REPORT

Examining Hyperhidrosis: An Update on New Treatments

Carolyn I. Jacob, MD

ABSTRACT

Primary hyperhidrosis is a debilitating condition that causes significant distress and financial burden for affected patients, triggering them to seek medical care for their excessive sweating. Once a diagnosis of primary hyperhidrosis has been established, treatment is initiated to help control sweat production and increase quality of life. While there are no current guidelines in the United States for the treatment of primary hyperhidrosis, there are International Hyperhidrosis Society guidelines that clinicians can use. Currently, a step-therapy approach with the least invasive treatments prioritized first is recommended; the patient's reported disability should also be taken into consideration when selecting a first-line treatment. This update will discuss new treatment modalities, surgical procedures, associated comorbidities, and the impact on managed care of hyperhidrosis, so clinicians can tailor therapy, improve outcomes, and increase patient satisfaction.

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For author information and disclosures, see end of text.

Hyperhidrosis is defined as excessive sweating beyond what is physiologically required for the body to thermoregulate.[1] Excessive sweating can lead to significant impairment in the affected individual's social life, mental health, and work/study life.[1] Hyperhidrosis is classified as either primary or secondary, and determining the etiology is important for treatment. Primary hyperhidrosis is idiopathic and usually involves excessive sweating of axillae, palms, soles, face, scalp, or inguinal folds. Secondary hyperhidrosis results either from a medical condition or the use of medication and is focal or generalized. About 90% of hyperhidrosis cases are primary and affect the axillae.[2,3]

Recent studies indicate that the prevalence of Americans affected by hyperhidrosis is higher than originally determined. However, less than half of patients discuss the issue with their doctor.[3] The exact mechanism causing primary hyperhidrosis is not well understood. It is thought that increased or uncontrollable sympathetic stimulation (via acetylcholine) of the eccrine sweat glands may be responsible for the excessive sweating.[4] Furthermore, it is known that individuals with primary hyperhidrosis have a higher-than-normal basal level of sweat production and an increased response to normal stimuli such as stress.[4] Once a diagnosis of primary hyperhidrosis has been determined, treatment is initiated to help control the sweating and increase the patient's quality of life (QOL).

In the United States, there are no official guidelines for the treatment of hyperhidrosis. Therefore, most practitioners use the clinical guidelines of the International Hyperhidrosis Society (IHHS) with treatment algorithms for primary axillary, facial, gustatory, palmar, plantar, and generalized hyperhidrosis.[5] The IHHS recommends a step-therapy approach in which patients would use conservative therapies first and step up to more invasive treatments depending on their responses.[5]

Nonsurgical Treatment Options

The IHHS guidelines recommend the use of topical antiperspirants as first-line treatment of primary focal hyperhidrosis.[5] Patients with primary axillary hyperhidrosis often use nonprescription products

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(eg, zirconium salts), typically labeled as "clinical strength," with good success. Patients who do not achieve relief will often seek care from their healthcare professional for something more effective, such as prescription topical or oral pharmacologic agents. The most common agents used orally for the treatment of hyperhidrosis are anticholinergic medications that competitively inhibit acetylcholine at muscarinic receptors.[6] These agents work quickly, with most individuals seeing some improvement within a week of starting. Limitations of their use include large dose adjustments and subsequent adverse effects (AEs), such as xerostomia, blurred vision, sedation, and urinary retention.[6,7]

Topical and Systemic Agents

Aluminum chloride. Aluminum chloride (usually 20%) is a prescription antiperspirant that is a first-line treatment of axillary hyperhidrosis. The mechanism of action of aluminum chloride is 2-fold: obstruction of the eccrine sweat glands and destruction of the secretory cells.[1] Proper education for application of this product is important to improve efficacy and decrease irritation. For example, topical aluminum chloride should be applied nightly for 1 week on dry, sweat-free skin (left in place for 6-8 hours) until desired sweat reduction occurs.[5] Afterward, patients can extend the application interval to maintain their desired sweat control. The most common AE of aluminum chloride is skin irritation due to the formation of hydrochloric acid that results from the interaction between aluminum chloride and sweat present on the skin.[5] If irritation occurs, the patient may apply topical hydrocortisone cream and should be advised to decrease frequency of application of aluminum chloride.

