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Treatment of Hyperhydrosis

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Related Policies (if applicable)
None

Disclaimer

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Coverage

Primary Focal Hyperhidrosis
Treatment of primary focal hyperhidrosis using the following therapies **may be considered medically necessary** for individuals with any of the following medical conditions, as outlined in Table 1 below:

- Acrocyanosis of the hands; or
- History of recurrent skin maceration with bacterial or fungal infections; or
- History of recurrent secondary infections; or
- History of persistent eczematous dermatitis despite medical treatments with topical dermatologic or systemic anticholinergic agents.

Table 1: Treatments Considered Medically Necessary and Experimental, Investigational and/or Unproven.

Focal Regions	Treatments Considered Medically Necessary	Treatments Considered Experimental, Investigational and/or Unproven

Axillary	• OnabotulinumtoxinA (see **NOTE 1**) for severe primary axillary hyperhidrosis inadequately managed with topical agents, in patients 18 years and older; • ETS and surgical excision of axillary sweat glands, if conservative treatment has failed.	• Axillary liposuction; • Iontophoresis; • Microwave treatment; • Radiofrequency ablation; • Subdermal laser treatment.
Palmar	• ETS if conservative treatment has failed.	• RimabotulinumtoxinB; • Iontophoresis; • Microwave treatment; • Radiofrequency ablation; • Subdermal laser treatment.
Plantar	N/A	• OnabotulinumtoxinA; • AbobotulinumtoxinA; • IncobotulinumtoxinA; • RimabotulinumtoxinB; • Iontophoresis; • Lumbar sympathectomy; • Microwave treatment; • Radiofrequency ablation; • Subdermal laser treatment.
Craniofacial	ETS, if conservative treatment has failed.	• OnabotulinumtoxinA; • AbobotulinumtoxinA; • IncobotulinumtoxinA; • RimabotulinumtoxinB; • Iontophoresis; • Microwave treatment; • Radiofrequency ablation; • Subdermal laser treatment.

ETS: endoscopic transthoracic sympathectomy. N/A: non-applicable

NOTE 1: OnabotulinumtoxinA is the only botulinum toxin product that is U.S. Food and Drug Administration approved for treatment of adults with severe axillary hyperhidrosis inadequately managed by topical agents.

Secondary Hyperhidrosis

The following treatments **may be considered medically necessary** for the treatment of severe secondary gustatory hyperhidrosis (see Description section for list of gustatory hyperhidrosis conditions):

- Surgical options (i.e., tympanic neurectomy) if conservative treatment has failed.

Other treatments **are considered experimental, investigational, and/or unproven** as a treatment for severe secondary gustatory hyperhidrosis including, but not limited to:

- Botulinum toxin;
- Iontophoresis;
- Subdermal laser treatment.

Other

Treatment of hyperhidrosis **is considered not medically necessary** in the absence of functional impairment or for any of the above medical condition not included above.

Policy Guidelines

A variety of iontophoretic devices can be purchased for home use. There are no specific HCPCS codes for these pieces of DME [durable medical equipment]. Code E1399 might be used.

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, oral medications, botulinum toxin, and surgical procedures.

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 (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors) or underlying diseases/conditions (e.g., febrile diseases, diabetes, menopause). Secondary hyperhidrosis is usually generalized or craniofacial sweating.

A multispecialty working group have 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: bilateral and relatively symmetric sweating, impairment of daily activities, frequency of at least once per week, age at onset younger than 25 years, positive family history, and cessation of focal sweating during sleep. (1)

The Hyperhidrosis Disease Severity Scale (HDSS) (2) is used by patients to rate the severity of their symptoms on a scale of 1 to 4. (see Table 2)

Table 2: The Hyperhidrosis Disease Severity Scale (HDSS)

Score	Symptom

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.

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, 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 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, 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 of 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; symptoms of botulism include cessation of 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.

Subdermal laser treatment (3) is being studied as a treatment modality for axillary hyperhidrosis with the goal to target, heat, and destroy sweat glands, which are primarily found in a specific layer of tissue under the skin of the axilla. Tiny incisions (often so small they don't even require a stitch) are made in the underarms to allow the laser tool to be passed under the skin. The procedure usually takes less than an hour to complete.

