studies), iontophoresis (2 studies), and topical glycopyrrolate (1 study). Sixteen studies treated axillary hyperhidrosis, 5 palmar hyperhidrosis, and 2 studies reported on treating axillary and/or palmar hyperhidrosis. Meta-analyses were conducted on studies comparing botulinum type A or B with placebo for the treatment of axillary hyperhidrosis (9 studies) and all estimates favored the botulinum injections: reduction in HDSS score of 2 or more points: relative risk, 3.3 (95% confidence interval [CI], 2.5 to 4.4); reduction in sweating by 50% or more at 2 to 4 weeks (relative risk, 3.3; 95% CI, 1.9 to 5.5); reduction in sweating by 75% or more at 2 to 4 weeks (relative risk, 6.7; 95% CI, 2.8 to 16.0); and reduction in sweating by 50% or more at 16 weeks (relative risk, 2.9; 95% CI, 1.9 to 4.3). The studies comparing botulinum injections with curettage (4 studies) were of very low quality, precluding meaningful conclusions. There is low-quality evidence for botulinum type A and B for treating palmar hyperhidrosis suggesting a positive effect (7 studies); however, there was a high incidence of adverse events reported with botulinum type B.

Obed et al (2021) conducted a systematic review and meta-analysis assessing botulinum injections for the treatment of focal hyperhidrosis in adults.⁷ The review incorporated only placebo-controlled RCTs, as opposed to any comparator in the Wade et al (2017) systematic review. Eight trials (N=937) were identified, 6 evaluated axillary hyperhidrosis, 1 evaluated craniofacial hyperhidrosis, and 1 evaluated lower limb hyperhidrosis. Six studies used botulinum type A (most often onabotulinumtoxinA 50 units) and 2 studies used botulinum type B (rimabotulinumtoxinB 2250 units or 2500 units). The quality of the included studies was mixed, with only 5 of the studies at low risk of bias for attrition. Further, only 5 studies included enough information to assess blinding of personnel and patients, and the majority of trials had an unclear risk of selection and reporting bias. Reduction in sweating by 50% or more from baseline to weeks 2 to 6 was more likely with botulinum injections as compared to placebo for axillary hyperhidrosis (risk difference, 0.62; 95% CI, 0.51 to 0.76). Improvements in reducing HDSS score by at least 2 points (risk difference, 0.56; 95% CI, 0.42 to 0.69) and mean change in the Dermatology Life Quality Index (mean difference, -5.55; 95% CI, -7.11 to -3.98) also favored botulinum injections over placebo. The analysis was limited by the availability of predominately short-term (8 weeks) trials.

Randomized Controlled Trials

Systematic reviews assessing the efficacy of botulinum toxin have pooled together results from a heterogeneous group of studies with different botulinum toxins used. The vast majority of the available RCTs in the systematic reviews evaluated botulinum toxin type A; the largest, long-term US-based trial assessing botulinum toxin A was published by Lowe et al (2007), which is summarized below. Only 1 trial, Baumann et al (2005), in the systematic reviews evaluated botulinum toxin type B in axillary hyperhidrosis. Additionally, RCTs that compared different botulinum toxin regimens are summarized below, as the systematic reviews focused on comparisons against placebo.

Botulinum Toxin versus Placebo

The largest RCT conducted in the US that evaluated botulinum toxin type A was published by Lowe et al (2007).⁸ This industry-sponsored, multicenter, double-blind, placebo-controlled trial evaluated the efficacy and safety study of botulinum toxin type A (onabotulinumtoxinA) in patients with persistent bilateral primary axillary hyperhidrosis. Enrollment criteria included a resting sweat production of at least 50 mg per axilla in 5 minutes and an HDSS score of 3 or 4. A total of 322 patients were randomized to onabotulinumtoxinA 50 units or 75 units or placebo. Retreatment after 4 weeks was allowed in patients with at least 50 mg of sweat (per axilla) over 5 minutes and an HDSS score of 3 or 4. Following the first injection, 75% of patients in the botulinum toxin type A groups showed at least a 2-point improvement in HDSS score, compared with 25% of patients in the placebo group. Sweat production decreased by 87% (75 units), 82% (50 units), and 33% (placebo). Similar results were obtained in patients requiring a second treatment. The median duration of effect was 197 (75 units), 205 (50 units), and 96 (placebo) days. Seventy-eight percent (n=252) of patients completed the 52-week trial: 96 (87%) of 110 in the 75- unit group, 83 (80%) of 104 in the 50- unit group, and 73 (68%) of 108 in the control group. An intention-to-treat analysis at 52 weeks showed more than 2-point improvement on HDSS score in 54 (49%) patients in the 75- unit group, 57 (55%) in the 50- unit group, and 6 (6%) in the placebo group. Injection-site pain was reported in approximately 10% of all groups, with a mean pain duration of 2.4 days (10-day maximum).

Baumann et al (2005) reported on a placebo-controlled randomized trial evaluating the use of botulinum toxin type B for axillary hyperhidrosis.⁹ Like another Baumann trial (reported below), this RCT did not address whether patients had failed previous treatments. The axillary hyperhidrosis trial included 20 patients who received subcutaneous injections of rimabotulinumtoxinB 2500 units or 0.5 mL per axilla (n=15) or placebo (n=5). Patients who received placebo were offered botulinum toxin type B at subsequent injections. Data were available on efficacy for 18 patients (15 in the initial botulinum toxin B group and 3 crossovers). There was a statistically significant reduction in axillary hyperhidrosis from baseline (before receiving an active injection) to day 30, according to the patient and physician assessment. Details on efficacy outcomes were not reported. The mean length of time to return to baseline sweating levels in the 18 patients was 151 days (range, 66 to 243 days). Sixteen patients reported 61 adverse events during the study. Five (8%) of 61 adverse events were determined to be trial-related (4 axillary bruising events, 1 instance of injection-site pain). Eleven (18%) adverse events were determined to be probably related to the trial (dry eyes [n=3], dry mouth [n=5], indigestion [n=3]). Flu-like symptoms were reported by 6 (30%) of 20 patients; however, the trial period coincided with flu season.

