

Don't Sweat Hyperhidrosis: A Review of Current Treatment

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Excessive sweating (hyperhidrosis) is a frustrating problem for both the physician and patient. Easily underappreciated, this common skin disorder may be an occupational hazard and may adversely affect a patient's self-esteem and quality of life. A variety of therapeutic options now exist that allow for safe and effective treatment of hyperhidrosis. We discuss topical, systemic, and iontophoretic therapies, as well as botulinum toxin type A injections and surgical interventions for the treatment of hyperhidrosis.

Hyperhidrosis is defined as sweating that occurs in excess of what is needed for physiologic thermoregulation. Although occasionally seen in a generalized form affecting many areas of the skin, focally distributed hyperhidrosis is more common. Most studies estimate a general worldwide prevalence of hyperhidrosis of 0.6% to 1.0%.^{1,2} However, a recent study by Strutton et al³ suggests that hyperhidrosis may be underreported. They found that only 38% of individuals with this disorder sought professional care for their condition, reflecting a true prevalence of 2.8% in the US population.³

Hyperhidrosis can be categorized as either primary or secondary. Primary hyperhidrosis, also known as *idiopathic hyperhidrosis*, most often symmetrically affects the palms (Figure), soles, and/or axillae. Secondary hyperhidrosis can be focal or generalized and can result from a number of conditions. Local secondary hyperhidrosis often is due to a neurologic disorder such as peripheral neuropathy, stroke, or gustatory sweating. Generalized secondary hyperhidrosis may result from exposure to heat or humidity or as a result of exercise. It also may occur secondary to a febrile disease such as tuberculosis

or cancer or as a response to medications such as beta-blockers, tricyclic antidepressants, or cholinergic medications. Furthermore, familial dysautonomia (Riley-Day syndrome); sympathetic discharge from pain, shock, syncope, or drug withdrawal; and metabolic causes such as menopause, hypoglycemia, thyroid disorders, or pheochromocytoma⁴ have been implicated as causes of secondary hyperhidrosis.⁵

Physiologic sweating is important in maintaining thermoregulation, overall skin hydration, and fluid and electrolyte balance. Three types of sweat glands carry out these functions: eccrine, apocrine, and apoeccrine.⁶

Eccrine sweat glands are responsible for thermoregulation. These glands are located all over the body but are found in highest concentrations in the axillae, palms, and soles. Eccrine glands are physiologically active from birth and produce a watery secretion at a rate that varies with a person's body temperature, amount of exercise, and stress level. Enervation to the eccrine glands is sympathetic; however, the terminal neurotransmitter is acetylcholine rather than norepinephrine. Although eccrine glands also respond to adrenergic stimuli, it is not known how important this effect is in vivo.⁷

Apocrine glands are found in a limited distribution that occurs mainly in the axillae, areola, vermilion border of the lip, and the perineum. These glands secrete a cloudy white fluid whose function may be related to body odor and pheromones. Apocrine glands are present at birth but do not become active until puberty. These glands are enervated by both adrenergic and cholinergic systems

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Palmar hyperhidrosis.

(much like eccrine glands) and also may respond to circulating catecholamines.⁸

Apoeccrine glands are present only in hair-bearing regions of the axilla and have features of both eccrine and apocrine glands. The secretory coil of an apoeccrine gland resembles an apocrine gland; however, the duct opens on the surface of the skin, similar to the duct of an eccrine gland. In addition, apoeccrine glands produce copious watery secretions similar to those of eccrine glands. Although the function of apoeccrine glands is not well known, it is unlikely to be related to thermoregulation because these glands are only found in the axillae, which is a poor site for sweat evaporation due to the relatively small surface area. Apoeccrine glands become prevalent during adolescence and may comprise 45% of axillary glands by age 18 years. Because this is the age of peak onset for axillary hyperhidrosis, it has been suggested that apoeccrine glands may be implicated.⁸

Although the physiologic significance and implications of hyperhidrosis are relatively well described and understood, the psychological implications are underappreciated. Hyperhidrosis often interferes with multiple aspects of a person's life, ranging from establishing interpersonal relationships to confidently performing a number of work-related tasks. In a study by Naumann et al,⁹ a questionnaire was administered to 320 patients to assess quality-of-life issues related to their hyperhidrosis. Of the responders, 81.0% reported feeling limited in meeting people for the first time, 71.8% said they felt less confident than they would like, 67.0% reported feeling moderately limited in public places, and 44.6% altered their choice of leisure activities. Only about 20.0% of those polled reported feeling satisfied in their ability to