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 (e.g., 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 effect. In addition, 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 HDSS (Table 2) has had 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 (BLA) 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 for non-cosmetic indications, but not specifically approved for treatment of hyperhidrosis, include:

- 2000: RimabotulinumtoxinB (Myobloc®, Solstice Neurosciences).
- 2009: AbobotulinumtoxinA (Dysport®, Medicis Pharmaceutical, Scottsdale, AZ).
- 2010: IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals).

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 one product to another botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products." (4)

The REMS requirement, provision of the medication guide, has since been removed and there are no current REMS requirements for botulinum toxin products. (5)

In 2011, the miraDry® System (Miramar Labs) was cleared for marketing by the FDA through the 510(k) process for treating primary axillary hyperhidrosis. (6) 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 local anesthetic is used. The device is currently not approved for the treatment of palmar or planter hyperhidrosis.

Rationale

Medical policies 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 one 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. RCTs 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 (i.e., 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 policy.

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 (e.g., 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 Table 2) 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). (7) 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 iontophoresis, botulinum injections, and microwave appear in the 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. (7) 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 (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. (8) The trial included 60 patients with a baseline HDSS score of 3 or 4. (2) 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=0.007). 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. (10) Most patients (n=16) had palmoplantar hyperhidrosis. Nineteen patients completed the course of 21 tap water iontophoresis sessions. Among study completers, 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 on 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. (11) 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. RCTs 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
Clinical Context and Therapy Purpose
The purpose of intradermal injections of botulinum toxin 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 policy.

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 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 (e.g., 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. (7) 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 U, though some studies used up to 250 U) and 2 studies used botulinum type B (2500 U or 5000 U). 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 (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. (11) The review incorporated only placebo-controlled RCTs, as opposed to any comparator in the Wade et al (2017) systematic review. Eight (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 U) and 2 studies used botulinum type B (rimabotulinumtoxinB 2250 U or 2500 U). 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 heterogenous 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 vs Placebo

The largest RCT conducted in the US that evaluated botulinum toxin type A was published by Lowe et al. (2007). (11) 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 U or 75 U 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 U), 82% (50 U), and 33% (placebo). Similar results were obtained in patients requiring a second treatment. The median duration of effect was 197 (75 U), 205 (50 U), and 96 (placebo) days. Seventy-eight percent (n=252) of patients completed the 52-week trial: 96 (87%) of 110 in the 75-U group, 83 (80%) of 104 in the 50-U 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-U group, 57 (55%) in the 50-U 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. (12) 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 U 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.

The clinical evidence cited below is based off the data provided to the U.S. Food and Drug Administration during the approval process for onabotulinumtoxinA (Botox®). (14)

The efficacy and safety of Botox for the treatment of primary axillary hyperhidrosis were evaluated in two randomized, multicenter, double-blind, placebo-controlled studies. Study 1 included adult patients with persistent primary axillary hyperhidrosis who scored 3 or 4 on a Hyperhidrosis Disease Severity Scale (HDSS) and who produced at least 50 mg of sweat in each axilla at rest over 5 minutes. HDSS is a 4-point scale with 1 = “underarm sweating is never noticeable and never interferes with my daily activities”; to 4 = “underarm sweating is intolerable and always interferes with my daily activities”. A total of 322 patients were randomized in a 1:1:1ratio to treatment in both axillae with either 50 Units of Botox, 75 Units of Botox, or placebo. Patients were evaluated at 4-week intervals. Patients who responded to the first injection were re-injected when they reported a re-increase in HDSS score to 3 or 4 and produced at least 50 mg sweat in each axilla by gravimetric measurement, but no sooner than 8 weeks after the initial injection.

Study responders were defined as patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study. Spontaneous resting axillary sweat production was assessed by weighing a filter paper held in the axilla over a period of 5 minutes (gravimetric measurement). Sweat production responders were those patients who demonstrated a reduction in axillary sweating from baseline of at least 50% at week 4.

