

Managing Hyperhidrosis Emerging Therapies



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KEYWORDS

- Hyperhidrosis • Topical botulinum toxin • Topical anticholinergics • Lasers • Ultrasound
- Radiofrequency

KEY POINTS

- Topical botulinum toxin A can be delivered through intact skin.
- Topical anticholinergic agents may provide efficacy with decreased adverse effects.
- Devices delivering energy such as lasers, ultrasound, and radiofrequency may reduce focal sweat.
- Limited data are available, and more research is needed.

INTRODUCTION

Treatment of severe axillary hyperhidrosis (HH) is limited to a few approved options. Botulinum toxin-A (BTX-A) injections provide temporary, albeit effective reduction in axillary sweating. Several surgical techniques have been used effectively for many years, but the invasiveness, down time, and adverse effects of such procedures are not ideal. Recently, the US Food and Drug Administration (FDA) approved a noninvasive microwave thermolysis device for axillary hyperhidrosis, which has shown long-term efficacy with minimal down time or adverse effects.^{1,2} Additionally, there is a real need for therapies targeting nonaxillary HH and secondary forms of HH such as those related to antidepressant medications and menopause. As newer technologies are developed and older technologies refined, there is a potential to develop more effective treatment options for HH.

Botulinum Toxins

Topical botulinum toxin

Although onabotulinum toxin-A (onaBoNT-A) is FDA-approved for the treatment of axillary HH, it

has been used effectively and safely to treat numerous hyperhidrotic areas. Multiple, repeat injections can be uncomfortable for some patients, especially in sensitive areas, such as the palms and soles. For these reasons, topical formulations of BTX-A are being developed and tested. A barrier to topical preparations is the large size of the botulinum toxin molecule. Revance Therapeutics, Incorporated (Newark, California), has developed a proprietary transport peptide that can be non-covalently coupled with the neurotoxin and successfully transport it across intact skin. A single, randomized, vehicle-controlled, within-patient comparison trial has been published with BTX-A (Botox, Allergan, Incorporated Irvine, California), 200 units in a proprietary vehicle delivery system in 12 patients.³ The BTX-A solution and control vehicle were mixed with Cetaphil (Galderma, Fort Worth, TX) cream and applied once to the respective axillae for 60 minutes. Gravimetrically measured sweat reduction at 4 weeks after treatment was 65%, compared with 25.3% in the vehicle-treated axilla.³ The 40% reduction in the quantitative sweat measurements was statistically significant ($P < .05$). There were no systemic adverse events, and no adverse events were considered to

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be related to the BTX-A treatment. Mild folliculitis, erythema, eczema, and tenderness were noted locally; all of these were seen in the vehicle-only axilla.³ Due to the small number of subjects, and short follow-up, long-term efficacy studies are warranted before topical BTX-A therapy can be accepted as an effective therapy for HH. Hopefully other body areas will be studied as well.

Topical Anticholinergics

Glycopyrrolate

First-line treatment for focal hyperhidrosis typically involves the use of aluminum chloride formulations, but their use has limited efficacy and is often irritating.⁴ There is a real need to find a less irritating topical alternative, and several anticholinergics are being investigated. It is unknown whether benefit is a result of a focal effect on the eccrine duct (such as a physical block or chemical alteration) or on the gland only, or possibly both.

Like other anticholinergic medications, glycopyrrolate inhibits the acetylcholine-induced activation of sweat glands. To avoid the systemic anticholinergic adverse effects, topical formulations (0.5% to 4% cream, gel, solution, or pads) of glycopyrrolate have the potential to treat several different types of hyperhidrosis and several different body areas. Few case reports^{5,6} and even fewer, randomized, placebo-controlled trials have looked at the effectiveness and safety of topical anticholinergic preparations on hyperhidrosis. Most of these studies evaluated gustatory hyperhidrosis, with limited data on other focal areas of hyperhidrosis.

