Treatment of Hyperhidrosis

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

Primary Focal Hyperhidrosis

Iontophoresis

For individuals who have primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial) who receive iontophoresis, the evidence includes a systematic review, a randomized controlled trial (RCT), and case series. The relevant outcomes are symptoms, quality of life (QOL), 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 type A or B, the evidence includes RCTs and a meta-analysis. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. Placebo-controlled randomized trials have generally found better outcomes in the botulinum toxin groups. A meta-analysis showed that botulinum toxin injections significantly decreased sweating in the short (2 to 4 weeks) and long-term (16 weeks), and significantly improved Hyperhidrosis Disease Severity Scale scores. Several RCTs have compared different botulinum toxin type A formulations with botulinum toxin type A and B formulations in patients with axillary hyperhidrosis. Although these studies had small sample sizes, their findings suggested that, with appropriate dosage adjustments, there are similar levels of efficacy and adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary palmar hyperhidrosis who receive botulinum toxin type A, the evidence includes RCTs. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. Placebo-controlled randomized trials have generally found better outcomes in the botulinum toxin groups. RCTs comparing botulinum toxin type A formulations in patients with
primary palmar hyperhidrosis have generally found no significant differences in outcomes. Although these studies had small sample sizes, their findings suggested that, with appropriate dosage adjustments, there are similar levels of efficacy and adverse events. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have primary palmar hyperhidrosis who receive botulinum toxin type B, the evidence includes an RCT. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. One small placebo-controlled randomized trial did not clearly demonstrate the efficacy of botulinum toxin type B in patients with palmar hyperhidrosis. Also, a high rate of adverse events was reported. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have primary plantar hyperhidrosis who receive botulinum toxin type A or B, the evidence includes no RCTs. The relevant outcomes are symptoms, QOL, 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.

Microwave

For individuals who have primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial) who receive microwave treatment, the evidence includes a systematic review, an RCT, and case series. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. The RCT, conducted in patients with primary axillary hyperhidrosis, found a short-term benefit of microwave treatment vs sham therapy, but there was a high rate of skin-related adverse events. Additional RCTs are needed comparing 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 (ie, axillary, palmar, plantar, craniofacial) who receive radiofrequency ablation, the evidence includes a nonrandomized cohort study. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. The cohort study, conducted in patients with palmar hyperhidrosis, found a higher cure rate in the surgery group than in the radiofrequency ablation group and found a similar rate of compensatory sweating in both groups. RCTs are needed comparing 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.

Surgery

For individuals who have primary axillary hyperhidrosis who receive surgical excision of axillary sweat glands, the evidence includes review articles. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. The evidence has shown that excision is highly effective, and this treatment is considered the 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. The relevant outcomes are symptoms, QOL, 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 case series. The relevant outcomes are symptoms, QOL, and treatment-related morbidity. Case series have reported high rates of clinical efficacy but findings are inconclusive due to the lack of control groups. 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. The relevant outcomes are symptoms, QOL, 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. The relevant outcomes are symptoms, QOL, 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.

II. Policy Criteria

A. Treatment of severe primary focal hyperhidrosis is covered (subject to Limitations and Administrative Guidelines) when the patient has a documented history of debilitating hyperhidrosis that prevents him or her from performing essential activities of daily living and employment, or has any of the following medical conditions:

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

   Specific treatments for the primary focal hyperhidrosis regions listed below are covered (subject to Limitations and Administrative Guidelines) when all of the criteria listed in A above are met, as well as any specific criteria relevant to a particular area:

   1. Axillary regions:
      Aluminum chloride 20% solution;
Botulinum toxin for severe primary axillary hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older; and Endoscopic transthoracic sympathectomy (ETS) and surgical excision of axillary sweat glands, if conservative treatment (i.e., aluminum chloride or botulinum toxin, individually and in combination) has failed.

b. Palmar region:
   a. Aluminum chloride 20% solution;
   b. Botulinum toxin type A products for severe primary palmar hyperhidrosis that is inadequately managed with topical agents, in patients 18 years and older; and ETS, if conservative treatment (i.e., aluminum chloride or botulinum toxin type A, individually and in combination) has failed.

2. Plantar region: Aluminum chloride 20% solution

3. Craniofacial region:
   a. Aluminum chloride 20% solution and ETS, if conservative treatment (i.e., aluminum chloride) has failed.

Note: Aluminum chloride solution is approved by the FDA for treatment of primary hyperhidrosis. At least 1 botulinum toxin product is FDA-approved for treatment in adults of severe axillary hyperhidrosis that is inadequately managed by topical agents. See HMSA’s Botulinum Toxins policy for guidelines regarding coverage of botulinum toxin products for treatment of hyperhidrosis.