In the three study groups the percentage of patients with baseline HDSS score of 3 ranged from 50% to 54% and from 46% to 50% for a score of 4. The median amount of sweat production (averaged for each axilla) was 102 mg, 123 mg, and 114 mg for the placebo, 50 Units and 75 Units groups respectively.

The percentage of responders based on at least a 2-grade decrease from baseline in HDSS or based on a >50% decrease from baseline in axillary sweat production was greater in both Botox groups than in the placebo group ($p<0.001$) but was not significantly different between the two Botox doses (see Table 3).

Duration of response was calculated as the number of days between injection and the date of the first visit at which patients returned to 3 or 4 on the HDSS scale. The median duration of response following the first treatment in Botox treated patients with either dose was 201 days. Among those who received a second Botox injection, the median duration of response was similar to that observed after the first treatment.

In study 2, 320 adults with bilateral axillary primary hyperhidrosis were randomized to receive either 50 Units of Botox (n=242) or placebo (n=78). Treatment responders were defined as subjects showing at least a 50% reduction from baseline in axillary sweating measured by gravimetric measurement at 4 weeks. At week 4 post-injection, the percentages of responders were 91% (219/242) in the Botox group and 36% (28/78) in the placebo group, $p<0.001$. The difference in percentage of responders between Botox and placebo was 55% (95% CI=43.3, 65.9).

Table 3: Study 1-Study Outcomes

Treatment Response	**Botox 50 Units (N=104)**	**Botox 75 Units (N=110)**	**Placebo (N=108)**	**Botox 50-placebo (95% CI)**	**Botox 75-placebo (95% CI)**
HDSS Score change >2 (n)[a]	55% (57)	49% (54)	6% (6)	49.3% (38.8, 59.7)	43% (33.2, 53.8)
>50% decrease in axillary sweat production % (n)	81% (84)	86% (94)	41% (44)	40% 28.1, 52.0)	45% (33.3, 56.1)

[a] Patients who showed at least a 2-grade improvement from baseline value on the HDSS 4 weeks after both of the first two treatment sessions or had a sustained response after their first treatment session and did not receive re-treatment during the study.

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, 5-17 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

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. To date, OnabotulinumtoxinA is the only botulinum toxin product that is U.S. Food and Drug Administration approved for treatment of adults with severe axillary hyperhidrosis inadequately managed by topical agents.

Primary Palmar 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 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 policy.

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 or 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 (e.g., 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

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. (16) 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).

In a placebo-controlled, randomized trial, Baumann et al. (2005) evaluated botulinum toxin type B for palmar hyperhidrosis. (17) Like the Baumann trial (2005), 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 U 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, 2.3-4.9 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 Plantar Hyperhidrosis Treated With Botulinum Toxin Type A or B

For palmar hyperhidrosis, evidence from RCTs do not support the efficacy and safety of botulinum toxin type A or B for treating palmar hyperhidrosis. Also, a high rate of adverse

events was reported. There is no botulinum toxin product, on label or off label, that is U.S. Food and Drug Administration approved for the treatment of primary palmar hyperhidrosis.

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 policy.

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 (e.g., 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 (i.e., 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 policy.

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 (e.g., 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. (18) 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, 7-120). Administration of a 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 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 (2017) 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. (7)

Randomized Controlled Trials

An RCT by Glaser et al. (2012) evaluated a microwave device for treating primary focal hyperhidrosis. (19) 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 (see Table 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<0.001). At 6 months, 67% of the active treatment group vs 44% of the sham group had an HDSS score of 1 or 2 (p=0.02). 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 vs 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. (20) 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 (e.g., 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. The evidence is insufficient to assess the use of microwave treatment as a treatment for primary focal hyperhidrosis.

Radiofrequency Ablation for Primary Focal Hyperhidrosis (i.e., 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 policy.

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 (e.g., 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. (21) 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. (22) 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

Purtuloglu et al. (2013) evaluated radiofrequency ablation (RFA) as a treatment for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment. (23) 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 hidrosis 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 ($p<0.01$). Six patients in each group reported moderate or severe compensatory sweating ($p=0.78$).