Comparison of Types of Botulinum Toxin Type A

Dressler (2010) reported on an RCT that assessed 46 patients with bilateral axillary hyperhidrosis and a previously stable onabotulinumtoxinA treatment for at least 2 years.¹⁰ Patients received onabotulinumtoxinA 50 units in randomly selected axilla and incobotulinumtoxinA 50 mouse units in the other axilla. All patients completed the trial. According to patient self-report in structured interviews, there were no between-group differences in therapeutic effect, including onset latency, extent, and duration, and no differences in injection-site pain. Moreover, clinical examination did not identify any differences between the 2 sides in the diffuse sweating pattern.

A small, double-blind RCT, published by Talarico-Filho et al (2007), included 20 patients with primary axillary hyperhidrosis who had sweat production greater than 50 mg/min.¹¹ Patients

received injections of 2 types of botulinum toxin A: onabotulinumtoxinA 50 units in 1 axilla and abobotulinumtoxinA 150 units in the other. Outcomes did not differ significantly between groups (eg, sweat rate was reduced by a mean of 98% in the onabotulinumtoxinA group and 99% in the abobotulinumtoxinA group; $p>.05$).

Comparison of Botulinum Toxin Type A With Type B

A few RCTs have compared botulinum toxin types A with B in patients who had primary axillary hyperhidrosis. Frasson et al (2011) conducted a small randomized trial of axillary hyperhidrosis treated with botulinum toxin type A and type B.¹² This trial included 10 patients with idiopathic focal axillary hyperhidrosis unresponsive to other nonsurgical treatments. Patients received onabotulinumtoxinA 50 units in 1 axilla and rimabotulinumtoxinB 2500 units in the contralateral axilla. Gravimetry was performed at baseline and follow-up as an objective measure of sweat production. At each follow-up point, the decrease in sweat weight from baseline was significantly greater on the type B side than on the type A side. For example, after 1 month, the sweat weight in 5 minutes was 13% of the baseline value on the type A side and 4% of the baseline value on the type B side ($p=.049$). By 6 months, the sweat weight returned to 91% of baseline on the type A side and to 56% of baseline weight on the type B side ($p=.02$). Findings were similar for the sweating area. All patients tolerated injections of types A and B well, and none reported systemic adverse events. This trial did use a higher dosage of botulinum toxin type B than previous studies.

An RCT by An et al (2015) randomized 24 patients with symmetrical axillary hyperhidrosis to injections of onabotulinumtoxinA 50 units in 1 axilla and rimabotulinumtoxinB 1500 units in the other (ie, a conversion rate of 1:30 was used).¹³ Baseline HDSS scores were 2 ($n=9$), 3 ($n=14$), and 4 ($n=1$); those who scored 3 or 4 were categorized as having severe axillary hyperhidrosis. The primary efficacy outcome (the proportion of patients with an HDSS score of 1 or 2 at the 2-week follow-up) was 100% in each group ($p=1.00$). At 12 weeks, all patients maintained a score of 1 or 2 on the HDSS ($p=1.00$), and at 20 weeks, 80% in each group had an HDSS score of 1 or 2 ($p=1.00$). A decrease of 2 or more points from baseline on the HDSS was reported at week 2 in 86.7% in each group ($p=1.00$). At week 12, the same decrease was reported in 80.0% in the botulinum toxin type A group and 86.7% in the botulinum toxin type B group ($p=.64$); and at week 20, the same decrease was only reported in 13.3% of the botulinum toxin type A group and 6.7% of the botulinum toxin type B group ($p=.56$). No major systemic adverse events were reported in any patients.

Comparison of Botulinum Toxin Type A With Microwave Thermolysis

Grove et al (2024) conducted an RCT that compared botulinum toxin type A to microwave thermolysis among 30 patients with axillary hyperhidrosis.¹⁴ Patients served as their own controls and were randomized to both treatments in contralateral axillae. The trial was not blinded. Sweat reduction (measured gravimetrically) was higher with botulinum toxin type A at 6 months ($p=.0053$), but there was no difference in sweat reduction between groups at 12 months ($p=.4282$). Both groups experienced a significant reduction in odor but only microwave thermolysis was associated with sustained odor reduction at 1 year. Hair reduction only occurred with microwave thermolysis.

Observational Studies

A retrospective chart review by Mirkovic et al (2018) focused on children receiving botulinum toxin for hyperhidrosis.¹⁵ Children receiving at least 1 botulinum treatment were included

(N=323); mean age was 15 years (range, 5 to 17 years). The most common focal locations of hyperhidrosis were palms, axillae, and feet. Sixty percent of the children received more than 1 treatment of botulinum. Of 183 who completed a follow-up Global Assessment of Therapy scale at a subsequent visit, 176 (96%) reported that sweating disappeared completely between 2 to 4 months posttreatment. No severe adverse events were reported.

Section Summary: Primary Axillary Hyperhidrosis Treated With Botulinum Toxin Type A or B

Evidence from systematic reviews and RCTs supports the efficacy and safety of botulinum toxin for treating axillary hyperhidrosis. Meta-analyses for botulinum toxin have demonstrated a positive effect for reduction of sweating in the short (2 to 4 weeks) and long (16 weeks) term, and improved HDSS scores by 2 or more points. Most studies evaluated botulinum toxin type A for axillary hyperhidrosis. Comparative RCTs have found similar outcomes among different botulinum type A formulations, between botulinum type A and B, and between botulinum toxin type A and microwave thermolysis for axillary hyperhidrosis.

PRIMARY PALMAR HYPERHIDROSIS TREATED WITH BOTULINUM TOXIN TYPE A

Clinical Context and Therapy Purpose

The purpose of intradermal injections of botulinum toxin type A into palmar sweat glands in individuals who have primary palmar hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary palmar hyperhidrosis. Primary palmar hyperhidrosis is idiopathic and involves the hands. Topical antiperspirant treatment is typically tried first.

Interventions

The therapy being considered is intradermal injections of botulinum toxin type A into palmar sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary palmar hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, iontophoresis, and endoscopic transthoracic sympathectomy.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

RANDOMIZED CONTROLLED TRIALS

Comparison of Botulinum Toxin Type A With Placebo

Lowe et al (2002) conducted an RCT of 19 patients who received injections of botulinum toxin type A in 1 palm and placebo in the other.¹⁶ The mean percentage of sweat reduction in the toxin-treated palms was significant compared with baseline. The sweat reduction in the placebo-injected palms did not differ statistically from baseline. Both physician and patient assessments showed significant improvements in the botulinum-injected palms compared with the placebo-injected palms.