Table 1. The Hyperhidrosis Disease Severity Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>My sweating is never noticeable and never interferes with my daily activities</td>
</tr>
<tr>
<td>2</td>
<td>My sweating is tolerable but sometimes interferes with my daily activities</td>
</tr>
<tr>
<td>3</td>
<td>My sweating is barely tolerable and frequently interferes with my daily activities</td>
</tr>
<tr>
<td>4</td>
<td>My sweating is intolerable and always interferes with my daily activities</td>
</tr>
</tbody>
</table>

III. Limitations

For the majority of patients, treatment of primary hyperhidrosis will not meet HMSA’s payment determination criteria for medical appropriateness based on the lack of an essential functional impairment or medical complications associated with the condition. Treatment of hyperhidrosis for cosmetic reasons is not a benefit of HMSA plans and is therefore ineligible for coverage.

The treatments for the primary focal hyperhidrosis regions listed below are not covered because they are not known to be effective in improving health outcomes.

Axillary region:
   - Axillary liposuction;
   - Iontophoresis;
   - Microwave treatment; and
   - Radiofrequency ablation
Palmar region:
- Rimabotulinumtoxin B;
- Iontophoresis;
- Microwave treatment; and
- Radiofrequency ablation.

Plantar region:
1. Botulinum toxin;
2. Iontophoresis;
3. Lumbar sympathectomy
4. Microwave treatment; and
5. Radiofrequency ablation.

Craniofacial region:
1. Botulinum toxin;
2. Iontophoresis;
3. Microwave treatment; and
4. Radiofrequency ablation
5. Other treatments for severe secondary gustatory hyperhidrosis are not covered including, but not limited to botulinum toxin and iontophoresis.

IV. Administrative Guidelines
   A. Precertification is required for the codes listed below. To precertify, complete the CVS Precertification Form and fax the form to CVS Caremark at 1-866-237-5512, or use CVS’ Novologix online tool as indicated along with the required documentation.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0585</td>
<td>Injection, onabotulinumtoxinA, 1 unit</td>
</tr>
<tr>
<td>J0586</td>
<td>Injection, abobotulinumtoxinA, 5 units</td>
</tr>
<tr>
<td>J0587</td>
<td>Injection, rimabotulinumtoxinB, 100 units</td>
</tr>
<tr>
<td>J0588</td>
<td>Injection, incobotulinumtoxinA, 1 unit</td>
</tr>
</tbody>
</table>

   Precertification is not required HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

   A. Applicable Codes:
   Precertification is not required for the following codes. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.

<table>
<thead>
<tr>
<th>CPT Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>32664</td>
<td>Thoracoscopy, surgical; with thoracic sympathectomy</td>
</tr>
<tr>
<td>64650</td>
<td>Chemodenervation of eccrine glands: both axillae</td>
</tr>
<tr>
<td>64653</td>
<td>Other area(s) (e.g., scalp, face, neck), per day</td>
</tr>
<tr>
<td>69676</td>
<td>Tympanic neurectomy</td>
</tr>
<tr>
<td>ICD-10-CM Code</td>
<td>Description</td>
</tr>
<tr>
<td>L74.510-L74.519</td>
<td>Focal hyperhidrosis code range</td>
</tr>
<tr>
<td>L74.52</td>
<td>Secondary focal hyperhidrosis</td>
</tr>
<tr>
<td>R61</td>
<td>Generalized hyperhidrosis</td>
</tr>
<tr>
<td>ICD-10-PCS Code</td>
<td>Description</td>
</tr>
<tr>
<td>015L4ZZ</td>
<td>Surgical, peripheral nervous system, destruction, sympathetic nerve, percutaneous endoscopic</td>
</tr>
<tr>
<td>01BK3ZZ, 015L4ZZ</td>
<td>Surgical, peripheral nervous system, excision, head</td>
</tr>
</tbody>
</table>
V. Scientific Background

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.

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

The consequences of hyperhidrosis are primarily psychosocial. Symptoms such as fever, night sweats, or weight loss require further investigation to rule out secondary causes. Sweat production can be assessed with the Minor starch-iodine test, which is a simple qualitative measure to identify specific sites of involvement.

Treatment

A variety of therapies have been investigated for primary hyperhidrosis, including topical therapy with aluminum chloride, 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 the treatment of the underlying cause, such as discontinuing certain drugs or hormone replacement therapy as a treatment for menopausal symptoms.