TABLE 1

Diagnostic Criteria for Focal Hyperhidrosis

Focal, visible, excessive sweating of at least 6 months' duration without apparent cause, with the patient exhibiting at least 2 of the following:

- Bilateral and relatively symmetric pattern
- Impairment of daily activities
- At least one episode per week
- Age of onset: >25 years
- Positive family history
- Cessation of focal sweating during sleep

confidently and adequately perform their work-related activities. Clearly, these psychological difficulties, which are the direct result of a specific physiologic affliction, can take an emotional toll. More than half of the patients in the study reported moderate to severe emotional damage due to their hyperhidrosis.⁹ Results of validated quality-of-life surveys have suggested that hyperhidrosis is comparable with diseases such as severe psoriasis, end stage renal disease, rheumatoid arthritis, and multiple sclerosis in terms of its negative psychological effects on an individual.¹⁰

Hyperhidrosis is typically a clinical diagnosis. If generalized hyperhidrosis is noted in the clinical setting, a thorough evaluation should be undertaken to determine the cause. For focal hyperhidrosis, a consensus panel suggests the diagnostic criteria outlined in Table 1.⁴

TREATMENTS FOR HYPERHIDROSIS

A number of treatments are available for hyperhidrosis including topical, systemic, and iontophoretic therapies, as well as botulinum toxin injections and surgical interventions (Table 2). Most patients should start with the least aggressive options before trying more invasive techniques. Before starting treatment, the physician should be certain the patient is educated in the proper use of over-the-counter antiperspirants, paying particular attention to the difference between antiperspirants and deodorants.

Topical Therapy

First-line treatment for focal hyperhidrosis generally consists of a trial of topical aluminum chloride hexahydrate

in absolute alcohol or salicylic acid gel.⁴ Conflicting opinions have been reported in the literature regarding the potential link between long-term exposure to aluminum or aluminum compounds and Alzheimer disease or other neurologic conditions. However, this link originally was suggested after patients who received long-term dialysis with fluids containing aluminum later demonstrated altered central nervous system signs and symptoms.¹¹ At present, whether this association is a true effect remains controversial. Furthermore, the minimal amount of aluminum chloride used in the topical application of antiperspirants is not believed to pose a risk of systemic absorption, and topical use of such products generally is regarded to be safe. Over-the-counter antiperspirants containing aluminum chloride 12% are helpful for most patients with mild symptoms. These antiperspirants work by physically occluding the sweat gland ducts and thereby serving as a barrier to the normal discharge of sweat from ductal openings. The antiperspirant should be applied to dry skin, typically at bedtime, when idiopathic hyperhidrosis is lowest, and washed off in 6 to 8 hours to minimize skin irritation. Initially, the antiperspirant should be applied every 24 to 48 hours until anhidrosis is achieved, at which point applications can be reduced to once every 1 to 3 weeks as needed for stabilization of symptoms.⁵ For patients with moderate symptoms, prescription-strength antiperspirants containing aluminum chloride hexahydrate 20% in anhydrous ethanol or aluminum chloride hexahydrate 6.25% are available. These agents have been shown to be effective in reducing excessive sweating, though they seem to provide better results for axillary hyperhidrosis than for palmar or plantar hyperhidrosis.¹²⁻¹⁵ The main side effect of these antiperspirants is skin irritation, which can be treated by reducing the frequency of application and alternating antiperspirant use with application of hydrocortisone 1% cream to the affected area.¹

Systemic Therapy

Systemic therapy for hyperhidrosis generally consists of the use of an anticholinergic medication such as glycopyrrolate or propantheline bromide. Anticholinergic drugs work by blocking cholinergic receptors in sweat glands. However, cholinergic receptors also are found on exocrine glands, autonomic ganglia, smooth muscle, cardiac muscle, as well as the sinoatrial node and atrioventricular node. Consequently, the use of such systemic medications may result in numerous untoward side effects, some of which may be serious (Table 3). Controlled studies using these drugs in the treatment of hyperhidrosis are limited, but anecdotal evidence sug-