Comparison of Different Doses of Botulinum Toxin Type A

Saadia et al (2001) conducted a single-blind (patients) randomized trial in which 24 patients received botulinum toxin type A 50 units or 100 units injected intradermally in 20 sites in each palm.¹⁷ Patients were evaluated every 2 weeks during the first month, then once every month up to month 6. Both groups experienced significant improvements in sweat reduction by month 1 of follow-up, lasting through 6 months. Temporary adverse events included pain and soreness. No significant adverse events were associated with the treatment by the end of 6 months.

Comparison of Types of Botulinum Toxin Type A

Two double-blind, randomized trials compared onabotulinumtoxinA with incobotulinumtoxinA. Campanati et al (2014) included 25 patients with moderate-to-severe primary palmar hyperhidrosis resistant to aluminum chloride or iontophoresis.¹⁸ Patients received injections of incobotulinumtoxinA in a randomly selected hand and onabotulinumtoxinA in the other hand. Botulinum toxin was given at a fixed dosage per square centimeter of the hand. There were no statistically significant differences in outcomes between groups, including changes in HDSS score (mean values significantly decreased by 2 points from baseline in each group), and the extent of sweating assessed using the Minor test (at both 4 weeks and 12 weeks).

Section Summary: Primary Palmar Hyperhidrosis Treated With Botulinum Toxin Type A

For palmar hyperhidrosis, evidence from RCTs supports the efficacy and safety of botulinum toxin type A for treating palmar hyperhidrosis. An additional RCT comparing types of botulinum type A reported similar effectiveness.

PRIMARY PALMAR HYPERHIDROSIS TREATED WITH BOTULINUM TOXIN TYPE B

Clinical Context and Therapy Purpose

The purpose of intradermal injections of botulinum toxin type B into palmar sweat glands in individuals who have primary palmar hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary palmar hyperhidrosis. Primary palmar hyperhidrosis is idiopathic and involves the hands.

Interventions

The therapy being considered is intradermal injections of botulinum toxin type B into palmar sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary palmar hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, iontophoresis, and endoscopic transthoracic sympathectomy.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Randomized Controlled Trials**

In a placebo-controlled, randomized trial, Baumann et al (2005) evaluated botulinum toxin type B for palmar hyperhidrosis.¹⁹ This RCT did not discuss whether patients had failed previous treatments for hyperhidrosis. This RCT included 20 patients with excessive palmar sweating. Fifteen patients received rimabotulinumtoxinB injections 50,000 units per palm, and 5 received

placebo. Nonresponders were offered an injection of botulinum toxin type B at day 30. At day 30, the 2 quality-of-life measures were significantly better in the botulinum toxin group than in the control group. However, the difference was not statistically significant for efficacy in physician analysis of the palmar iodine-starch test at day 30 ($p=.56$). No further details were provided on the efficacy outcome measures. Mean duration of action according to self-report in 17 patients (15 in the initial treatment group, 2 who crossed over from the placebo group) was 3.8 months (range, 2.3 to 4.9 months). Patients were asked about specific adverse events: 18 (90%) of 20 reported dry mouth/throat, 12 (60%) reported indigestion, 12 (60%) reported excessively dry hands, 12 (60%) reported muscle weakness, and 10 (50%) reported decreased grip strength.

Section Summary: Primary Palmar Hyperhidrosis Treated With Botulinum Toxin Type B

One small RCT did not demonstrate the efficacy of botulinum toxin type B for the treatment of palmar hyperhidrosis. Also, a high rate of adverse events was reported.

PRIMARY PLANTAR HYPERHIDROSIS TREATED WITH BOTULINUM TOXIN TYPE A OR B

Clinical Context and Therapy Purpose

The purpose of intradermal injections of botulinum toxin type A or B into plantar sweat glands in individuals who have primary plantar hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary plantar hyperhidrosis. Primary plantar hyperhidrosis is idiopathic and involves the feet.

Interventions

The therapy being considered is intradermal injections of botulinum toxin type A or B into plantar sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary plantar hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, and iontophoresis.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

No relevant evidence has been identified.

Section Summary: Primary Plantar Hyperhidrosis Treated With Botulinum Toxin Type A or B

There is insufficient evidence to assess the use of any botulinum toxin formulation for plantar hyperhidrosis.

MICROWAVE TREATMENT FOR PRIMARY FOCAL HYPERHIDROSIS (IE, AXILLARY, PALMAR, PLANTAR, CRANIOFACIAL)**Clinical Context and Therapy Purpose**

The purpose of microwave treatment of sweat glands in individuals who have primary focal hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary focal hyperhidrosis. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), feet (plantar), or axillae (underarms).

Interventions

The therapy being considered is microwave treatment of sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, intradermal injections of botulinum toxin, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-

iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Hsu et al (2017) conducted a systematic review of studies investigating the use of microwave-based therapies for the treatment of axillary hyperhidrosis.²⁰ The literature search, conducted through June 2016, identified an RCT (described below) and 4 single-arm observational studies (one of which is described below). Studies were published between 2012 and 2016. The total number of patients in the 5 studies was 189 (range, 7 to 120). Administration of microwave therapy differed by frequency (1 to 3 times) and length of treatment intervals (2 weeks to 3 months) among the studies. Follow-up extended to 1 year in 4 of the studies. All studies reported HDSS scores. Additional outcomes included osmidrosis evaluation (3 studies), gravimetric assessments (2 studies), and the Dermatologic Life Quality Index (1 study). All studies reported that microwave therapy was effective in reducing sweating in patients with axillary hyperhidrosis, with HDSS scores decreasing by at least 1 point throughout follow-up. The most common adverse events reported were swelling, pain, edema, hair loss, altered sensation, and palpable bumps. Reviewers concluded that while efficacy was indicated and side effects were mild, additional RCTs with larger sample sizes and longer follow-up would be needed.

The Wade et al (2017)² systematic review included only a single RCT in its evaluation (the same RCT included in the Hsu systematic review described above) and detailed below in the RCT section. While the RCT results suggested a benefit of microwave compared with placebo, the evidence was of low quality. Also, evidence of safety was insufficient.