Section Summary: Radiofrequency Ablation

One nonrandomized comparative study found RFA inferior to surgical sympathectomy for patients with severe palmar hyperhidrosis resistant to conservative treatment. Two small RCTs that compared RFA to botulinum toxin A inpatients 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.

Subdermal Laser Treatment

Generally, axillary hyperhidrosis is treated with antiperspirant agents, botulinum toxin, or local surgery. In 2008, Goldman et al. (24) aimed to present the Nd-YAG laser as a safe and effective option for the treatment of axillary hyperhidrosis. Seventeen patients (15 women and 2 men) with axillary hyperhidrosis were treated using a subdermal 1,064-nm Nd-YAG laser. The results were evaluated by the patients as well as by the physician. The objective evaluation was realized by Minor's iodine starch test combined with planimetry. Histology was performed in axillary skin after the laser treatment. The subdermal laser-assisted axillary hyperhidrosis treatment using a 1,064-nm Nd-YAG laser resulted in significant clinical improvement. The authors concluded that the treatment of axillary hyperhidrosis using the 1,064-nm Nd-YAG laser has the advantage of a minor invasive procedure without leaving large scars and causing temporary impairment. The laser proved to be effective and safe. Although the laser treatment has shown promising results in this pilot trial, further studies are necessary for final conclusions.

In 2012, Bechara et al. (25) performed a randomized half sided controlled trial to study the effect of laser treatment on sweat secretion in patients with axillary hyperhidrosis. Twenty-one patients were treated with 5 cycles of an 800-nm diode laser. Sweat rates were documented using gravimetry and a visual analogue scale. Histologic examination was performed in all patients before and after treatment. A significant reduction in sweat rate was observed on the laser-treated (median 89 mg/min, range 42-208 mg/min vs 48 mg/min, range 17-119 mg/min; $p < .001$) and the untreated contralateral (median 78 mg/min, range 25-220 mg/min vs median 65 mg/min, range 24-399 mg/min; $p = .04$) sides, although no significant difference was found between the treated and untreated sides ($p = .10$). The authors observed a decrease in sweat rate on laser-treated sites, laser epilation was not able to reduce the sweat rate significantly more than on the untreated contralateral side. The authors believed these results potentially indicate a placebo effect rather than a direct therapeutic effect of laser epilation.

In 2012, Letada and colleagues (26) evaluated the effects of 1064 nm laser hair reduction on sweat production in a pilot study in patients with focal axillary hyperhidrosis. This was a prospective, case-controlled, randomized pilot study; one axilla from 6 different subjects with axillary hyperhidrosis was treated with monthly laser hair reduction sessions using the 1064 nm Nd-YAG laser at typical settings. The contralateral axilla acted as a control. Subjects were asked to subjectively classify improvement of axillary sweating using a Global Assessment Questionnaire (GAQ) weekly after each treatment. Qualitative evaluation of sweating was also performed using a modified starch iodine test monthly after each treatment. In addition, prior to the first treatment and at 1 month following the final treatment, a punch biopsy was performed on the treatment axilla to assess for histologic changes to the eccrine gland and surrounding structures. Statistically significant improvements in subjective ratings of sweating using the GAQ compared to baseline were observed. Objective improvements in sweating with modified starch iodine testing comparing treated versus non-treated axillae were also seen for at least 9 months in selected subjects. No significant differences in pre- and post-treatment biopsies were noted on routine histology. The authors reported that laser hair reduction using the 1064 nm Nd- YAG laser hair removal provides subjective and objective improvements in patients with focal axillary hyperhidrosis.