TABLE 2

Treatment Options for Hyperhidrosis

- Topical therapy (eg, aluminum chloride)
- Systemic therapy (eg, anticholinergics, beta-blockers, anxiolytics)
- Iontophoresis
- Botulinum toxin injections
- Surgical intervention (eg, excision, curettage, liposuction, sympathectomy)

gests that side effects often are intolerable at the doses needed to achieve control of hyperhidrosis.^{5,16,17}

For hyperhidrosis induced by stress, administration of a low-dose beta-blocker such as propranolol may adequately reduce the effect of the emotional stimulus and consequent hyperhidrosis.⁵ Anxiolytics may be another option.

Iontophoresis

Iontophoresis, the application of a current to the skin, was introduced as a treatment for hyperhidrosis in 1952.¹⁸ Iontophoresis is thought to introduce ions of soluble salts and other molecules through the skin. The exact mechanism of action is debated, but a theory by Hill et al¹⁹ asserts that iontophoresis causes disruption of individual ion channels in the sweat glands and thus interferes with sweat secretion. It also is postulated that iontophoresis results in temporary superficial plugging of the eccrine glands because the application of tape to the skin followed by quick removal reverses the effect.²⁰

The most common iontophoresis devices sold in the United States for the treatment of hyperhidrosis are the Drionic[®] and the Fischer MD-1a. The Drionic is battery operated and available without a prescription. The more robust MD-1a is plugged into a standard wall outlet. Iontophoresis involves placing adequate amounts of tap or sterile water in a plastic basin to cover the hyperhidrotic areas of skin. Electrodes in the water basin allow passage of the electrical current. In our office, a specific sequence of instructions is always followed (Table 4). Some experts believe that anodes are more efficacious than cathodes and recommend that the direction of the current be switched periodically.²⁰⁻²² Treatment with a current of 15 to 20 mA per palm or

TABLE 3

Side Effects of Anticholinergic Medications

- Constipation
- Dry mouth
- Drowsiness
- Blurred vision
- Urinary retention
- Tachycardia
- Cardiac arrhythmia
- Cardiac arrest
- Heat stroke
- Dry eyes

sole for about 30 minutes per day has been shown to be effective.²¹

Iontophoresis therapy can be time-consuming initially because 3 to 4 treatments may be needed per week. However, after 10 treatments, improvement typically is seen and patients may be able to control their hyperhidrosis with maintenance treatments every 1 to 4 weeks.^{1,23} Iontophoresis seems to be effective in controlling symptoms in 85% to 90% of patients with palmar or plantar hyperhidrosis.²²⁻²⁵ For this reason, many physicians prefer iontophoresis to topical agents as a first-line treatment for palmar or plantar hyperhidrosis. However, the utility of iontophoresis in the treatment of axillary hyperhidrosis is limited because, though a special electrode is available for application to the axilla, the procedure remains difficult and often produces skin irritation severe enough to cause many patients to discontinue therapy.⁴

Although iontophoresis is a relatively safe procedure, it is contraindicated in patients with seizure disorders, electrical implants, or cancer, and in women who are pregnant. Adverse effects associated with iontophoresis include skin irritation, hyperesthesia, xerosis, and the development of vesicles or bullae in treated areas.²³ Skin irritation and dryness often can be controlled by reducing the number of treatments and applying moisturizing cream. Hydrocortisone 1% cream may be applied to ameliorate the minor inflammatory side effects associated with treatment.⁴ Iontophoresis has been shown to be safe for long-term use.²⁶

The efficacy of iontophoresis with anticholinergic agents (glycopyrronium bromide, poldine methylsulfate, or hexopyrronium bromide) added to tap water for the treatment of hyperhidrosis has been examined in several small trials. This method improves the efficacy of iontophoresis, with quicker results and longer duration. However, multiple side effects of the anticholinergic medications (including but not limited to dry mouth, blurry vision, urinary retention, constipation, and dry eyes) are seen in some patients.²⁷⁻²⁹ For this reason, iontophoresis with tap water alone should be attempted first; for those patients whose response is refractory to treatment with ordinary tap water alone, anticholinergic agents may be added.²³ Recently, Kavanagh et al³⁰ published case reports of 2 patients in whom iontophoresis was used to deliver botulinum toxin. Encouraging initial results were reported, though further investigations are needed to establish the efficacy of this novel approach.