Iontophoresis uses an 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 the underlying tissue. The benefits of this method would be an enhancement of treatment effects and a reduction in adverse events associated with systemic administration of the drug.
Botulinum toxin is a potent neurotoxin that blocks cholinergic nerve terminals, which prevents hyperstimulation of eccrine sweat glands that lead to excessive sweating. Therefore, intracutaneous injections have been investigated as a treatment of gustatory hyperhidrosis and focal primary hyperhidrosis, most frequently involving the axillae or palms. The drawback of this approach is the need for repeated injections, which have led some to consider surgical approaches.

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

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

Outcome Measures

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

Regulatory Status

Drysol™ (Person and Covey), an aluminum chloride (hexahydrate) 20% topical solution, was approved by the U.S. Food and Drug Administration (FDA) as an aid in the management of hyperhidrosis (axillae, palmar, plantar, craniofacial); it is available by prescription. Additional topical medicines approved by the FDA include Hypercare Topical and Xerac AC. Qbrexza™ (glycopyrronium) 2.4% topical cloth was FDA-approved for use in the treatment of primary axillary hyperhidrosis in 2018.

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

2000: RimabotulinumtoxinB (Myobloc®; Solstice Neurosciences)

2009: AbobotulinumtoxinA (Dysport®; Medicis Pharmaceutical)

2010: IncobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals).

None of the other botulinum toxin products is specifically approved for the treatment of hyperhidrosis.

The FDA (2009) 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.”

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

RATIONALE

This evidence review was created in July 1999 and has been updated regularly with searches of the MEDLINE database. The most recent literature updated was performed through October 18, 2018.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and 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 technology, two domains are examined: the relevance, and 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.

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).1, 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 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.

Iontophoresis for Treatment of Primary Focal Hyperhidrosis

Clinical Context and Therapy Purpose

The purpose of iontophoresis is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial).

The question addressed in this evidence review is: Does the use of iontophoresis improve the net health outcome for individuals who have any primary focal hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary focal hyperhidrosis.

Interventions

The therapy being considered is iontophoresis.

Comparators
The following therapies are currently being used to treat primary focal hyperhidrosis: topical antiperspirant, oral medication, and botulinum toxin.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary focal hyperhidrosis are actively managed by dermatologists in an outpatient 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.

Systematic Reviews

The Wade et al (2017) systematic review identified 10 studies using iontophoresis: 4 RCTs, 5 nonrandomized comparative studies, and a case series.1 All studies were rated as having a high or unclear risk of bias. Comparators differed across studies: placebo (three studies), botulinum (two studies), no treatment (two studies), and iontophoresis plus anticholinergic (two 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.

A TEC Assessment (2003) on iontophoresis for a variety of medical conditions concluded that the evidence was insufficient to determine whether its impact on the treatment of any hyperhidrosis exceed those of placebo or an alternative treatment.2 TEC Assessment investigators identified only 3 small studies (range, 10-60 patients), all of which were conducted in patients with palmar hyperhidrosis.
Randomized Controlled Trials

The RCT by Rajagopal et al. (2014) compared iontophoresis plus topical aluminum chloride hexahydrate with botulinum toxin injection but did not provide data on the efficacy of this therapy compared with placebo.3 The trial included 60 patients with a baseline Hyperhidrosis Disease Severity Scale (HDSS) score of 3 or 4 (see Appendix Table 1 for scoring).4 Patients were randomized to treatment with iontophoresis three times weekly or to one botulinum toxin injection in each hand, with two weeks between treatments. HDSS scores were recorded at four weeks; nonresponders were permitted to cross over 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 one of the six patients who crossed over to the iontophoresis arm showed improvement after a second, four-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 18.5 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.6 Patients received a minimum of 9 treatments over 21 days in a clinical setting. Twenty (80%) of the 25 patients for whom data were available after hospital administration of tap water iontophoresis reported a moderate or great amount of improvement in symptoms and a moderate or great improvement in the QOL.

Section Summary: Iontophoresis for Treatment of Primary Focal Hyperhidrosis

There is insufficient evidence that iontophoresis is an effective treatment of primary focal hyperhidrosis. A systematic review of ten studies suggested a potential benefit of iontophoresis; however, the studies had either low or unclear risk of bias. The single RCT among the ten 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.