Randomized Controlled Trials

An RCT by Glaser et al (2012) evaluated a microwave device for treating primary focal hyperhidrosis.²¹ This device applied microwave energy to superficial skin structures with the intent of inducing thermolysis of the eccrine and apocrine sweat glands. This industry-sponsored, double-blind trial randomized 120 adults with primary axillary hyperhidrosis 2:1 to active (n=81) or sham (n=39) treatment. Treatment consisted of 2 sessions, separated by approximately 2 weeks. Patients who responded adequately after 1 session or declined further treatment did not undergo the second session; a third procedure was allowed within 30 days for patients who still had a high level of sweating after 2 sessions. All patients in the sham group had 2 sessions. In the active treatment group, 11 (9%) patients had 1 session, 60 (74%) had 2 sessions, and 10 (8%) patients had 3 sessions. The primary efficacy end point was an HDSS score of 1 or 2 at the

30-day follow-up; HDSS score at 6 months was a secondary outcome. A total of 101 (84%) of 120 patients completed the study. At 30 days, 89% of the active treatment group and 54% of the sham group had an HDSS score of 1 or 2 ($p<.001$). At 6 months, 67% of the active treatment group versus 44% of the sham group had an HDSS score of 1 or 2 ($p=.02$). Unblinding occurred at 6 months. Twelve-month data were available for the active treatment group only; 69% reported an HDSS score of 1 or 2. There were 45 procedure-related adverse events in 23 (28%) of the active treatment group versus 5 (13%) of the sham group. The most frequently reported adverse event was altered sensation; no serious adverse events were reported. Compensatory sweating was reported by 2 patients in each group (mean duration, 52 days). The authors noted that study data provided an opportunity to identify areas for improvement in the treatment protocol including waiting longer between treatments and using a higher dose of energy at the second session.

Observational Studies

Hong et al (2012) conducted an industry-sponsored case series of 31 patients with primary axillary hyperhidrosis treated with microwave therapy using the miraDry system.²² All patients had an HDSS score of 3 or 4 at baseline. The primary efficacy outcome (the proportion of patients whose HDSS score decreased to 1 or 2) was 28 (90%) at 6 and 12 months posttreatment. Longer term skin-related adverse events (that all resolved over time) were altered sensation in the skin of the axillae (65% of patients; median duration, 37 days) and palpable bumps under the skin of the axillae (71% of patients; median duration, 41 days).

Section Summary: Microwave Treatment for Primary Focal Hyperhidrosis

A systematic review and RCT found a short-term benefit of microwave treatment in reducing hyperhidrosis but also reported skin-related adverse events (eg, pain, altered sensation). A case series also reported reductions in sweating, but sample sizes were small. Additional controlled trials with long-term follow-up in the treatment and control groups, a longer period of blinding, and a consistent treatment protocol would be needed to confirm the efficacy of this treatment and better define the risk-benefit ratio.

RADIOFREQUENCY ABLATION FOR PRIMARY FOCAL HYPERHIDROSIS (IE, AXILLARY, PALMAR, PLANTAR, CRANIOFACIAL)

Clinical Context and Therapy Purpose

The purpose of radiofrequency ablation (RFA) of sweat glands in individuals who have primary focal hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary focal hyperhidrosis. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), feet (plantar), or axillae (underarms).

Interventions

The therapy being considered is RFA of sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, intradermal injections of botulinum toxin, microwave treatment, endoscopic transthoracic sympathectomy, and surgical excision of axillary sweat glands.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Randomized Controlled Trials**

Mostafa et al (2019) conducted a RCT of RFA compared to botulinum toxin type A in 80 patients with primary palmar hyperhidrosis.²³ Both groups showed improvements from baseline in HDSS scores at 1 week, 1 month, and 2 months after treatment, but scores in the RFA group were significantly lower (indicating more improvement with RFA) than in the botulinum toxin group at 1 week, 1 month, and 2, 6, and 12 months after treatment.

Rummaneethorn et al (2019) compared RFA to botulinum toxin A in 20 patients with primary axillary hyperhidrosis.²⁴ At the endpoint visit (week 12), the botulinum toxin A group had a significantly lower reduction of mean HDSS score than the RFA group with 1.60 (0.59) versus 2.05 (0.68), respectively ($p=.0332$).

Nonrandomized Comparative Studies

Zhong et al (2024) published a multicenter retrospective cohort study that compared RFA and video-assisted thoracoscopic sympathectomy in 807 patients with palmar hyperhidrosis.²⁵ The study was conducted in China and all patients were followed for a median of 1.5 to 1.7 years. At baseline, the study population underwent propensity score matching. At 1 year postoperatively, clinical efficacy (defined as complete remission after treatment) was observed in 80.1% of patients who underwent RFA compared to 91% of patients who underwent video-assisted thoracoscopic sympathectomy ($p<.001$). Patients in the RFA group also had significantly more

symptom recurrence and compensatory hyperhidrosis compared to the video-assisted thoracoscopic sympathectomy group.

Purtuloglu et al (2013) evaluated RFA as a treatment for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment.²⁶ The study was conducted in Turkey and retrospectively reviewed outcomes after RFA (n=48) or transthoracic sympathectomy (n=46). Patients were not randomized to treatment group. After a mean follow-up of 15 months, palmar hydrosis was absent in 36 (75%) patients in the RFA group and 44 (96%) patients in the surgery group. The difference in outcomes between groups was statistically significant, favoring the surgical intervention ($p<.01$). Six patients in each group reported moderate or severe compensatory sweating ($p=.78$).

Section Summary: Radiofrequency Ablation

One nonrandomized comparative study found that RFA was inferior to surgical sympathectomy for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment. Two small RCTs that compared RFA to botulinum toxin A in patients with palmar or axillary hyperhidrosis had conflicting results. The body of evidence is insufficient to assess the use of RFA as a treatment for hyperhidrosis.

PRIMARY AXILLARY HYPERHIDROSIS TREATED WITH SURGICAL EXCISION OF AXILLARY SWEAT GLANDS

Clinical Context and Therapy Purpose

The purpose of surgical excision of axillary sweat glands in individuals who have primary axillary hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary axillary hyperhidrosis. Primary axillary hyperhidrosis is idiopathic and involves the axillae (underarms).

Interventions

The therapy being considered is surgical excision of the axillary sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, and intradermal injections of botulinum toxin.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific

surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Surgical Excision of Axillary Sweat Glands

Surgery may involve removal of the subcutaneous axillary sweat glands without removal of any skin, limited excision of skin, and removal of surrounding subcutaneous sweat glands, or a more radical excision of skin and subcutaneous tissue en bloc.²⁷ Depending on the completeness of surgical excision, treatment is effective in 50% to 95% of patients.