Botulinum Toxin Injections

The gram-positive anaerobe *Clostridium botulinum* produces a potent neurotoxin that irreversibly blocks the release of acetylcholine from presynaptic nerve terminals near sweat glands and neuromuscular junctions. Specifically, it acts by cleaving synaptosomal-associated protein 25 kDa and preventing the release of acetylcholine from the presynaptic nerve terminal, which ultimately blocks the transmission of a successful secretory impulse by these glands. Doses are measured in units, with one unit being the amount lethal to 50% of mice. This toxin has been in use since 1980 to effect specific muscle blocks that are useful in the treatment of strabismus, dystonia, torticollis, and achalasia.³¹⁻³³ The first use of botulinum toxin for hyperhidrosis was reported in 1996,³⁴ and since that time, numerous studies have been done to assess this therapy.^{10,35-43} Although many commercial preparations of botulinum toxin are available worldwide, we have chosen to discuss only Botox® Cosmetic (botulinum toxin type A). A review of other preparations less commonly used in the United States is beyond the intended scope of this article.

Prior to treatment, visualization of the hyperhidrotic area can be done using the Minor starch-iodine test.²³ Iodine is applied to the skin followed by a thin layer of cornstarch. As sweat interacts with the starch, hyperhidrotic areas are visualized as dark regions. Hyperhidrotic areas can be delineated with a surgical marker to facilitate placement of the injection.

A typical dose for the axilla is 50 U of botulinum toxin type A injected over 12 to 18 sites.^{35,36} Because botulinum toxin type A is known to diffuse locally over a 0.5- to 1-cm² area of injection, placing injections approximately

TABLE 4

Instructions for Iontophoresis With the Fischer MD-1a Unit

1. Fill water trays
2. Connect cords from machine to trays
3. Remove all jewelry
4. Cover any cut with petrolatum
5. Place patient's left hand and foot in respective trays
6. Turn unit on
7. Gradually increase intensity to 15–18 mA as tolerated
8. Keep patient's hand and foot in the trays for 20 minutes
9. Gradually decrease intensity to zero
10. Repeat steps 4 to 9 with the patient's right hand and left foot

1-cm apart is reasonable for covering a treatment area. For palmar injections, a higher dose is necessary, usually 100 to 165 U per palm.³⁶⁻³⁸ The multiple injections needed to cover areas of hyperhidrotic skin can be painful, particularly on the palm. For this reason, regional topical anesthesia and/or an anesthetic nerve block should be provided. For axillary applications, topical anesthesia is sufficient. A median and ulnar nerve block should be considered for palmar and plantar injections.³⁹ This method does not affect the efficacy of botulinum toxin type A injections and reduces pain considerably compared with simply cooling the skin with an ice pack before treatment.⁴⁰

Multiple studies have demonstrated the safety and efficacy of botulinum toxin type A injections for the treatment of axillary hyperhidrosis.^{10,34-36,41,42} In the largest of these trials, 320 patients were randomized to receive either 50 U of botulinum toxin type A or placebo in both axillae.⁴¹ Patients who demonstrated a greater than 50% reduction in sweat production were defined as responders. At 4 weeks after the initial treatment, 94% of patients in the treatment group responded with a significant (50%; $P, .05$) reduction in sweat production compared with 36% of patients in the placebo group. The positive effect of therapy had a

demonstrable long-term effect. At week 16, 82% of treated patients were still classified as responders compared with only 21% of those randomized to placebo. Furthermore, patients in the treatment group rated their quality of life as significantly better ($P, .001$), and none of the patients reported serious side effects, such as muscle weakness.⁴¹ In a follow-up trial with 207 patients, the mean duration of symptom relief after botulinum toxin type A injection was 7 months; 28% of patients completed the entire study (16 months) and required only 1 treatment to achieve desired results.⁴²

Similar results have been shown for palmar hyperhidrosis.¹⁰ Most studies have reported relief of palmar hyperhidrosis for at least 4 months, with many patients remaining anhidrotic for 12 months or more.⁴³ The most noteworthy side effect in these studies was transient weakness of the intrinsic hand muscles.⁴³ Although this side effect generally is well tolerated, patients should be informed that they may experience minor temporary functional deficits in fine motor control of the hand.⁴ Furthermore, patients should be advised that these effects are transitory and typically resolve after a few days.