In 2015, Leclère et al. (27) evaluated the efficacy of the use of a laser diode device emitting at wavelengths of 924 and 975 nm and classical curettage either alone, simultaneously or in combination. A randomized prospective controlled trial was carried out on 100 patients divided into 4 groups, each with a different protocol: Laser alone at 975 nm (group 1), laser alone at 924/975 nm simultaneously (group 2), curettage alone (group 3), and finally laser at 924/975 nm followed by curettage (group 4). HDSS, starch test and GAIS were used to assess treatment efficacy. The follow-up extended up to one year. Statistical analysis (SPSS) was used to determine the accuracy of the results. Two patients of group 1 experienced burns during treatment, which took over a month to heal. This group of patients achieved the worst results: The starch test scale results after treatment were 2.48 ± 0.51 and 2.76 ± 0.44 (at 1 and 12 months). The GAIS results were 1.04 ± 0.35 and 0.92 ± 0.28 (1 and 12 months). In group 2 the starch test scale results after treatment were 1.36 ± 0.49 and 1.48 ± 0.51 (at 1 and 12 months). The GAIS results were 2.36 ± 0.49 and 2.72 ± 0.46 (at 1 and 12 months). In group 3, the starch test scale results after treatment were 1.56 ± 0.51 and 1.76 ± 0.60 (at 1 and 12 months), which corresponds to small to substantially smaller dark areas. The GAIS results were 2.28 ± 0.46 and 2.64 ± 0.49 (at 1 and 12 months). The best results were obtained in group 4: HDSS scores were reduced from 3.88 ± 0.33 before treatment to 1.24 ± 0.44 and 0.48 ± 0.51 at the 1 and 12 months' controls. The starch test scale results after treatment were 0.40 ± 0.50 and 0.44 ± 0.51 (at 1 and 12 months). The GAIS results were 3.72 ± 0.54 and 3.76 ± 0.44 (at 1 and 12 months). The study concluded that the laser at 924/975 nm combined with curettage was determined to be the optimal treatment option of those tested for axillary hyperhidrosis. This treatment was safe, with few side effects and improvement that persisted to the one-year follow-up.

In a clinical evidence search, current through December 1, 2022, UpToDate for evidence that stated laser therapy can be useful for the treatment of axillary hyperhidrosis. "Further study is necessary to determine the role of these therapies." (28)

Section Summary: Subdermal Laser Treatments

Laser therapy has been proposed as a potential method to treat hyperhidrosis by disrupting the cellular integrity of sweat glands. Most studies have small sample sizes (n=1-18) and lack data on long term health outcomes. Currently, there is insufficient evidence to determine whether or not this treatment method is effective. Additional randomized studies with a larger number of subjects are needed to evaluate the efficacy of laser therapy treatment with greater certainty.

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 policy.

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 (e.g., 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. (29) 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 policy.

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 (e.g., 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. Deng et al. (2011) published a meta-analysis of data from RCTs and observational studies published through 2010 that evaluated endoscopic thoracoscopic sympathectomy for patients with palmar hyperhidrosis. (30) Reviewers pooled outcomes data from different approaches to sympathectomy (i.e., 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) approaches and T3-4 (2 studies) had the "best" clinical efficacy (i.e., 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 (i.e., <100 patients). For example, Baumgartner et al. (2011) in the United States studied 121 patients with disabling palmoplantar hyperhidrosis. (31) 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 (i.e., 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 (0-10 severity scale) was 4.7 for the T2 group and 3.8 for the T3 group (p=NS). 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=0.09). Yuncu et al. (2013) in Turkey randomized 60 patients with axillary hyperhidrosis to T3-4 surgery (n=17) or to

T3 surgery (n=43). (32) 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. (33-36) 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, Karamustafouglu et al. (2014) in Turkey reported on 80 patients with primary hyperhidrosis (axillary and/or palmar). (34) 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. (33) Thirty days after surgery, 1531 (88%) of 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). (37) 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. (38) 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). (39) 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 11-19 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. (40)

<u>Section Summary: Endoscopic Transthoracic Sympathectomy</u>

RCTs 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 policy.

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 (e.g., 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. (41) 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. (42) 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. (43) 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 policy.

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 (e.g., glycopyrronium, aluminum chloride) and treatment of the underlying cause (e.g., 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
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. (44) 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 policy.

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 (e.g., glycopyrronium, aluminum chloride) and treatment of the underlying cause (e.g., 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) (45) and de Bree et al. (2007) (46) 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.