Section Summary: Surgical Excision of Axillary Sweat Glands

Sweat gland excision has been found to be effective in 50% to 95% of appropriately selected patients.

ENDOSCOPIC TRANSTHORACIC SYMPATHECTOMY FOR PRIMARY AXILLARY, PALMAR, AND CRANIOFACIAL HYPERHIDROSIS

Clinical Context and Therapy Purpose

The purpose of endoscopic transthoracic sympathectomy of sweat glands in individuals who have primary focal hyperhidrosis, within the axillary, palmar, or craniofacial area, is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary focal hyperhidrosis, within the axillary, palmar, or craniofacial area. Primary focal hyperhidrosis is idiopathic, typically involving the hands (palmar), head/face (craniofacial), or axillae (underarms).

Interventions

The therapy being considered is endoscopic transthoracic sympathectomy of sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral

anticholinergic medications, intradermal injections of botulinum toxin, microwave treatment, iontophoresis, and surgical excision of axillary sweat glands.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Systematic Reviews

Several RCTs and a meta-analysis have compared different surgical approaches; there were no sham-controlled randomized trials identified. Deng et al (2011) published a meta-analysis of data from RCTs and observational studies published through 2010 that evaluated endoscopic thoroscopic sympathectomy for patients with palmar hyperhidrosis.²⁸ Reviewers pooled outcomes data from different approaches to sympathectomy (ie, single-ganglia blockage [T2, T3, T4], multiganglia blockage [T2-3, T2-4, T3-4]). (Note that T refers to the rib.) Based on these analyses, reviewers concluded that T3 (11 studies) and T3-4 (2 studies) approaches had the "best" clinical efficacy (ie, postoperative resolution of symptoms). The T3 approach resulted in a 97.9% pooled efficacy rate, and the T3-4 approach resulted in a 100% pooled efficacy rate. In the studies for which data were available, the pooled rate of postoperative compensatory sweating was 40% after T3 surgery. Data on compensatory sweating after T3-4 surgery were available from only 1 study (60 patients); a pooled analysis could not be performed.

Randomized Controlled Trials

Subsequent RCTs have compared levels (rib location) of sympathectomy. These trials tended to have relatively small sample sizes (ie, <150/100 patients). For example, Baumgartner et al (2011) in the United States studied 121 patients with disabling palmoplantar hyperhidrosis.²⁹ Patients were randomized to bilateral sympathectomy over T2 (n=61 patients) or T3 (n=60 patients). Six (5%) of 121 patients (3 in each group) were considered treatment failures (ie, had recurrent palmar sweating to a bothersome level). There were no significant differences between groups in the reported subjective change in plantar or axillary sweating after surgery. At 6 months, the mean level of compensatory sweating (0 to 10 severity scale) was 4.7 for the T2 group and 3.8 for the T3 group (p-value was not significant). Similarly, at 1 year, the mean severity rating of

compensatory sweating was 4.7 in the T2 group and 3.7 in the T3 group ($p=.09$). Yuncu et al (2013) in Turkey randomized 60 patients with axillary hyperhidrosis to T3-4 surgery ($n=17$) or to T3 surgery ($n=43$).³⁰ There were no significant differences between groups in postoperative satisfaction. At 1-year follow-up, the incidence of compensatory sweating was lower in the T3 group (79%) than in the T3-4 group (100%).

Case Series

There also are case series on transthoracic sympathectomy for treating primary focal hyperhidrosis.^{31,32,33,34} Case series have generally reported high success rates for palmar and axillary hyperhidrosis, although there are potential adverse events, most commonly compensatory sweating. For example, Karamustafoglu et al (2014) in Turkey reported on 80 patients with primary hyperhidrosis (axillary and/or palmar).³² All 80 patients responded to a questionnaire a mean of 35 months after surgery. Seventy-one (89%) of the 80 patients were very satisfied with the surgical outcome, and the other 11% were dissatisfied. Compensatory sweating was reported by 62 (78%) patients. Moreover, a series by de Andrade Filho et al (2013) reported on complications after thoracic sympathectomy in 1731 patients with palmar, axillary, or craniofacial hyperhidrosis.³¹ Thirty days after surgery, 1531 (88%) patients reported compensatory sweating. Among the 1531 patients, compensatory sweating was mild in 473 (31%), moderate in 642 (42%), and severe in 416 (27%). Gustatory sweating was reported by 334 (19%) of the 1731 patients.

Several retrospective chart reviews evaluated the effects of the procedure on subgroups of patients with hyperhidrosis. Lembranca et al (2017) reviewed the charts of patients with palmar or axillary hyperhidrosis who did not respond to oxybutynin chloride treatment who then underwent thoracic sympathectomy ($n=167$) and patients who were referred directly to surgical treatment ($n=570$).³⁵ Both groups showed improvements in hyperhidrosis and quality of life ($>90\%$). De Campos et al (2017) assessed the quality of life among 15 patients with palmar hyperhidrosis who were unresponsive following a thoracic sympathectomy and underwent a resympathectomy.³⁶ Quality of life scores improved from "poor" or "very poor" to "excellent" or "very good" in 14 of the 15 patients. Fukuda et al (2018) reviewed charts of patients with craniofacial hyperhidrosis as a primary complaint ($n=40$) and patients with craniofacial hyperhidrosis as a secondary complaint ($n=136$).³⁷ Over 90% of patients in both groups reported a moderate or great reduction in hyperhidrosis following the procedure. Greater improvements in quality of life were reported among the patients with craniofacial hyperhidrosis that was a secondary complaint, though both groups had improved quality of life. A large proportion of patients (92%) reported compensatory hyperhidrosis. Vasconcelos-Castro et al (2019) reported a case series of 23 pediatric patients (ages 11 to 19 years) with primary palmar hyperhidrosis who underwent bilateral thoracoscopic sympathectomy. Sweating severity improved in all patients, with a mean decrease from baseline of 1.95 on the HDSS ($p<.05$ compared to baseline). Compensatory sweating occurred in 47.8% of patients.³⁸

Section Summary: Endoscopic Transthoracic Sympathectomy

Randomized controlled trials and a meta-analysis of RCTs have supported the efficacy of endoscopic transthoracic sympathectomy at various levels for palmar, axillary, and craniofacial hyperhidrosis. These data are complemented by case series, which have found high efficacy rates, but also high rates of compensatory sweating for these conditions.