Glycopyrrolate. Glycopyrrolate is used off label for the treatment of primary hyperhidrosis. Its approved indication is for adjunctive treatment for peptic ulcer disease and chronic drooling but is known to decrease sweat production. Glycopyrrolate competes with acetylcysteine at muscarinic receptors, causing anticholinergic effects.[8] Furthermore, because glycopyrrolate has a quaternary ammonium group, it is highly polar and cannot pass the blood–brain barrier, limiting its central nervous system effects. Multiple studies have evaluated the efficacy of glycopyrrolate in the treatment of hyperhidrosis.[8-13] For example, a 2012 study by Lee et al reported that glycopyrrolate (1 mg twice daily, then 2-8 mg/day) resulted in a 75% reduction in perspiration ($P < .0001$).[8] In addition, the Milanez de Campos scale showed a significant change in mean scores (57.9 compared with 38.7).[8] A 2017 systematic review by Cruddas et al was not able to collate outcome measures for glycopyrrolate due to too much variability.[14] Treatment doses ranged from a start of 1 mg every other day or daily to doses that were increased gradually to 6 mg per day. Dry mouth was reported in 38.6% (range, 27.8%-63.2%) of individuals taking glycopyrrolate.[14] For patients with craniofacial hyperhidrosis, pharmacy-compounded topical glycopyrrolate 2% can be used as a first-line treatment agent.[15,16] This product can be applied every 2 to 3 days; it has a 96% success rate and nominal AEs.[15,16]

Glycopyrronium tosylate. Glycopyrronium tosylate (GT) is an anticholinergic treatment approved by the FDA for axillary hyperhidrosis in June 2018.[17] It was the first therapy approved since miraDry and botulinum toxin (Botox) were approved for use.[18] A topical therapy applied once daily to the axillae using a premoistened cloth, GT (Qbrexza) is approved for use in the United States for patients 9 years and older.[19] In clinical trials, symptoms of sweating were improved as early as 1 week after starting treatment.[20] Furthermore, pooled trial results showed that after 4 weeks, sweating severity improved by about 32% (vs 5% with placebo).[20] AEs were mild to moderate and included dry mouth (16.9%-24.2%), erythema/area redness (17%), and burning/stinging (14.1%).[20,21] The ATMOS-1 and ATMOS-2 trials were replicate, randomized, double-blind, vehicle-controlled, 4-week phase 3 trials. Coprimary end points were responder rate (≥4-point improvement from baseline) on item 2 (sweating severity) of the Axillary Sweating Daily Diary (ASDD) along with absolute change from baseline in axillary gravimetric sweat production at week 4.[20] Pooled data from ATMOS-1 and ATMOS-2 showed that more GT-treated patients achieved ASDD item 2 response compared with vehicle (59.5% vs 27.6%) and had reduced sweat production from baseline (–107.6 mg/5 min vs –92.1 mg/5 min) at week 4 ($P < .001$ for both coprimary end points).[20] Fewer than 4% of participants discontinued use of GT due to AEs.

Propantheline. Propantheline bromide and methantheline bromide are 2 other agents that are commonly used off label for the treatment of hyperhidrosis. Evidence for propantheline bromide is anecdotal, as no trials support its efficacy.[14] However, it is still used as a secondary treatment for its anticholinergic properties. In addition, oral propantheline was studied by Danish researchers in the 1960s for the treatment of hyperhidrosis; it was found to be effective but had undesirable atropine-like AEs (eg, dry mouth and blurry vision).[22] Topical propantheline bromide 5% solution (equal parts ethanol and glycerol) was also found to be effective, especially for axillae and plantar hyperhidrosis, without the AEs seen with oral therapy.[22] More recently, a 2017 systematic review by Cruddas et al found reductions of 41% in axillary sweating and 16.4% in palmar sweating, and a 40.9% increase in the Dermatology Life Quality Index score with propantheline use.[14]