In 2020, Marchese et al. conducted a prospective, observational study on 18 patients (53). Symptoms were assessed symptom severity before therapy, after 15 days, 1, 3 and 6 months' follow-up with the sweating-flushing-itch-paresthesia-pain (SFIPP) Frey scale. Before botulinum neurotoxin A (BoNT-A) injection, all patients (100%) complained gustatory sweating, 80% paresthesia, 77% gustatory flushing, 60% pain and 60% gustatory itch. The SFIPP-Frey overall score and the symptom-specific ones decreased significantly at each post-therapy control. The gustatory sweating is the most severe followed by paresthesia and flushing. The preauricular and temporal areas were the most frequently affected. The BoNT-A treatment reduced the syndrome severity and its effect lasted in average 8 months. The clearest improvement was observed for gustatory sweating that, however, 6 months after BoNT-A therapy remained the predominant symptom. The prevalence of “unusual” manifestations is not negligible. BoNT-A improves symptoms severity. The SFIPP-Frey scale may be useful to assess symptoms and to monitor post-therapy outcomes.

Section Summary: Tympanic Neurectomy for Secondary Gustatory Hyperhidrosis

Prospective observational studies and several literature reviews support the use of tympanic neurectomy for patients with severe gustatory sweating. Intracutaneous injection of botulinum toxin A is an effective, long-lasting, and well-tolerated treatment of Frey syndrome in cases of secondary gustatory hyperhidrosis.

Summary of Evidence

Primary Focal Hyperhidrosis

Iontophoresis

For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive iontophoresis, the evidence includes a systematic review, a randomized controlled trial (RCT), and case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The RCT found that iontophoresis was less effective than botulinum toxin in the short-term treatment of palmar hyperhidrosis. Additional RCTs are needed comparing iontophoresis with sham or active treatment in patients with various types of primary focal

hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Botulinum Toxins
For individuals who have primary axillary hyperhidrosis who receive botulinum toxin, the evidence includes systematic reviews and RCTs. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Meta-analyses showed that botulinum toxin injections significantly decreased sweating and significantly improved Hyperhidrosis Disease Severity Scale (HDSS) scores by as much as 55%. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome. To date, OnabotulinumtoxinA is the only botulinum toxin product that is U.S. Food and Drug Administration approved for treatment of adults with severe axillary hyperhidrosis inadequately managed by topical agents.

For individuals who have primary palmar hyperhidrosis who receive botulinum toxin, the evidence includes RCTs. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Placebo-controlled randomized trials have generally found better outcomes in the botulinum toxin groups. RCTs comparing botulinum toxin formulations in patients with primary palmar hyperhidrosis have generally found no significant differences in outcomes. Also, a high rate of adverse events was reported. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome. Currently botulinum toxin, on or off label, is not United States FDA approved for the use in patients with palmar hyperhidrosis.

For individuals who have primary plantar hyperhidrosis who receive botulinum toxin, the evidence includes no RCTs. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. RCTs are needed comparing botulinum toxin with placebo or active treatment in patients who had primary plantar hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes. There is no botulinum toxin product, on label or off label, that is U.S. Food and Drug Administration approved for the treatment of primary plantar hyperhidrosis.

Microwave Treatment
For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive microwave treatment, the evidence includes a systematic review, a RCT, and a case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The systematic review and RCT found a short-term benefit of microwave treatment in reducing hyperhidrosis but also reported skin-related adverse events (e.g., pain, altered sensation). Additional RCTs are needed comparing microwave radiofrequency ablation with sham or active treatment in patients with various types of primary focal hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

Radiofrequency Ablation

For individuals who have primary focal hyperhidrosis (i.e., axillary, palmar, plantar, craniofacial) who receive radiofrequency ablation, the evidence includes 2 small RCTs and a nonrandomized cohort study. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. One nonrandomized comparative study found RFA inferior to surgical sympathectomy for patients with severe bilateral palmar hyperhidrosis resistant to conservative treatment. Two small RCTs that compared RFA to botulinum toxin in patients with palmar or axillary hyperhidrosis had conflicting results. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Subdermal Laser Treatment

For individuals who have auxiliary hyperhidrosis who receive subdermal laser treatment, the evidence includes small size studies. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Most studies have small sample sizes (n=1-18) and lack data on long-term health outcomes. Additional randomized studies with a larger number of subjects are needed to evaluate the efficacy of laser therapy treatment with greater certainty. The literature is insufficient to determine the effects of the technology on health outcomes.