A randomized, double-blind, placebo-controlled, crossover study of 13 diabetic patients with gustatory sweating showed that a 2-week application of 0.5% glycopyrrolate cream reduced sweating by 82%, as measured by sweat challenge testing.⁷ A more recent study of 25 patients with craniofacial and gustatory hyperhidrosis showed that a single application of a 2% topical glycopyrrolate pad decreased sweat production by a mean of 61.8%, as measured by gravimetrics.⁸ Although the results are promising, these studies evaluated a small subset of patients for a short period of time, which is not adequate to establish long-term safety or efficacy.

In a recent uncontrolled study of 35 patients with axillary hyperhidrosis, 1% glycopyrrolate cream was used once nightly for 4 weeks.⁴ Only 9 of the 35 patients had a significant reduction in their sweating, based on a greater than 50% reduction in the patients' Dermatology Life Quality Index (DLQI) score.⁴ However, the preparation was well tolerated without significant irritation or other compliance-limiting factors; 1 patient did develop

significant xerostomia and mydriasis. It is possible that the 1% concentration of the active drug or the formulation was not sufficient for the therapy to be effective.

In general, topical glycopyrrolate is well tolerated, with few reported adverse effects. These include headache, mydriasis, dry mouth, sore throat, skin irritation, and difficulty with accommodation.^{4,7-10} Because of the reported effectiveness and safety of topical glycopyrrolate, larger randomized, placebo-controlled trials are necessary to establish the safety and efficacy of this therapy.

Oxybutynin

Oxybutynin, a competitive muscarinic receptor antagonist like other anticholinergic agents, has been used off-label for patients with hyperhidrosis. A new topical formulation of oxybutynin 3% topical gel was developed recently to increase tolerability of treatment compared with other transdermal formulations.¹¹ Adverse effects of topical oxybutynin gel are comparable to topical glycopyrrolate. These include skin irritation, dry mouth, constipation, headache, application site pruritus, nasopharyngitis, and dizziness.¹¹ Studies evaluating the safety and efficacy of topical oxybutynin gel for focal hyperhidrosis are warranted, because few effective topical therapies exist for hyperhidrosis.

Devices to Reduce Sweating

Devices that can deliver heat targeted at the eccrine units or to the surrounding tissue may be able to focally reduce sweat production via injury to the sweat gland. Devices currently exist that use various technologies such as laser, radiofrequency, and ultrasound to deliver energy to the soft tissue of skin. Some are applied externally to the skin, while others need to be inserted into the soft tissue. There are limited data on the use of these devices in treating HH, but they may hold promise. One device, MiraDry (Miramar Labs, Sunnyvale, California) uses microwave technology and is already cleared by the FDA to treat axillary HH; it is discussed in the article "Local Procedural Approaches for Axillary Hyperhidrosis" by Drs Glaser and Galperin in this issue.

Fractional microneedle radiofrequency treatment

Fractional microneedle radiofrequency (FMR) is a recently developed, minimally invasive procedure that delivers thermal energy to the reticular dermis, via rapid penetration with insulated microneedles, without causing epidermal injury. Bipolar radiofrequency energy is delivered in a fractional mode by 49 insulated microneedle electrodes (occupying a 1 cm² area) within the tip of a nonconductive

probe. The bipolar electrode pins form a closed circuit with the treated skin, and can penetrate 0.5 to 3.5 mm below the skin surface.¹² Depending on the program selected, FMR can deliver up to 20 J of energy within 0.01 to 1 second, with a 5% or 10% coverage rate. In relation to the radio-frequency treatment level (range 1–20), and conduction time (range 10–1000 ms), the adjustable voltage can reach a maximum of 50 V.¹² FMR devices have been used effectively in the treatment of acne scars, facial pores, and wrinkles.¹² A recent pilot trial wanted to test the effectiveness of FMR for axillary HH, and provided 2 FMR treatments at 4-week intervals to 20 patients.¹²