Botulinum Toxins for Treatment of Primary Axillary Hyperhidrosis

The 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.1 Fourteen studies were considered high-risk of bias, eight studies unclear risk, and one 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
Treat ment of Hyperhi drosis

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, five palmar hyperhidrosis, and two studies reported on treating axillary and/or palmar hyperhidrosis. Meta-analyses were conducted on studies comparing botulinum type A with placebo for the treatment of axillary hyperhidrosis and all estimates favored the botulinum injections: reduction in HDSS score of 2 or more points: 3.3 (95% confidence interval [CI], 2.5 to 4.4); reduction in sweating by 50% or more at 2 to 4 weeks (3.3; 95% CI, 1.9 to 5.5); reduction in sweating by 75% or more at 2 to 4 weeks (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 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; however, there was a high incidence of adverse events reported with botulinum type B.

A retrospective chart review by Mirkovic et al (2018) focused on children receiving botulinum toxin for hyperhidrosis. Children receiving at least 1 botulinum treatment were included (n=323); mean age was 15 years (range, 5-17 years). Sixty percent of the children received more than one 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.

Several RCTs have addressed botulinum toxin injections in adults as treatment of axillary and palmar hyperhidrosis. The discussion below is grouped by hyperhidrosis site and toxin type as dictated by trial.

Clinical Context and Therapy Purpose for Treating Primary Axillary Hyperhidrosis with Botulinum Toxin Type A or B

The purpose of botulinum toxin type A or B is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary axillary hyperhidrosis.

The question addressed in this evidence review is: Does the use of botulinum toxin improve the net health outcome for individuals who have primary axillary hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary axillary hyperhidrosis.

Interventions

The therapy being considered is botulinum toxin type A or B.

Comparators

The following therapies are currently being used to treat primary axillary hyperhidrosis: topical antiperspirant and oral medication.
Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary axillary hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Botulinum Toxin vs Placebo

One of the larger RCTs was published by Lowe et al (2007).8 This industry-sponsored, multicenter, double-blind, placebo-controlled trial evaluated the efficacy and safety study of botulinum toxin type A 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 (see Appendix Table 1). A total of 322 patients were randomized to botulinum toxin type A (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 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.10 Like another Baumann et al (2005) trial (reported below), this RCT did not address whether patients had failed previous treatments for hyperhidrosis. 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 the efficacy for the 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. Mean length of time to return to baseline sweating levels in these 18 patients was 151 days (range, 66-243 days). Sixteen patients reported 61 adverse events during the study. Five (8%) of 61 adverse events were determined to be trial related (4 axillary bruising events, 1 instance of injection-site pain). Eleven (18%) adverse events were determined to be probably related to the trial (dry eyes [n=3], dry mouth [n=5], indigestion [n=3]). Flu-like symptoms were reported by 6 (30%) of 20 patients; however, the trial period coincided with flu season.

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

A small, double-blind RCT, published by Talarico-Filho et al (2007), included 20 patients with primary axillary hyperhidrosis who had sweat production greater than 50 mg/min. Patients received injections of 2 types of botulinum toxin A: onabotulinumtoxinA 50 U in 1 axilla and abobotulinumtoxinA 150 U in the other. Outcomes did not differ significantly between groups (eg, sweat rate was reduced by a mean of 98% in the onabotulinumtoxinA group and 99% in the abobotulinumtoxinA group; p>0.05).

Comparison of Botulinum Toxin Type A with Type B

A few RCTs have compared botulinum toxin types A with B in patients who had primary axillary hyperhidrosis. An RCT by An et al (2015) randomized 24 patients with symmetrical axillary hyperhidrosis to injections of onabotulinumtoxinA 50 U in 1 axilla and rimabotulinumtoxinB 1500 U in the other (ie, a conversion rate of 1:30 was used). Baseline HDSS scores were 2 (n=9), 3 (n=14), and 4 (n=1); those who scored 3 or 4 were categorized as having severe axillary hyperhidrosis. The primary efficacy outcome (the proportion of patients with an HDSS score of 1 or 2 at the 2-week follow-up) was 100% in each group (p=1.00). At 12 weeks, all patients maintained a score of 1 or 2 on the HDSS (p=1.00), and at 20 weeks, 80% in each group had an HDSS score of 1 or 2 (p=1.00). A decrease of 2 or more points from baseline on the HDSS was reported at week 2 in 86.7% in each group (p=1.00); at week 12, the same decrease was reported in 80.0% in the botulinum toxin type A group and 86.7% in the botulinum toxin type B group (p=0.64); and at week 20, the same decrease was only reported in 13.3% of the botulinum toxin type A group and 6.7% of the botulinum toxin type B group (p=0.56). No major systemic adverse events were reported in any patients.