Oxybutynin. Oxybutynin is an FDA-approved muscarinic antagonist that is indicated for overactive bladder. Due to its anticholinergic properties, it is used off label for the treatment of primary hyperhidrosis and has been shown to be safe and effective.[23] A systematic review by Cruddas et al showed that oxybutynin 2.5 mg daily (up to 10 mg daily) improved symptoms by an average of 76.2% (range, 60%-97%) and also improved QOL in 75.6% (range, 57.6%-100%) of patients.[14] Dry mouth (the most common AE) occurred in 73.4%

(range, 43.3%-100%) of patients who were taking 10 mg/day. In addition, patients may experience constipation, urinary retention, tachycardia, blurry vision, and drowsiness. As a result of these associated AEs, about 11% of patients stop taking oxybutynin despite good control of hyperhidrosis.[14,24] In addition, there are many patients for whom oxybutynin would not be an appropriate treatment, such as geriatric patients and anyone with gastrointestinal disorders, urinary retention, or glaucoma.

Oxybutynin is now available in a different dosage form and/or combination that may be more tolerable. For example, transdermal oxybutynin was recently studied by Millán-Cayetano et al in oxybutynin-naïve patients and patients previously treated with oral oxybutynin.[23] The study had a small sample size, but results indicated that transdermal oxybutynin may be more effective in patients who have not previously taken oral anticholinergic drugs.[23] The authors concluded that larger studies are necessary to confirm their findings. Transdermal oxybutynin is available without a prescription. Patients should be counseled to rotate application sites and be informed that anticholinergic AEs usually are mitigated but are still possible with the transdermal patch.[25] Another randomized study evaluated the safety, efficacy, QOL impact, and dry mouth AE of THVD-102, a fixed-dose combination of oxybutynin (7.5 mg) and pilocarpine (7.5 mg) in patients with primary focal hyperhidrosis.[21] Results of the study showed no significant differences between THVD-102 and oxybutynin in primary focal hyperhidrosis. Furthermore, there was a statistically significant difference in reported dry mouth, with participants reporting less severe dry mouth with THVD-102 compared with oxybutynin.[21]

Other systemic agents. Antiadrenergics, clonidine, and propranolol may also be used off label in the treatment of hyperhidrosis.[14] For example, a case report of a 32-year-old man was reported in which 20 mg paroxetine (initiated at 10 mg) was prescribed, and after a month the patient reported a reduction in sweating and an improvement in socio-occupational function.[26] This improvement was sustained at 6 months follow-up with no reported AEs. The authors state that paroxetine's beneficial effect in palmar-plantar hyperhidrosis may be a result of its anticholinergic effect, or it may be secondary to its antianxiety mechanism of action via central mechanisms.[26] Similarly, clonidine, a centrally acting α-adrenergic receptor agonist, decreases sympathetic stimulation and was shown to be effective for primary hyperhidrosis.[27] A retrospective review showed 13 patients received clonidine (0.1 mg twice daily) and had a response rate of 46%.[27] Furthermore, β-blockers such as propranolol have positive anecdotal reports of efficacy for hyperhidrosis that results from emotional stimulus (eg, giving a presentation or speaking in front of a large number of people).[6,7]

Iontophoresis. Iontophoresis is the process by which an ionized substance (eg, water) is passed through the skin via direct electrical current. Tap water is poured into a device tray with a direct electrical current (15-20 mA) and then hands and/or feet are submerged for about 20 to 30 minutes.[1,7] The exact mechanism of action is not known, but theories include the clogging of eccrine sweat glands due to ion deposition, blockade of sympathetic nerve transmission, a decrease in pH due to accumulation of hydrogen ions, and a complex mechanism that involves changes in the reabsorption of ductal sodium.[28,29]

Iontophoresis has been shown to be effective (either in the first or second line) for the treatment of palmar and plantar hyperhidrosis.[4] This intervention may be performed at home, and AEs are typically mild (eg, erythema, vesiculation, paresthesia) and do not require discontinuing iontophoresis treatment. Iontophoresis usually is conducted 3 times a week until the desired sweat control is reached, and then maintenance is performed once per week.[1] Patients can add a tablespoon of baking soda or 2 to 4 tablets of glycopyrrolate to the tap water to improve efficacy.[27] Patients can apply petroleum jelly to damaged skin areas before submerging to protect the skin (eg, scratches/skin nicks, tender cuticles). If a patient's skin becomes irritated, they may apply hydrocortisone cream after treatment.