For individuals with secondary gustatory hyperhidrosis, subdermal laser treatment has not been proven to effective. The mechanism of hyperhidrosis is not based on excessive sweating but on damage to secretory parasympathetic fibers of the facial nerve. The evidence is insufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Surgery

For individuals who have primary axillary hyperhidrosis who receive surgical excision of axillary sweat glands, the evidence includes review articles. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The evidence has shown that excision is highly effective, and this treatment is considered standard of care for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary axillary and palmar hyperhidrosis who receive endoscopic transthoracic sympathectomy, the evidence includes several RCTs, a meta-analysis, and case series. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The meta-analysis found a high rate of clinical efficacy after endoscopic transthoracic sympathectomy, although the rate of postoperative compensatory sweating was substantial. Subsequent studies have supported these findings. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary plantar hyperhidrosis who receive lumbar sympathectomy, the evidence includes 1 RCT conducted at a single center in Brazil, case series, and a systematic review. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. Case series have reported high rates of clinical efficacy, but findings are inconclusive due to lack of control groups. The RCT was limited by its small sample size and lack of blinded outcome

assessment. Moreover, there have been substantial rates of compensatory sweating and concerns about adverse events on sexual functioning. The evidence is insufficient to determine the effects of the technology on health outcomes.

Secondary Gustatory Hyperhidrosis

For individuals who have severe secondary gustatory hyperhidrosis who receive iontophoresis or botulinum toxin, the evidence includes uncontrolled studies and systematic reviews. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The systematic reviews did not identify any relevant RCTs. RCTs are needed to evaluate the safety and efficacy of these treatments for severe secondary gustatory hyperhidrosis. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have severe secondary gustatory hyperhidrosis who receive tympanic neurectomy, the evidence includes uncontrolled studies and systematic reviews. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. This treatment has high success rates, without the need for repeated interventions, and is considered standard of care for this indication. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have secondary gustatory hyperhidrosis, the evidence is extremely limited. Relevant outcomes are symptoms, quality of life, and treatment-related morbidity. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements

Society of Thoracic Surgeons (STS)

In 2011, the STS published an expert consensus statement on the surgical treatment of hyperhidrosis. (47) 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/m^2;
- No sweating during sleep;
- No significant comorbidities;
- Resting heart rate <55 beats per minute.

American Academy of Neurology (AAN)

In 2008, the AAN issued guidelines on the use of botulinum toxin for the treatment of autonomic disorders and pain. (48) These guidelines were updated in 2013. (49) Table 4 summarizes the recommendations for botulinum toxin injection as a treatment of hyperhidrosis, by site and type of toxin:

Table 4. 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 (NICE)

In 2014, the NICE issued guidance in 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. (50)

The Institute also issued guidance in 2014 on endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb. (51) 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. (52) The guidance stated that there is inadequate evidence in both quantity and quality to evaluate the safety and efficacy of microwave ablation.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 5.

Table 5: Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
Unpublished			
NCT03433859	Prospective Multicentric Open Randomised Controlled Trial Comparing Topical Aluminium Chloride to OnabotulinumtoxinA Intradermal Injections in Residual Limb Hyperhidrosis (Lower Limbs)	54	Mar 2021
NCT01930604	Botulinum Toxin Treatment in Craniofacial, Inguinal, Palmar, Plantar and Truncal Hyperhidrosis, a Randomized, Double Blind, Placebo Controlled Study	588	Oct 2019 (status unknown)
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
Ongoing			
NCT02295891	Microwave Energy-induced Thermolysis of Axillary Apocrine Glands and Hair Follicles Will Result in Improvement of Secondary Psychopathology Related to Hyperhidrosis	24	Nov 2023
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
NCT05737914	Bilateral Endoscopic Thoracic T3 Sympathectomy Versus T3 Radiofrequency Ablation for Treatment of Primary Palmar Hyperhidrosis	68	Oct 2023
NCT05057117	Longevity of Microwave Thermolysis and Botulinum Toxin A for Treatment of Axillary Hyperhidrosis: a Randomized Intra-Individual Trial	30	Jul 2023