Frasson et al (2011) conducted a small randomized trial of axillary hyperhidrosis treated with botulinum toxin type A and type B. This trial included ten patients with idiopathic focal axillary hyperhidrosis unresponsive to other nonsurgical treatments. Patients received onabotulinumtoxinA 50 U in 1 axilla and rimabotulinumtoxinB 2500 U in the contralateral axilla. Gravimetry was performed at baseline and follow-up as an objective measure of sweat production. At each follow-up point, the decrease in sweat weight from baseline was significantly greater on the type B side than on the type A side. For example, after 1 month, the sweat weight in 5 minutes was 13% of the baseline value on the type A side and 4% of the baseline value on the type B side (p=0.049). By 6 months, the sweat weight returned to 91% of baseline on the type A side and to 56% of baseline weight on the type B side (p=0.02). Findings were similar for the sweating area. All patients tolerated injections of types A and B well, and none reported systemic adverse events. This trial did use a higher dosage of botulinum toxin type B than previous studies.

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

Evidence from RCTs supports the efficacy and safety of botulinum toxin for treating axillary hyperhidrosis. Most studies evaluated type A for axillary hyperhidrosis and a meta-analysis of these studies showed that botulinum toxin type A reduced sweating in the short (2 to 4 weeks) and long-term (16 weeks) and improved HDSS scores by 2 or more points. Also, RCTs have found similar outcomes among different botulinum type A formulations and between botulinum type A and B for axillary hyperhidrosis.

Clinical Context and Therapy Purpose Treating Primary Palmar Hyperhidrosis with Botulinum Toxin Type A
The purpose of botulinum toxin type A is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary palmar hyperhidrosis.

The question addressed in this evidence review is: Does the use of botulinum toxin type A improve the net health outcome for individuals who have primary palmar hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary palmar hyperhidrosis.

Interventions

The therapy being considered is botulinum toxin type A.

Comparators

The following therapies are currently being used to treat primary palmar hyperhidrosis: topical antiperspirant and oral medication.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary palmar hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Comparison of Botulinum Toxin Type A with Placebo

Lowe et al (2002) conducted an RCT of 19 patients who received injections of botulinum toxin type A in 1 palm and placebo in the other.17, The mean percentage of sweat reduction in the toxin-treated palms was significant compared with baseline. The sweat reduction in the placebo-injected palms did not differ statistically from the baseline. Both physician and patient assessments showed significant improvements in the botulinum-injected palms compared with the placebo-injected palms.

Comparison of Different Doses of Botulinum Toxin Type A

Saadia et al (2001) conducted a single-blind (patients) randomized trial in which 24 patients received botulinum toxin type A 50 U or 100 U injected intradermally in 20 sites in each palm.18, Patients were evaluated every two weeks during the first month, then once every month up to six months. Both groups experienced significant improvements in sweat reduction by month one of follow-up, lasting through six months. Temporary adverse events included pain and soreness. No significant adverse events were associated with the treatment by the end of six months.
Comparison of Types of Botulinum Toxin Type A

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

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

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

Clinical Context and Therapy Purpose for Treating Primary Palmar Hyperhidrosis with Botulinum Toxin Type B

The purpose of botulinum toxin type B is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary palmar hyperhidrosis.

The question addressed in this evidence review is: Does the use of botulinum toxin type B improve the net health outcome for individuals who have primary palmar hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary palmar hyperhidrosis.

Interventions

The therapy being considered is botulinum toxin type B.

Comparators

The following therapies are currently being used to treat primary palmar hyperhidrosis: topical antiperspirant and oral medication.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary palmar hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

Randomized Controlled Trials

In a placebo-controlled, randomized trial, Baumann et al (2005) evaluated botulinum toxin type B for palmar hyperhidrosis. Like the Baumann et al 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 50000 U per palm, and 5 received a placebo. Nonresponders were offered an injection of botulinum toxin type B at day 30. At day 30, the 2 QOL 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=0.56). 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 Palmar Hyperhidrosis Treated with Botulinum Toxin Type B

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

Primary Plantar Hyperhidrosis Treated with Botulinum Toxin Type A or B

There is a lack of RCTs on the use of any botulinum toxin formulation for plantar hyperhidrosis.

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 for Treatment of Primary Focal Hyperhidrosis

Clinical Context and Therapy Purpose

The purpose of microwave treatment is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial).

The question addressed in this evidence review is: Does the use of microwave therapy improve the net health outcome for individuals who have any primary focal hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary focal hyperhidrosis.

Interventions

The therapy being considered is microwave treatment.