Injectable Agents

Botulinum toxin. Botulinum toxin type A (BoNTA) exerts its antisweat properties through the temporary blockade of cholinergic neurons in eccrine sweat glands that release acetylcholine.[30] It is used off label for the treatment of primary hyperhidrosis of the axillae, palms, soles, and face.[1] The safety, efficacy, and effect on health-related QOL was evaluated by Lowe et al in a long-term, placebo-controlled, double-blind study of BoNTA in patients with primary axillary hyperhidrosis.[30] This study randomized 322 patients to either 75 U or 50 U/axilla or placebo over 52 weeks. After 4 weeks, participants who received BoNTA reported a significant reduction in limitations of their activities of daily living, and 75% of them had a 2-point improvement on the 4-point Hyperhidrosis Disease Severity Scale (HDSS) compared with 25% in the placebo group ($P < .001$).[30]

Furthermore, there were no significant between-group differences in occurrence of AEs from the treatment intervention. Similarly, no participants discontinued the study due to AEs. The only reported AEs from treatment with BoNTA were injection-site pain (mean duration, 2.4 days), injection-site bleeding, and nonaxillary sweating.[30] BoNTA is administered intradermally to the affected area. When used for the axilla, 50 units per axilla are injected in 0.1-mL aliquots per cm^2.[2,31] The typical response time post injection is approximately 2 to 4 days and on average persists for 9 months.[31]

Botulinum toxin type B (BoNTB) also blocks acetylcholine release from cholinergic neurons.[32] A 2002 study by Dressler et al used 2000 MU or 4000 MU per axilla and found that BoNTB worked within 3 to 5 days, had a maximum effect about 1 to 2 weeks post

injection, and persisted for a minimum of 9 weeks to 16 weeks.[32] While botulinum toxin is generally well tolerated, approximately 25% of patients reported experiencing AEs post injection.[6]

The most common AE with palmar and plantar injections is pain.[6] Other AEs include localized hemorrhage, flulike symptoms, indigestion, and potential compensatory sweating at alternative sites of the body.[6] Furthermore, calcium channel blockers, aminoglycosides, quinine, and penicillamine are known to potentiate the effects of botulinum toxin and should not be used concomitantly.[33]

Medical Devices

Microwave technology is a nonsurgical treatment for hyperhidrosis that was developed to address the shortcomings of traditional treatments, such as short-term efficacy and poor tolerability.[34] The IHHS recommends microwave technology as a second-line treatment option in patients who do not respond to topical treatments.[5] As reported by Jacob in 2013, "microwaves lie in the electromagnetic spectrum between infrared waves (such as carbon dioxide lasers) and radio waves (radiofrequency devices) at 10^4-10^5 µm."[34]

Microwaves use dielectric heating to heat substances; electric dipole molecules rotate, and their rapid movement causes frictional heat. To reach the eccrine sweat glands, an antenna targets the skin–adipose interface where most of these glands reside.[34] A focal energy zone is created along the dermal–adipose, and continuous hydroceramic cooling prevents the conduction of heat superficially. This concentrated heat at the dermal–adipose zone causes thermolysis of the eccrine sweat glands. The only FDA-approved microwave technology device currently is miraDry, which uses cooling and suctioning for uniform treatment and prevents damage to surrounding tissues.[35,36]

The procedure typically entails 3 steps: (1) a template is applied to the axillary vault to guide the use of the handpiece later, (2) tumescent anesthesia is applied, and (3) the treatment is applied to a grid at predetermined points.[36] Five treatment settings are available for use. The upper part of the axilla is treated with level 1 (lowest setting) to avoid damage to the brachial plexus, and the rest of the treatment area is usually treated with level 5 (highest setting). Depending on the size of the axillae, 12 to 39 applications will be made to each axilla, and treatment time can vary from 25 to 40 minutes per axilla.[36] Previously, local anesthesia was used to numb the axillary vault because the procedure is painful. Depending on the size of the axillary vault, local anesthesia injections vary from 26 to 60 in each axilla and can also be quite painful. Therefore, tumescent anesthesia is now the preferred method, with 80 mL to 120 mL of epinephrine and 1% lidocaine (in saline) injected into each axilla. The use of tumescent anesthesia has several advantages: (1) the procedure is relatively painless, which allows for higher levels to be used on the device; (2) injury to the brachial plexus is less likely due to the high volume of saline/anesthetic that insulates the tissues; and (3) overall, less volume of anesthesia is used compared with local anesthesia.[36]