All subjects received tumescent anesthesia prior to treatment. All axillae were treated with a total of 6 passes, starting at a depth of 3.5 mm for 150 milliseconds and at an energy level of 25 V for the first 2 passes. The second 2 passes went to a depth of 3.0 mm, and the final 2 passes were at a depth of 2.5 mm, with the duration (150 ms) and energy level (25 V) remaining constant.¹² Visible target area petechiae were the preferred irradiation end point. Ice packs were applied during treatment and for 10 minutes after treatment, and a hydrocolloid dressing was applied at the end.¹²

The mean HDSS score decreased from 3.5 at baseline to 2.3 2 months after treatment, and 60% of patients reached an HDSS score of 1 or 2 2 months after treatment. Histologic data from 3 patients showed a decrease in the number and size of apocrine and eccrine sweat glands 1 month after the final treatment. In most patients, only minimal adverse effects were noted, including mild pain, swelling, and redness after treatment. Compensatory HH was noted in 2 patients, and 1 patient had temporary arm numbness.¹² The results of this pilot study are promising, and further studies are needed for this novel treatment technique.

Long-pulsed 800 nm diode laser

Bechara and colleagues¹³ used a long-pulsed 800 nm diode laser to treat 21 patients with axillary HH. In this half-side controlled trial, 5 treatment cycles were performed at 4 week intervals, using an energy setting of 50 mJ/cm² and pulse duration of 30 milliseconds (1.6 Hz). Sweating was reduced, as measured by gravimetric assessment, from 89 mg/min and 78 mg/min at baseline to 48 mg/min and 65 mg/min 4 weeks after the last treatment in the treated and control axillae, respectively.¹³ Histologic examination of skin biopsies before and after the laser treatment revealed no change in the number or size of apocrine or eccrine glands, and no damage to the glands was found. The only adverse effect noted was temporary axillary skin depigmentation in a single

patient. The results were not statistically significant, and the authors noted that a larger sample size is needed to identify a therapeutic effect.

1064-nm Nd-YAG laser

A subdermal 1064-nm neodymium-doped yttrium aluminium garnet (Nd-YAG) laser has been used successfully for bromhidrosis,¹⁴ and has the potential for treating axillary HH. Seventeen patients were numbed with tumescent anesthesia with or without sedation, and at least 1 1 mm incisions is made within the axillary crease. A 300 μ m fiber optic laser cable transported in an 18-gauge epidural needle was inserted into the incision. The 100 millisecond pulsed laser (40 Hz and 15 mJ) was guided slowly against the dermis in a crisscross pattern. Treatment of both axillae took 30 minutes.¹⁴ Patients were followed every 3 months for a period of 12 to 43 months.

According to the patient's global assessment (PGA), there was an excellent result in 70.6% of patients, and based on the physician's global assessment, 82.3% of patients had good or excellent results. There was 1 relapse out of 17 patients within 5 months of treatment. Adverse effects included temporary dysesthesia in all patients, edema, alopecia (47.1%), and seroma formation (5.9%).¹⁴ The results of this pilot study have yet to be replicated, and further research is needed to verify the efficacy of this technique.

A recent randomized, within-patient, case-controlled pilot study of 6 patients used a 1064-nm Nd-YAG laser externally at hair reduction settings to treat axillary HH.¹⁵ Up to 6 laser hair reduction treatments were performed at 1-month intervals with 24 to 56 J/cm² (20 ms pulse duration) depending on the patient's skin type. Three subjects were followed for 1 month after the last treatment; 2 subjects were followed for 3 months, and 1 patient was followed for 13 months after the last treatment.

All of the patients reported good-to-excellent results 1 month after treatment, and 2 of 3 patients reported similar results 3 months after treatment, according to the PGA. There was decreased sweating in all 6 patients as noted by pre- and post-treatment starch iodine testing. There was no change in the sweat gland density or morphology on histologic analysis of the pre- and post-treatment biopsy samples.¹⁵ The histologic findings suggest that sweat reduction is only temporary.