Comparators
The following therapies are currently being used to treat primary focal hyperhidrosis: topical antiperspirant, oral medication, and botulinum toxin.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary focal hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews

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

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

Randomized Controlled Trials

An RCT by Glaser et al (2012) evaluated a microwave device for treating primary focal hyperhidrosis.21 This device applied microwave energy to superficial skin structures with the intent of inducing thermolysis of the eccrine and apocrine sweat glands. This industry-sponsored, double-blind trial randomized 120 adults with primary axillary hyperhidrosis 2:1 to active (n=81) or sham (n=39) treatment. Treatment consisted of two sessions, separated by approximately two 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 two 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 endpoint was an HDSS score of 1 or 2 (see Appendix Table 1) 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 six 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. 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 Treatment of Primary Focal Hyperhidrosis

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

Radiofrequency Ablation for Treatment of Primary Focal Hyperhidrosis

Clinical Context and Therapy Purpose

The purpose of RFA is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary focal hyperhidrosis (ie, axillary, palmar, plantar, craniofacial).

The question addressed in this evidence review is: Does the use of RFA improve the net health outcome for individuals who have primary focal hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary focal hyperhidrosis.

Interventions

The therapy being considered is RFA.

Comparators

The following therapies are currently being used to treat primary focal hyperhidrosis: topical antiperspirant, oral medication, and botulinum toxin.
Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary focal hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Retrospective Studies

Purtuloglu et al (2013) evaluated 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 hydrosis was absent in 36 (75%) patients in the RFA group and 44 (96%) patients in the surgery group. The difference in outcomes between groups was statistically significant, favoring the surgical intervention (p<0.01). Six patients in each group reported moderate or severe compensatory sweating (p=0.78).

Section Summary: RFA for Treatment of Primary Focal Hyperhidrosis

One nonrandomized comparative study represents insufficient evidence to assess the use of RFA as a treatment of hyperhidrosis. In this single available study, RFA was inferior to surgical sympathectomy.

Surgical Interventions for Primary Axillary, Palmar, and Craniofacial Hyperhidrosis

Clinical Context and Therapy Purpose for Surgical Excision of Axillary Sweat Glands

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

The question addressed in this evidence review is: Does the use of surgical procedures improve the net health outcome for individuals who have primary axillary hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary axillary hyperhidrosis.

Interventions

The therapy being considered is surgical excision of axillary sweat glands.

Comparators
The following therapies are currently being used to treat primary axillary hyperhidrosis: topical antiperspirant, oral medication, and botulinum toxin.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary axillary hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews

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. 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.

Clinical Context and Therapy Purpose of Endoscopic Transthoracic Sympathectomy for Primary Axillary, Palmar, and Craniofacial Hyperhidrosis

The purpose of endoscopic transthoracic sympathectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary axillary, palmar, and craniofacial hyperhidrosis.

The question addressed in this evidence review is: Does the use of endoscopic transthoracic sympathectomy improve the net health outcome for individuals who have any primary axillary, palmar, and craniofacial hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals with primary axillary, palmar, and craniofacial hyperhidrosis.

Interventions

The therapy being considered is endoscopic transthoracic sympathectomy.
Comparators

The following therapies are currently being used to treat primary axillary, palmar, and craniofacial hyperhidrosis: topical antiperspirant, oral medication, and botulinum toxin.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary axillary, palmar, and craniofacial hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

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.25, Reviewers pooled outcomes data from different approaches to sympathectomy (ie, single-ganglia blockage [T2, T3, T4], multiganglia blockage [T2-3, T2-4, T3-4]). (Note that T refers to the rib.) Based on these analyses, reviewers concluded that T3 (11 studies) approaches and T3-4 (2 studies) had the “best” clinical efficacy (ie, postoperative resolution of symptoms). The T3 approach resulted in a 97.9% pooled efficacy rate, and the T3-4 approach resulted in a 100% pooled efficacy rate. In the studies for which data were available, the pooled rate of postoperative compensatory sweating was 40% after T3 surgery. Data on compensatory sweating after T3-4 surgery were available from only 1 study (60 patients); a pooled analysis could not be performed.

Randomized Controlled Trials

Subsequent RCTs have compared levels (rib location) of sympathectomy. These trials tended to have relatively small sample sizes (ie, <100 patients). For example, Baumgartner et al (2011) in the U. S. studied 121 patients with disabling palmar plantar hyperhidrosis.26, Patients were randomized to bilateral sympathectomy over T2 (n=61 patients) or T3 (n=60 patients). Six (5%) of 121 patients (3 in each group) were considered treatment failures (ie, had recurrent palmar sweating to a bothersome level). There were no significant differences between groups in the reported subjective change in plantar or axillary sweating after surgery. At six 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=N5). Similarly, at one 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).27, 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. 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). 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. 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). Both groups showed improvements in hyperhidrosis and QOL (>90%). De Campos et al (2017) assessed the QOL among 15 patients with palmar hyperhidrosis who were unresponsive following a thoracic sympathectomy and underwent a resympathectomy. QOL 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). Over 90% of patients in both groups reported a moderate or great reduction in hyperhidrosis following the procedure. Greater improvements in QOL were reported among the patients with craniofacial hyperhidrosis that was a secondary complaint, though both groups had improved QOL. A large proportion of patients (92%) reported compensatory hyperhidrosis.