Surgical Intervention

Although the symptoms of most patients with hyperhidrosis are treated successfully with the aforementioned therapies, a small percentage of patients are unresponsive to these treatments. For this group, several surgical options are available. Direct removal of the sweat glands is possible via excision, curettage, or liposuction. Sympathectomy, another surgical intervention, interrupts the autonomic outflow to target sweat glands.

Excision of the skin—once considered a viable treatment option for axillary hyperhidrosis—typically is no longer performed because the large wound created by this procedure may lead to infection, severe scarring, and/or restricted arm movement.⁴⁴ In addition, a failure rate of approximately 10% to 20% is associated with this method.⁴⁵

Axillary sweat glands also can be removed through curettage or liposuction. These methods have the benefit of more long-lasting results than those achieved with botulinum toxin type A injections, and produce less scarring than local excision and fewer complications than sympathectomy.⁴⁶ Both curettage and liposuction have been shown to be effective treatments for hyperhidrosis.⁴⁶⁻⁵¹ However, Proebstle et al⁵¹ reported the successful use of curettage to remove sweat glands remaining after liposuction, suggesting that curettage may be a more thorough procedure than liposuction alone.

Another option for surgical therapy is sympathectomy. In this procedure, the surgeon denervates the affected

sweat glands by cutting or clipping the sympathetic trunk leading to that area (T2 for the face, T2 to T4 for palms, T4 for axillae). Sympathectomy has been shown to be effective in reducing hyperhidrosis, with many studies showing initial success rates of 95% to 100%.⁵²⁻⁵⁵ The advent of an endoscopic transthoracic approach to sympathectomy has reduced the morbidity seen with open surgery.²³ However, a number of side effects still are seen. Acute and potentially severe complications associated with this procedure include pneumothorax, hemothorax, bleeding from intercostal vessels, atelectasis, pneumonia, wound infection, and persistent intercostal pain. Fortunately, these complications combined occur in less than 2% of patients undergoing this procedure.^{1,56} Long-term complications are more common. Compensatory hyperhidrosis in other areas of the body may occur in nearly 90% of patients.⁵⁶ Most of these patients consider this side effect minor⁵⁷; however, in some surveys, up to 16% of patients ultimately regret having had the surgery.⁵⁸ Another study found that compensatory sweating occurs in 87% of patients treated with endoscopic thoracic sympathectomy. When questioned, 36% of affected patients described the compensatory hyperhidrosis as "serious" and 6% describe it as "incapacitating."⁵⁹ Other complications include gustatory sweating (in approximately 50% of patients) and Horner syndrome (in 2.5% of patients).⁵³ Relapse rates vary between 0% to 16%.¹⁰ Palmar hyperhidrosis is slightly more effectively treated than axillary hyperhidrosis after sympathetic block of T4 alone.⁶⁰ Given the high success rates and usually modest side effect profile, 90% of the patients in 1 study reported being "satisfied" or "very satisfied" after endoscopic thoracic sympathectomy.⁵⁹

Although sympathectomy is a successful treatment for hyperhidrosis, the numerous severe side effects associated with this procedure must be strongly considered. Given the number of successful and minimally invasive options, sympathectomy should be reserved for patients with a refractory response to other treatments and only after a thorough discussion of the possible complications.

CONCLUSION

Idiopathic hyperhidrosis, though not life-threatening, can result in serious physiologic, psychosocial, and occupational impairment for patients. A number of therapies exist for the treatment of this disorder, and each should be discussed with the patient in the context of his/her individual needs and goals. Treatment typically begins with a topical agent, though some physicians start with iontophoresis for patients with palmar-plantar hyperhidrosis. Systemic therapy may be considered, though it may be limited by side effects. Botulinum toxin type A injections

have proven to be an effective, albeit temporary, measure to control hyperhidrosis in many patients. Surgical intervention using curettage and/or liposuction generally is reserved for cases in which more conservative options have failed. Finally, sympathectomy, though effective, has many associated risks that must be weighed before this treatment is offered.

Many effective treatments are available for idiopathic hyperhidrosis. Most patients, with the help of their dermatologist, are able to find one that allows them to experience diminished symptoms and improved quality of life.

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