Ultrasound

The VASER (Solta Medical, Incorporated, Hayward, California) ultrasound system has been cleared by the FDA for body contouring and soft tissue emulsification. It focuses ultrasonic energy at the tip of a probe that is inserted into the soft tissue. Thirteen

patients with axillary HH and/or bromhidrosis were treated with the system.¹⁶ Local anesthesia and tumescent anesthesia were used in addition to intravenous sedation. A single 0.5 cm incision was made in the axillary crease; a protective skin port was sewn into the incision site, and the VASER probe was used with an amplitude setting of 80% in continuous mode during phase 1. The probe was passed evenly with radial strokes. Then the amplitude was reduced to 70%, and in continuous mode, phase 2 was completed. Lastly, an aspiration cannula was used to remove liquefied tissue and fluids. Based on 6-month post-treatment subjective scores, there was a mean 2.8 point reduction (on a scale of 1–5) in axillary sweating, and a mean 3 point improvement (on a scale of 1–5) in patient satisfaction. Only minor and temporary adverse effects were noted. A single case of blister formation, seroma formation, and hyperpigmentation was noted. All patients experienced temporary (1–2 days) postoperative pain. This study has promising results. Long-term follow-up and an objective assessment would have been beneficial in evaluating long-term efficacy. Further research is needed with this modality.

Externally applied ultrasound

Intense focused ultrasound (IFUS) has recently been developed to provide direct transcutaneous heat to the dermis and subcutaneous tissue for collagen remodeling. Ulthera (Ulthera, Incorporated, Mesa, Arizona) developed an IFUS device that has been cleared by the FDA and used for skin tightening and lifting procedures.¹⁷ It has been tested for treating axillary HH (clinicaltrials.gov [NCT01708551, NCT01713673, NCT01713959 and NCT01722461]). The Ulthera system consists of a central power unit and monitor, a hand piece, and several interchangeable transducers, which vary in their energy level and depth of penetration. Energy levels vary from 0.5 to 10 J, with a frequency of 4 to 7 MHz, and pulse duration of 50 to 200 milliseconds. The hand piece uses diagnostic ultrasonography that is capable of imaging the epidermis/dermis, subcutaneous tissue, and blood vessels, and also contains the transducer for energy delivery.¹⁷ The focused energy is absorbed by local dermal/subcutaneous tissues, leading to heat production and thermal injury. Thermal injury leads to wound healing and collagen remodeling. The heat may induce injury to the eccrine units, inducing a reduction in sweating.

Prior to the procedure, an anesthetic should be used to help with treatment discomfort. There is no particular anesthetic recommendation, but practitioners have used topical and local anesthetics,

oral or intravenous analgesics, and conscious sedation, depending on the type and location of treatment. For cosmetic purposes, treatments are performed at 2 depths, with a single pass for each desired depth level. There is no specific aftercare for this procedure, and there is no down time after treatment. Temporary erythema and edema are common sequelae of treatment. Temporary numbness in the treatment area has also been reported.

At the time of writing, there are no publications outlining the results of the IFUS for HH, but the technology is promising.

SUMMARY

There is still a need for new therapies for the treatment of primary and secondary forms of hyperhidrosis. Understanding the location of the sweat glands and the pharmacology of sweat will help to drive new developments.