**Section Summary: Endoscopic Transthoracic Sympathectomy for Primary Axillary, Palmar, and Craniofacial Hyperhidrosis**

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.

**Clinical Context and Therapy Purpose of Lumbar Sympathectomy for Primary Plantar Hyperhidrosis**

The purpose of lumbar sympathectomy is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with primary plantar hyperhidrosis.

The question addressed in this evidence review is: Does the use of lumbar sympathectomy improve the net health outcome for individuals who have primary plantar hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

**Patients**

The relevant population of interest are individuals with primary plantar hyperhidrosis.

**Interventions**

The therapy being considered is lumbar sympathectomy.
The following therapies are currently being used to treat primary plantar hyperhidrosis: topical antiperspirant and oral medication.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with primary plantar hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Case Series

No RCTs on the use of lumbar sympathectomy to treat primary plantar hyperhidrosis were identified but several case series were. Reisfeld (2010) reported on a study of bilateral endoscopic lumbar sympathectomy in 63 patients with focal plantar hyperhidrosis from a specialized hyperhidrosis clinic in the U.S.35, Thirteen (21%) patients were male and 50 (79%) were female. Clamps were placed at L3 (47%), L4 (52%), and L2 (1%). There was a learning curve with this procedure, and five early cases were converted to an open procedure. Fifty-six (89%) patients had previously undergone some form of thoracic sympathectomy, and all had tried conservative measures. After a mean follow-up of 7 months, all patients considered their plantar hyperhidrosis symptoms to be “cured” or “improved”; 97% reported “cure.” All patients with previous thoracic sympathectomy had some degree of compensatory sweating. After lumbar sympathectomy, 51 (91%) of the 56 patients reported that their compensatory sweating was unchanged. In the seven patients who did not have a previous thoracic sympathectomy, one reported mild, and six reported moderate compensatory sweating. Male patients reported no sexual problems; investigators did not report possible sexual problems among female patients.

A series by Rieger et al (2009) from Austria evaluated surgical results in 90 patients (59 men, 31 women with severe plantar hyperhidrosis).36, Thirty-seven (41%) patients had only plantar hyperhidrosis, and 53 (59%) had plantar and palmar hyperhidrosis. All patients had previously used other treatments including topical antiperspirant (ie, aluminum chloride). There were a total of 178 procedures, 90 on the right side and 88 on the left side. The technique involved resecting a segment of the sympathetic trunk between the third and fourth lumbar bodies together with the ganglia (L3 and/or L4). After a mean follow-up of 24 months (range, 3-45 months), hyperhidrosis was eliminated in 87 (97%) of 90 patients. Postoperative neuralgia occurred in 38 (42%) patients between the seventh and eighth day. The pain lasted less than 4 weeks in 11 patients, 1 to 3 months in 19 patients, 4 to 12 months in 5 patients, and more than 12 months in 3 patients. Three men reported temporary sexual symptoms; one was incapable of ejaculation for two months. None of the women reported postoperative sexual dysfunction.

It is worth noting that, unlike earlier concerns about this procedure being associated with risks of permanent sexual dysfunction in men and women, these case series found no instances of permanent sexual dysfunction. 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.37, To date, there are very few studies on endoscopic lumbar sympathectomy for focal plantar hyperhidrosis and no comparative studies.
Section Summary: Lumbar Sympathectomy for Primary Plantar Hyperhidrosis

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. There are insufficient data to conclude that any particular approach to surgery results in lower rates of compensatory sweating.

Iontophoresis or Botulinum Toxin for Severe Secondary Gustatory Hyperhidrosis

Clinical Context and Therapy Purpose of Iontophoresis or Botulinum Toxin for Secondary Gustatory Hyperhidrosis

The purpose of iontophoresis and botulinum toxin is to provide a treatment option that is an alternative to or an improvement on existing therapies in patients with severe secondary gustatory hyperhidrosis.

The question addressed in this evidence review is: Does the use of iontophoresis and botulinum toxin improve the net health outcome for individuals who have severe secondary gustatory hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is iontophoresis and botulinum toxin.