Table Key: NCT: national clinical trial

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	11450, 11451, 32664, 64650, 64653, 64802, 64804, 64809, 64818, 64820, 64823, 69676, 95873, 95874, 97033
HCPCS Codes	E1399, J0585, J0586, J0587, J0588, J3490

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/15/2024	Reviewed. No changes.
02/01/2024	Document updated with literature review. The following change was made in Coverage: Added radiofrequency ablation as experimental, investigational, and/or unproven for plantar hyperhidrosis. Added references 11, 13 and 53; others updated.
10/15/2022	Reviewed. No changes.
12/01/2021	Document updated with literature review. Coverage unchanged. Added references 5, 12, 15, 20-21, 36, 39-41, 49 and 51. Others removed.
10/01/2020	Reviewed. No changes.
09/15/2019	Document updated with literature review. The following change was made in Coverage: Added radiofrequency ablation as experimental, investigational, and/or unproven for primary focal hyperhidrosis (axillary and craniofacial). Added references 6, 11 21, 37-39, 48, and 50.
11/15/2017	Document updated with literature review. Coverage unchanged.
05/10/2017	The following changes were made to Coverage on Table 1: 1) Removed the following bullet from palmar section: “OnabotulinumtoxinA product for severe primary palmar hyperhidrosis inadequately managed with topical agents, in patients 18 years and older;” 2) Removed parenthetical description of conservative treatment under both axillary and palmar sections.
02/15/2017	Document updated with literature review. The following changes were made to Coverage: 1) Added the word "despite" to the primary focal hyperhidrosis medically necessary criteria to state "History of persistent eczematous dermatitis despite medical treatments with topical dermatologic or systemic anticholinergic agents." 2) Added "and older" to the medically necessary criteria for palmar hyperhidrosis to state "OnabotulinumtoxinA product for severe primary palmar hyperhidrosis inadequately managed with topical agents, in patients 18 years and older" 3) Removed symbol ”>” to state “in patients 18 years and older” 4) Removed aluminum chloride 20% from the Coverage section.
12/15/2015	Document updated with literature review. The following was added to Coverage: Subdermal laser treatment is experimental, investigational and/or unproven for all primary hyperhidrosis and secondary hyperhidrosis. The word “secondary” was added to this statement: The following treatments may be considered medically necessary for the treatment of severe secondary gustatory hyperhidrosis.
03/01/2014	Document updated with literature review. The following was added to Coverage and may be considered medically necessary for the palmar region: 1) OnabotulinumtoxinA* for severe primary axillary hyperhidrosis that is inadequately managed with topical agents*, in patients 18 years and older.

	The following was added to Coverage as experimental, investigational, and/or unproven: 1) Microwave treatment for all regions; 2) Radiofrequency ablation for palmar region. CPT/HCPCS code(s) updated. Rationale revised.
11/01/2011	Document updated with literature review. CPT/HCPCS code(s) updated. The following was added: Tympanic Neurectomy may be considered medically necessary if conservative treatment has failed. Lumbar sympathectomy is considered experimental, investigational and unproven for Plantar Hyperhidrosis. The coverage statement for Instrumental Activities of Daily Living (IADL) was removed. The entire document was completely revised.
06/15/2008	Policy reviewed without literature review; new review date only. This policy is no longer scheduled for routine literature review and update.
08/01/2007	Revised/updated entire document
01/01/2006	CPT/HCPCS code(s) updated
10/01/2005	CPT/HCPCS code(s) updated
06/01/2005	New medical document originating from Bulletin
08/15/2003	Bulletin document originating from Medical Policy
11/01/2000	New medical document