REFERENCES

1. Jacob C. Treatment of hyperhidrosis with microwave technology. *Semin Cutan Med Surg* 2013;32(1):2–8.
2. Glaser DA, Coleman WP, Fan LK, et al. A randomized, blinded clinical evaluation of a novel microwave device for treating axillary hyperhidrosis: the dermatologic reduction in underarm perspiration study. *Dermatol Surg* 2012;38(2):185–91. <http://dx.doi.org/10.1111/j.1524-4725.2011.02250.x>.
3. Glogau RG. Topically applied botulinum toxin type A for the treatment of primary axillary hyperhidrosis: results of a randomized, blinded, vehicle-controlled study. *Dermatol Surg* 2007;33(1 Spec No):S76–80. <http://dx.doi.org/10.1111/j.1524-4725.2006.32335.x>.
4. MacKenzie A, Burns C, Kavanagh G. Topical glycopyrrolate for axillary hyperhidrosis. *Br J Dermatol* 2013; 169(2):483–4. <http://dx.doi.org/10.1111/bjd.12320>.
5. Luh JY, Blackwell TA. Craniofacial hyperhidrosis successfully treated with topical glycopyrrolate. *South Med J* 2002;95(7):756–8.
6. Garnacho Saucedo GM, Moreno Jiménez JC, Jiménez Puya R, et al. Therapeutic hotline: topical glycopyrrolate: a successful treatment for craniofacial hyperhidrosis and eccrine hidrocystomas. *Dermatol Ther* 2010;23(1):94–7. <http://dx.doi.org/10.1111/j.1529-8019.2009.01296.x>.
7. Shaw JE, Abbott CA, Tindle K, et al. A randomised controlled trial of topical glycopyrrolate, the first specific treatment for diabetic gustatory sweating. *Diabetologia* 1997;40(3):299–301. <http://dx.doi.org/10.1007/s001250050677>.
8. Kim WO, Kil HK, Yoon KB, et al. Topical glycopyrrolate for patients with facial hyperhidrosis. *Br J Dermatol* 2008;158(5):1094–7. <http://dx.doi.org/10.1111/j.1365-2133.2008.08476.x>.

9. Kim WO, Kil HK, Yoon DM, et al. Treatment of compensatory gustatory hyperhidrosis with topical glycopyrrolate. *Yonsei Med J* 2003;44(4):579–82.
10. Cladellas E, Callejas MA, Grimalt R. A medical alternative to the treatment of compensatory sweating. *Dermatol Ther* 2008;21(5):406–8. <http://dx.doi.org/10.1111/j.1529-8019.2008.00222.x>.
11. Goldfischer ER, Sand PK, Thomas H, et al. Efficacy and safety of oxybutynin topical gel 3% in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study. *NeuroUrol Urodyn* 2013. <http://dx.doi.org/10.1002/nau.22504>.
12. Kim M, Shin JY, Lee J, et al. Efficacy of fractional microneedle radiofrequency device in the treatment of primary axillary hyperhidrosis: a pilot study. *Dermatology* 2013;227(3):243–9. <http://dx.doi.org/10.1159/000354602>.
13. Bechara FG, Georgas D, Sand M, et al. Effects of a long-pulsed 800-nm diode laser on axillary hyperhidrosis: a randomized controlled half-side comparison study. *Dermatol Surg* 2012;38(5):736–40. <http://dx.doi.org/10.1111/j.1524-4725.2012.02339.x>.
14. Goldman A, Wollina U. Subdermal Nd-YAG laser for axillary hyperhidrosis. *Dermatol Surg* 2008;34(6):756–62. <http://dx.doi.org/10.1111/j.1524-4725.2008.34143.x>.
15. Letada PR, Landers JT, Uebelhoer NS, et al. Treatment of focal axillary hyperhidrosis using a long-pulsed Nd:YAG 1064 nm laser at hair reduction settings. *J Drugs Dermatol* 2012;11(1):59–63.
16. Commons GW, Lim AF. Treatment of axillary hyperhidrosis/bromidrosis using VASER ultrasound. *Aesthetic Plast Surg* 2009;33(3):312–23. <http://dx.doi.org/10.1007/s00266-008-9283-y>.
17. Brobst RW, Ferguson M, Perkins SW. Ulthera: initial and six month results. *Facial Plast Surg Clin North Am* 2012;20(2):163–76, vi. <http://dx.doi.org/10.1016/j.fsc.2012.02.003>.