Comparators

The following therapies are currently being used to treat secondary gustatory hyperhidrosis: diet and topical medications.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with severe secondary gustatory hyperhidrosis are actively managed by dermatologists in an outpatient setting.

Study Selection Criteria

Methodologically credible studies were selected using the principles outlined for indication 1.

Iontophoresis
As noted in the section on primary focal hyperhidrosis, a TEC Assessment (2003) assessing iontophoresis for a variety of medical conditions concluded that the evidence was insufficient to determine whether iontophoresis for the treatment of any hyperhidrosis improves outcomes. Neither the TEC Assessment nor subsequent literature searches have identified any RCTs evaluating iontophoresis for gustatory hyperhidrosis.

Botulinum Toxin

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

Section Summary: Iontophoresis or Botulinum Toxin for Secondary Gustatory Hyperhidrosis

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

Clinical Context and Therapy Purpose for Tympanic Neurectomy for Secondary Gustatory Hyperhidrosis

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

The question addressed in this evidence review is: Does the use of tympanic neurectomy improve the net health outcome for individuals who have severe secondary gustatory hyperhidrosis?

The following PICOTS were used to select literature to inform this review.

Patients

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

Interventions

The therapy being considered is tympanic neurectomy.

Comparators

The following therapies are currently being used to treat severe secondary gustatory hyperhidrosis: diet and topical medications.

Outcomes

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

Timing

Follow-up would range from weeks to months for the outcomes of interest.

Setting

Patients with severe secondary gustatory hyperhidrosis are actively managed by dermatologists in an outpatient clinical setting.

Study Selection Criteria
Methodologically credible studies were selected using the principles outlined for indication 1.

Systematic Reviews

Review articles by Clayman et al (2006)39, and de Bree et al (2007)40, have described various medical and surgical treatments for Frey syndrome. Tympanic neurectomy has been described as a treatment, with satisfactory control reported in 82% of patients. Also, this surgical treatment is generally definitive without a need for repeated interventions.

Section Summary: Tympanic Neurectomy for Secondary Gustatory Hyperhidrosis

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

Summary of Evidence

Overwrite with Summary.

VI. Supplemental Information

Practice Guidelines and Position Statements

Society of Thoracic Surgeons

The Society of Thoracic Surgeons (2011) published an expert consensus statement on the surgical treatment of hyperhidrosis.41, 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 the time of surgery

- Body mass index <28 kg/m²,
· No sweating during sleep
· No significant comorbidities
· Resting heart rate <55 beats per minute

American Academy of Neurology

The American Academy of Neurology (2008) issued guidelines on the use of botulinum toxin for the treatment of autonomic disorders and pain. These guidelines were updated in 2013.42, Table 1 summarizes the recommendations for botulinum toxin injection as a treatment of hyperhidrosis, by site and type of toxin:

<table>
<thead>
<tr>
<th>Botulinum Toxin</th>
<th>Axillary</th>
<th>Palmar</th>
<th>Gustatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulinum neurotoxin type A</td>
<td>A</td>
<td>B</td>
<td>U</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>B</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>B</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td>U</td>
<td>U</td>
<td>U</td>
</tr>
</tbody>
</table>

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

The NICE (2017) stated that evidence is “inadequate in quantity and quality” on the use of transcutaneous microwave ablation for treatment of severe primary axillary hyperhidrosis.44,

The NICE (2014) issued guidance stating that there was sufficient evidence for the efficacy and safety of endoscopic thoracic sympathectomy for primary facial blushing to support the use of the procedure.45,

The NICE (2014) also issued guidance on endoscopic thoracic sympathectomy for primary hyperhidrosis of the upper limb.46, 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.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

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

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
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<tr>
<td>NCT01930604</td>
<td>Botulinum Toxin Treatment in Craniofacial, Inguinal, Palmar, Plantar and Truncal Hyperhidrosis</td>
<td>588</td>
<td>Oct 2017 (ongoing)</td>
</tr>
<tr>
<td>NCT02854540</td>
<td>Management of Palmar Hyperhidrosis with Hydrogel-based Iontophoresis</td>
<td>18</td>
<td>Aug 2018 (ongoing)</td>
</tr>
<tr>
<td>NCT02295891</td>
<td>MiraDry Treatment for Focal Axillary Hyperhidrosis (MiraDry Tx)</td>
<td>24</td>
<td>Jan 2019</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

VII. References


2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Iontophoresis for Medical Indications. TEC Assessments 2003; Volume 18, Tab 3.


47. Blue Cross Blue Shield Association Medical Policy Reference Manual Policy 8.01.19 Treatment