LUMBAR SYMPATHECTOMY FOR PRIMARY PLANTAR HYPERHIDROSIS

Clinical Context and Therapy Purpose

The purpose of lumbar sympathectomy of plantar sweat glands in individuals who have primary plantar hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with primary plantar hyperhidrosis. Primary plantar hyperhidrosis is idiopathic and involves the feet.

Interventions

The therapy being considered is lumbar sympathectomy of plantar sweat glands. Topical antiperspirant treatment is typically tried first in these patients.

Comparators

A variety of therapies have been investigated for primary plantar hyperhidrosis that does not respond to topical antiperspirants, including topical therapy with anticholinergics (eg, glycopyrronium), oral anticholinergic medications, iontophoresis, and intradermal injections of botulinum toxin.

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Systematic Reviews**

Lima et al (2020) conducted a systematic review and meta-analysis of lumbar sympathectomy for plantar hyperhidrosis.³⁹ Eight studies were identified, including a total of 517 patients. One RCT met inclusion criteria; the other studies were case series. In all of the studies, lumbar sympathectomy was conducted following transthoracic sympathectomy. Resolution of symptoms

occurred in 92% of patients when mechanical sympathectomy was used with clipping or resection of the lymph nodes between L2 and L5, with similar results regardless of resection level. Overall, 44% of patients had mild to severe compensatory sweating after a mean 6 months of follow-up. The RCT was conducted in 30 women at a single hospital in Brazil.⁴⁰ The primary outcome measure was a quality of life questionnaire that was developed for use in patients undergoing thoracic sympathectomy. After 6 months, patients in the intervention group had a greater improvement in quality of life relative to the control group patients; 53% reported worsening compensatory sweating. This study was limited by its small sample size, use of an unvalidated outcome measure, and lack of blinded outcome assessment.

A 2004 review from a multispecialty working group on hyperhidrosis stated that lumbar sympathectomy is not recommended for plantar hyperhidrosis because of associated sexual dysfunction; this article did not cite any data documenting sexual dysfunction.⁴¹ To date, there are very few studies on endoscopic lumbar sympathectomy for focal plantar hyperhidrosis and only 1 small comparative study with methodological limitations.

Section Summary: Lumbar Sympathectomy

There is insufficient evidence in support of lumbar sympathectomy for treating plantar hyperhidrosis; case series have found lower rates of efficacy for plantar compared with axillary or palmar hyperhidrosis, and there are concerns for adverse events in sexual functioning. One RCT conducted among 30 women at a single center in Brazil was limited by its small sample size and lack of blinded outcome assessment. There are insufficient data to conclude that any particular approach to surgery results in lower rates of compensatory sweating.

IONTOPHORESIS AND BOTULINUM TOXIN FOR SEVERE SECONDARY GUSTATORY HYPERHIDROSIS

Clinical Context and Therapy Purpose

The purpose of iontophoresis and intradermal injections of botulinum toxin in individuals who have severe secondary gustatory hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with severe secondary gustatory hyperhidrosis.

Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. Frey syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve.

Interventions

The therapies being considered are iontophoresis and intradermal injections of botulinum toxin.

Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment for menopausal symptoms.

Comparators

Alternatives for treatment of secondary gustatory hyperhidrosis include topical therapy (eg, glycopyrronium, aluminum chloride) and treatment of the underlying cause (eg, dietary changes).

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE**Iontophoresis**

A TEC Assessment (2003) assessing iontophoresis for a variety of medical conditions concluded that the evidence was insufficient to determine whether iontophoresis for the treatment of any hyperhidrosis improves outcomes.⁴² Neither the TEC Assessment nor subsequent literature searches have identified any RCTs evaluating iontophoresis for gustatory hyperhidrosis.

Botulinum Toxin

A Cochrane review by Li et al (2015) did not identify any RCTs or quasi-randomized RCTs evaluating the efficacy of botulinum toxin injections for the treatment of gustatory hyperhidrosis as a result of Frey syndrome.⁴³ No RCTs were identified in literature searches.

Section Summary: Iontophoresis and Botulinum Toxin for Secondary Gustatory Hyperhidrosis

Systematic reviews for both iontophoresis and botulinum toxin for gustatory hyperhidrosis have not found evidence supporting these methods.

TYMPANIC NEURECTOMY FOR SEVERE SECONDARY GUSTATORY HYPERHIDROSIS

Clinical Context and Therapy Purpose

The purpose of tympanic neurectomy in individuals who have severe secondary gustatory hyperhidrosis is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with severe secondary gustatory hyperhidrosis.

Secondary gustatory hyperhidrosis is excessive sweating on ingesting highly spiced foods. Frey syndrome is an uncommon type of secondary gustatory hyperhidrosis that arises from injury to or surgery near the parotid gland resulting in damage to the secretory parasympathetic fibers of the facial nerve.

Interventions

The therapy being considered is tympanic neurectomy.

Treatment of secondary hyperhidrosis focuses on treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment for menopausal symptoms.

Comparators

Alternatives for treatment of secondary gustatory hyperhidrosis include topical therapy (eg, glycopyrronium, aluminum chloride) and treatment of the underlying cause (eg, dietary changes).

Outcomes

The general outcomes of interest are symptoms, quality of life, and treatment-related morbidity.

Outcomes from different surgical and medical treatment modalities are best assessed using a combination of tools. Quantitative tools include gravimetry, evaporimetry, and the Minor starch-iodine test. Qualitative assessment tools include general health surveys and hyperhidrosis-specific surveys. Of these, the HDSS has had a good correlation to other assessment tools and is practical in the clinical setting.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Review articles by Clayman et al (2006)⁴⁴, and de Bree et al (2007)⁴⁵, have described various medical and surgical treatments for Frey syndrome. Tympanic neurectomy has been described as a treatment, with satisfactory control reported in 82% of patients. Also, this surgical treatment is generally definitive without a need for repeated interventions.