Almost all patients experience some AEs from the miraDry procedure, such as bruising and/or localized swelling. Patients may also experience local inflammation and subcutaneous nodules that normally disappear gradually. They are encouraged to take an oral anti-inflammatory (eg, ibuprofen) and apply cold therapy for the first 72 hours after the procedure. Most patients report discomfort that usually lasts for a few weeks (sometimes as long as 3-4 months) but generally does not impede their ability to carry out their activities of daily living.[36]

Fractionated microneedle radiofrequency. Fractionated microneedle radiofrequency is an emerging treatment option for axillary hyperhidrosis.[37,38] The procedure involves placing microneedles 2 to 3 mm under the skin and then applying radiofrequency energy. Data have shown that this treatment option decreases the HDSS score by at least 1 point in almost 80% of patients.[37,38]

Laser therapy. Laser therapy is commonly associated with varicose vein treatment or laser eye surgery. However, it has also been used for the treatment of hyperhidrosis because the laser can target, heat, and destroy sweat glands. The majority of data for use of lasers in hyperhidrosis are uncontrolled case reports with small sample sizes. Two studies evaluated 33 patients over 6 months and found that a single laser treatment significantly reduced underarm sweating.[39] Laser therapy can be expensive, and it can be difficult to find a provider who offers it. Insurance also may not cover it, and only certain healthcare providers are trained in how to administer the treatment. Lastly, patients who undergo laser treatment can experience swelling, bruising, and soreness.[39]

Surgical Treatment Options

Surgical treatment of hyperhidrosis is reserved as a last-line therapy option for patients with severe hyperhidrosis who have not responded adequately to any other treatments. Local surgical treatments, such as radical surgical excision, limited skin excision, liposuction, and curettage have been tried.[20,40,41] However, some (eg, radical surgical excision) can cause serious complications and can have high relapse rates several months post procedure.[42]

Endoscopic thoracic sympathectomy. Endoscopic thoracic sympathectomy (ETS) is the most invasive form of surgery available for the treatment of hyperhidrosis and is reserved for the most severe and debilitating cases.[43] ETS interrupts the upper thoracic sympathetic chain by clipping sympathetic nerves. It has been used for palmar, axillary, craniofacial, and sometimes plantar hyperhidrosis.[6] Although ETS typically reduces sweating in the problem area, it frequently causes serious, irreversible compensatory sweating, extreme hypotension, arrhythmia, and heat intolerance.[43] In a study conducted in Dallas, Texas, compensatory sweating occurred in more than 80% of patients undergoing ETS.[43] Patients must be

properly informed of the permanent risks and serious complications before consenting to obtain this therapy.

Managed Care Perspective for Hyperhidrosis

Impact on Health and QOL

Hyperhidrosis causes excessive sweating beyond what the body needs to normally produce. As such, studies from Germany, Brazil, and Japan have documented that 30% to 37.9% of patients with hyperhidrosis report being frequently or constantly bothered by their excessive sweating, which causes impairment in their mental health, activities of daily living, and study/work life.[44-46]

The impact of hyperhidrosis on QOL has been found to be equal to or greater than that of psoriasis, severe acne, Darier disease, Hailey–Hailey disease, vitiligo, and chronic pruritus.[47] In a study by Walling et al, those with hyperhidrosis had a greater risk (30% [with hyperhidrosis] vs 12% [without hyperhidrosis]) of skin infections, with overall risk of any cutaneous infection being significant (odds ratio, 3.2; 95% CI, 2.2-4.6; $P < .001$).[48] Patients with hyperhidrosis were also found to be at greater risk for fungal, bacterial, and viral infections at affected hyperhidrosis sites on the body.[48] Therefore, managing excessive sweating is necessary to prevent these associated infections.