Section Summary: Tympanic Neurectomy for Secondary Gustatory Hyperhidrosis

Review articles have supported the use of tympanic neurectomy for patients with severe gustatory sweating.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Academy of Neurology

In 2008, the American Academy of Neurology issued guidelines on the use of botulinum toxin for the treatment of autonomic disorders and pain.⁴⁶ These guidelines were updated in 2013⁴⁷, and retired in 2017. Table 1 summarizes the recommendations for botulinum toxin injection as a treatment of hyperhidrosis, by site and type of toxin:

Table 1. Recommendation Levels^a by Hyperhidrosis Site and Botulinum Toxin Type

Botulinum Toxin	Axillary	Palmar	Gustatory
Botulinum neurotoxin type A	A	B	U
AbobotulinumtoxinA	B	U	U
IncobotulinumtoxinA	U	U	U
OnabotulinumtoxinA	B	U	U
RimabotulinumtoxinB	U	U	U

^a A: established as effective, has at least 2 consistent Class I studies; B: probably effective, has at least 1 class I study or at least 2 consistent class II studies; C: possibly effective, has at least 1 class II study or at least 2 consistent class II studies; U: inadequate or conflicting data, treatment is unproven.

National Institute for Health and Care Excellence

In 2014, NICE issued guidance stating that there was sufficient evidence for the efficacy and safety of endoscopic thoracic sympathectomy for primary facial blushing to support the use of the procedure.⁴⁸

The Institute also issued guidance in 2014 on endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb.⁴⁹ The guidance stated that "current evidence on the efficacy and safety of endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb is

adequate to support the use of this procedure." Also: "Due to the risk of side effects, this procedure should only be considered in patients suffering from severe and debilitating primary hyperhidrosis that has been refractory to other treatments."

For severe primary axillary hyperhidrosis, NICE issued guidance in 2017 on the use of transcutaneous microwave ablation.⁵⁰ The guidance stated that there is inadequate evidence in both quantity and quality to evaluate the safety and efficacy of microwave ablation.

Society of Thoracic Surgeons

In 2011, the Society of Thoracic Surgeons published an expert consensus statement on the surgical treatment of hyperhidrosis.⁵¹ The document stated that endoscopic thoracic sympathectomy is the treatment of choice for patients with primary hyperhidrosis. It further recommended the following treatment strategies (with R referring to rib and the number to which rib):

- R3 interruption for palmar hyperhidrosis; an R4 interruption is also reasonable. The authors note a slightly higher rate of compensatory sweating with R3, but R3 is also more effective at treating hyperhidrosis.
- R4 or R5 interruption for palmar-axillary, palmar-axillary-plantar, or axillary hyperhidrosis alone; R5 interruption is also an option for axillary hyperhidrosis alone.
- R3 interruption for craniofacial hyperhidrosis without blushing; an R2 and R3 procedure is an option but may lead to a higher rate of compensatory sweating, and also increases the risk of Horner syndrome.

According to the statement, endoscopic thoracic sympathectomy has been recommended for patients with severe symptoms that cannot be managed with other therapies who meet the following criteria:

- Onset of hyperhidrosis at an early age (before 16 years)
- <25 years of age at time of surgery
- Body mass index <28 kg/m²
- No sweating during sleep
- No significant comorbidities
- Resting heart rate <55 beats per minute

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Unpublished</i>			
NCT03433859	Prospective Multicentric Open Randomised Controlled Trial Comparing Topical Aluminium Chloride to OnabotulinumtoxinA Intradermal Injections in Residual Limb Hyperhidrosis (Lower Limbs)	54	Mar 2021

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02854540	Management of Palmar Hyperhidrosis with Hydrogel-based Iontophoresis	13	Aug 2018
NCT03236012	Hyperhidrosis of the Residual Limb in Patients With Amputations: Developing a Treatment Approach	25	Feb 2022
NCT05057117	Longevity of Microwave Thermolysis and Botulinum Toxin A for Treatment of Axillary Hyperhidrosis: a Randomized Intra-Individual Trial	30	Apr 2023
<i>Ongoing</i>			
NCT02295891	Microwave Energy-induced Thermolysis of Axillary Apocrine Glands and Hair Follicles Will Result in Improvement of Secondary Psychopathology Related to Hyperhidrosis	24	Nov 2024
NCT03921320	Evaluation of Compensatory Sweating After Unilateral Videothoracoscopic Sympathectomy of the Dominant Side or Sequential Bilateral Videothoracoscopic Sympathectomy: a Multicentric Randomized Trial	200	Dec 2023 (status unknown)
NCT05737914	Bilateral Endoscopic Thoracic T3 Sympathectomy Versus T3 Radiofrequency Ablation for Treatment of Primary Palmar Hyperhidrosis	68	Oct 2023 (status unknown)

NCT: national clinical trial.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
11450	Excision of skin and subcutaneous tissue for hidradenitis, axillary; with simple or intermediate repair
11451	Excision of skin and subcutaneous tissue for hidradenitis, axillary; with complex repair
32664	Thoracoscopy, surgical; with thoracic sympathectomy
64650	Chemodenervation of eccrine glands; both axillae
64653	Chemodenervation of eccrine glands; other area(s) (eg, scalp, face, neck), per day
64818	Sympathectomy, lumbar
69676	Tympanic neurectomy
97024	Application of a modality to 1 or more areas; diathermy (eg, microwave)
97033	Application of a modality to 1 or more areas; iontophoresis, each 15 minutes
J0585	Injection, onabotulinumtoxinA, 1 unit
J0586	Injection, abobotulinumtoxinA, 5 units
J0587	Injection, rimabotulinumtoxinB, 100 units
J0588	Injection, incobotulinumtoxinA, 1 unit

REVISIONS	
09-23-2009	Policy added to the bcbsks.com web site as a stand-alone policy. Hyperhidrosis was previously discussed in the Botulinum Toxin medical policy.
01-26-2010	<p>In Policy Section:</p> <ul style="list-style-type: none"> ▪ Clarified policy language by changing 4.A. From: "Botulinum toxin when other treatments have failed" to " Botulinum toxin when symptoms are at a severity level of 3 or 4 (see severity scale below) and other treatments have failed" ▪ Clarified policy language by changing B.1. from: " Thoracic sympathectomy when symptoms are severe and other treatments have failed" to "Thoracic sympathectomy when symptoms are at a severity level of 3 or 4 (see severity scale below) and other treatments have failed"
03-31-2014	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ Revised to create distinction between Primary Focal Hyperhidrosis and Secondary Hyperhidrosis. ▪ Updated Primary Focal Hyperhidrosis information From: "Treatment of hyperhidrosis resulting in significant impairment of daily activities_may be considered medically necessary with the following:

REVISIONS

A. Non-surgical: 1. Topical treatments such as aluminum chloride, glutaraldehyde, anticholinergics, 2. Systemic treatments, such as anti-cholinergics, tranquilizers, 3. Iontophoresis, 4. Botulinum toxin when symptoms are at a severity level of 3 or 4 (see severity scale below) and other treatments have failed

B. Surgical: 1. Thoracic sympathectomy when symptoms are at a severity level of 3 or 4 (see severity scale below) and other treatments have failed"

To:

"Treatment of primary hyperhidrosis may be considered medically necessary with any of the following medical complications:

1. acrocyanosis of the hands; or
2. history of recurrent skin maceration with bacterial or fungal infections; or
3. history of recurrent secondary infections; or
4. history of persistent eczematous dermatitis in spite of medical treatments with topical dermatological or systemic anticholinergic agents.

Focal Regions	Treatments Considered Medically Necessary	Treatments Considered Investigational
Axillary	<ul style="list-style-type: none"> ▪ aluminum chloride 20% solution* ▪ botulinum toxin* for severe primary axillary hyperhidrosis that is inadequately managed with topical agents*, in patients 18 years and older ▪ endoscopic transthoracic sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum toxin, individually and in combination) has failed 	<ul style="list-style-type: none"> ▪ axillary liposuction ▪ iontophoresis ▪ microwave treatment
Palmar	<ul style="list-style-type: none"> ▪ aluminum chloride 20% solution* ▪ botulinum toxin A products for severe primary palmar hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older ▪ endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride or botulinum toxin type A, individually and in combination) has failed 	<ul style="list-style-type: none"> ▪ RimabotulinumtoxinB ▪ iontophoresis ▪ microwave treatment ▪ radiofrequency ablation
Plantar	<ul style="list-style-type: none"> ▪ aluminum chloride 20% solution* 	<ul style="list-style-type: none"> ▪ botulinum toxin ▪ iontophoresis ▪ lumbar sympathectomy ▪ microwave treatment
Craniofacial	<ul style="list-style-type: none"> ▪ aluminum chloride 20% solution* ▪ endoscopic transthoracic sympathectomy (ETS), if conservative treatment (i.e., aluminum chloride) has failed 	<ul style="list-style-type: none"> ▪ botulinum toxin ▪ iontophoresis ▪ microwave treatment

▪ Added section on indications for treatment of Secondary Gustatory Hyperhidrosis:

REVISIONS	
	<p>"1.The following treatments would be considered medically necessary for the treatment of severe gustatory hyperhidrosis:</p> <ul style="list-style-type: none"> a. aluminum chloride 20% solution* b. surgical options (i.e., tympanic neurectomy), if conservative treatment has failed. <p>2. The following treatments are considered experimental / investigational as a treatment for severe gustatory hyperhidrosis including, but not limited to:</p> <ul style="list-style-type: none"> a. botulinum toxin is considered investigational for treatment of gustatory hyperhidrosis. (See Policy Guidelines for list of conditions) b. iontophoresis <p>*FDA approved indication (in the case of botulinum toxin, FDA approved for at least one botulinum toxin product)</p> <p>3. Treatment of hyperhidrosis is considered not medically necessary in the absence of functional impairment or medical complications."</p> <ul style="list-style-type: none"> ▪ Removed "Lumbar sympathectomy, axillary liposuction or resection of axillary sweat glands are considered experimental / investigational." ▪ Added Policy Guidelines leaving reference to the Severity Scale. <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added CPT and HCPCS codes: 69676, J0586, J0588 ▪ Revised nomenclature for HCPCS codes: J0585, J0587 ▪ Added ICD-10 Diagnosis Codes <p>References updated</p>
12-13-2016	<p>Description section updated</p> <p>In Policy section:</p> <ul style="list-style-type: none"> ▪ In Item A 1 added "focal" and "using the following therapies (see Table PG1)" and removed "(see definition of primary hyperhidrosis in Policy Guidelines)" to read "Treatment of primary focal hyperhidrosis using the following therapies (see Table PG1) may be considered medically necessary with any of the following medical complications:" ▪ Updated Table PG1 ad renamed to "Treatments Considered Medically Necessary" ▪ Updated Table PG1 footnotes ▪ Created Item A 2 to separate the experimental / investigational treatments from the medically necessary treatments with "Treatment of primary focal hyperhidrosis using the following therapies (see Table PG2) are considered experimental / investigational:" No changes to the E/I treatment were made. ▪ Created Table PG2 pulling experimental / investigational treatments from old PG1 Table labeling as "Table PG2 Treatments Considered Experimental / Investigational" ▪ In Item B 1 added "secondary" and "(A list of gustatory hyperhidrosis conditions are: Frey syndrome, encephalitis, syringomyelia, diabetic neuropathies, herpes zoster parotitis, parotid abscess)" ▪ In Item B 1 removed "*FDA approved indication. Note: In the case of botulinum toxin, FDA approved for at least one botulinum toxin product." ▪ In Item B 2 added "Other" and "secondary" and removed "The following" to read, "Other treatments are considered experimental / investigational as a treatment for severe secondary gustatory hyperhidrosis including, but not limited to:" ▪ In Item B 2 a removed "is considered investigational for treatment of gustatory hyperhidrosis" to read "botulinum toxin" ▪ Updated Policy Guidelines <p>Rationale section updated</p> <p>In Coding section:</p> <ul style="list-style-type: none"> ▪ Added HCPCS Codes: J0585, J0587

REVISIONS	
	<ul style="list-style-type: none"> ▪ Updated coding notations.
	References updated
03-15-2021	Description section updated
	In Policy section: <ul style="list-style-type: none"> ▪ In Item 2 Table P2 added E/I treatment "Radiofrequency ablation" to the following focal regions "axillary, plantar, and craniofacial" ▪ Updated Policy Guidelines
	Rationale section updated
	In Coding section: <ul style="list-style-type: none"> ▪ Added CPT Codes: 11450, 11451, 64818, 97023, 97033
	References updated
08-19-2021	Description section updated
	Rationale section updated
	References updated
07-26-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
07-25-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section <ul style="list-style-type: none"> ▪ Removed ICD-10 Codes
	Updated References Section
08-27-2024	Updated Description Section
	Updated Rationale Section
	Update References Section
07-22-2025	Updated Description Section
	Updated Rationale Section
	Update References Section

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