A recent study by Kamudoni et al found that the burden experienced by patients with hyperhidrosis was similar regardless of where the excessive sweating on the body was occurring.[49] Furthermore, 17 major themes were identified that captured the impact of hyperhidrosis, covering all areas of daily life. For example, 69% of the study participants stated they had negative emotions from their hyperhidrosis and reported constantly worrying about noticeable sweat. The majority of participants also reported that their self-image was negatively affected, with low self-esteem and confidence. Furthermore, 50% of participants reported that hyperhidrosis restricts their life or makes them feel as if they have lost control. Performance at work or school was impacted by sweating among 63% of the study participants, and the majority also stated this was the most important impact of their condition. One-third of participants said they specifically chose careers that would accommodate their sweating. Additionally, some participants reported passing up job opportunities and said that hyperhidrosis has an impact on their career progression. In this same study, 40% of participants stated that hyperhidrosis causes them physical discomfort either from being in wet clothes all day, having wet feet, or sweat dripping into the eyes. Finally, 17% of participants reported having other skin conditions, such as sore and cracked skin from the constant dampness of hyperhidrosis.[49]

Kamudoni et al also found that 61% of participants stated their sweating influences what clothes they wear and which activities they enjoy, such as traveling to warm-weather destinations. Everyday activities (eg, holding objects, turning door handles, working with tools, driving) were also a challenge reported by the majority of study participants. Furthermore, most participants reported not being satisfied with the management of their hyperhidrosis. Study participants mainly reported concerns about poor relationships with clinicians, difficulty in obtaining an accurate diagnosis, and limited access to treatments that were effective without having AEs. In addition, participants reported the process of being diagnosed as humiliating and/or belittling due to clinicians not taking their sweating problems seriously. Study participants also cited that there was inadequate information available about their condition. This study by Kamudoni et al suggests that important healthcare needs are not being met for patients with hyperhidrosis.[49]

Managed Care Implications

Results of studies have shown that hyperhidrosis has a severe psychological impact on patients that affects all areas of their lives.[47,49] As a result, hyperhidrosis has the potential to increase direct and indirect healthcare costs due to increased risk of infections and other comorbidities, such as depression and associated skin infections. For example, Naumann et al indicated that 5% of individuals with hyperhidrosis reported taking antidepressants or antianxiety medications due to their excessive sweating.[50] Patients also report distress and constant worry about needing to control their sweating. It is important that clinicians are well informed about hyperhidrosis and its diagnosis as patients report frustration and humiliation with the diagnosis process. Patients may also experience financial burdens related to the costs of self-treating and to seeking care by healthcare providers for hyperhidrosis treatment. Many therapies and treatments are not covered by medical insurance and can cause a severe financial burden and/or psychological distress for patients who cannot afford to pay out-of-pocket for newer treatments that are effective and have fewer AEs. As newer treatments become available in the marketplace, it will be essential that those who make policy decisions follow treatment guidelines and consider the impact of hyperhidrosis on comorbidities and patient satisfaction.

Conclusions

Hyperhidrosis is a very debilitating condition that affects every aspect of a patient's life, often severely limiting QOL. Although there are no current guidelines in the United States for the treatment of primary hyperhidrosis, there are IHHS guidelines for clinicians. Currently, a step-therapy approach with the least invasive treatments prioritized first is recommended, and the patient's reported disability should also be taken into consideration when a first-line treatment is selected. To aid in this selection, results of multiple research studies conducted over the past decade have provided evidence for a variety of pharmacologic treatment options that have shown to be effective and reduce patient-reported disability. Furthermore, in the last 3 years, the FDA has approved new medical devices and a novel topical treatment that are efficacious in controlling sweating and improving patient satisfaction and are less

invasive. Hyperhidrosis can also cause comorbidities, such as depression and skin infections, which can drive up the costs of care and increase the economic burden on society. Treatment can be costly and often is not covered by a patient's insurance, which can cause financial burden and additional distress. As a result, it is essential that clinicians are educated on hyperhidrosis treatment, can tailor therapy to a patient's individual circumstances, and provide necessary education and support to help improve outcomes and patient satisfaction. ■

Author affiliations: Director, Chicago Cosmetic Surgery and Dermatology; affiliate clinical instructor, Northwestern University Feinberg School of Medicine, Chicago, IL.

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Address correspondence to: cjacob@chicagodermatology.com.

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