

# Topical Therapies in Hyperhidrosis Care



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## KEYWORDS

- Antiperspirants • Hyperhidrosis topical treatments • Topical glycopyrrolate • Aluminum chloride
- Aluminum salts • Aluminum chloride hexahydrate • Aluminum zirconium trichlorohydrate

## KEY POINTS

- When used correctly, topical treatments for primary focal hyperhidrosis can provide significant benefit and, with patient education on usage, skin irritation can be limited and tolerable.
- Topical agents are a useful adjunct to other treatments such as onabotulinumtoxinA.
- Antiperspirants are most effective when applied to thoroughly dried skin at night.
- Many insurance companies consider treatment of hyperhidrosis with iontophoresis or onabotulinumtoxinA medically necessary only when topical aluminum chloride or other extrastrength antiperspirants are ineffective or result in a severe rash.
- Knowledge of the appropriate use of topical treatments is important for patient care on multiple levels.

## PRIMARY HYPERHIDROSIS

### *The Nature of the Problem*

Hyperhidrosis, also known as excessive sweating, is a dermatologic disorder characterized by sweating that is beyond what is anticipated or necessary for thermoregulation in the person's environment.<sup>1</sup> Primary, or idiopathic, hyperhidrosis and secondary hyperhidrosis are the chief categories of the condition.<sup>2</sup> Primary hyperhidrosis (hyperhidrosis that is not caused by another medical condition or as a side effect of medication) presents in approximately 3% of the population.<sup>3</sup> The excessive sweating experienced by people with primary hyperhidrosis is most often manifested at a focal body region such as on the palms, on the soles of the feet, in the axillae, or (less frequently) in the craniofacial region.<sup>3</sup> Patients with primary hyperhidrosis often experience focal

excessive sweating at more than one of the body locations listed earlier.

Hyperhidrosis is of great concern to patients because of its physical, occupational, psychological, and social impacts on quality of life. For instance, patients with hyperhidrosis report physical discomfort caused by wet clothing and shoes.<sup>1</sup> In addition, skin maceration from persistent wetness can lead to bacterial and fungal overgrowth. This overgrowth can then cause intertrigo in the axillae as well as bromhidrosis (foul-smelling sweat), pitted keratolysis (an infection of the plantar surface characterized by pits or craters), and gram-negative bacterial infection and macerative infection of the feet.<sup>4</sup> From a practical and economic standpoint, excessive sweat can stain and eventually destroy clothing and shoes.<sup>5</sup> Patients may need to spend thousands of dollars annually for dry-cleaning and clothing replacement.<sup>6</sup>

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Psychosocial ramifications can be severe because of patient's embarrassment and the cultural stigma associated with sweating. Stereotypes regarding the causes of sweating (other than as a reaction to heat or exercise) may include nervousness, incompetence at a task, lack of cleanliness, or dishonesty. Day-to-day lives are also affected severely by excessive sweating; patients may find that their activities of daily living are negatively affected such that simple tasks become difficult, and household, educational, or job-related tools and documents may become damaged by wetness. Baseline evaluation of a series of patients treated for axillary hyperhidrosis found that 90% of the group reported an effect on their emotional status, and more than 70% had to change clothes 2 or more times per day.<sup>7</sup> More than 50% of patients with axillary hyperhidrosis identified in a US national consumer survey reported feeling less confident, 38% said they became frustrated by some daily activities, 34% were unhappy, and 20% said they were depressed.<sup>8</sup>

Palmar hyperhidrosis can interfere with activities of daily living as well as with occupational tasks. Having sweaty palms makes it difficult to grip tools, play musical instruments, and use electronic devices, and paper can be stained and ink smeared by dripping sweat.<sup>1,5</sup> Patients experiencing palmar excessive sweating have reported difficulty writing or drawing, frequent electric shocks, and dropping glass objects.<sup>9</sup> Occupational problems for those with axillary or generalized hyperhidrosis include needing to change clothes frequently and anxiety regarding presentations in front of audiences because of sweat-stained clothing and resultant embarrassment.<sup>10</sup> In the US national consumer survey mentioned earlier, 13% of patients with axillary hyperhidrosis reported a related decrease in work time.<sup>8</sup>

## PATIENT EVALUATION OVERVIEW

The first step when evaluating a patient presenting with hyperhidrosis is a detailed clinical history with a focus on features of primary hyperhidrosis in order to support the diagnosis of primary focal hyperhidrosis (**Box 1**). It is also critical to know the patient's medical and surgical history as well as any medications, supplements, or complementary therapies that have been used. Review of systems should focus on the endocrine and neurologic systems. Physical examination includes an inspection for signs of excess sweating and/or related skin breakdown but such symptoms may not reliably be present.<sup>3</sup> Laboratory testing is usually not required.<sup>3</sup> The Hyperhidrosis Disease Severity Scale (HDSS) is a quick diagnostic tool providing

### Box 1

#### Diagnostic features of primary hyperhidrosis

- Excessive sweating occurring in at least 1 of the following sites: axillae, palms, soles, or craniofacial region
- At least 6 months' duration
- Without apparent secondary causes (eg, medications, endocrine disease, neurologic disease)
- Including 2 or more of the following characteristics:

Bilateral and approximately symmetric

Age of onset less than 25 years

Frequency of episodes at least once per week

Positive family history

Cessation of excessive sweating on sleep

Impairment of daily activities

*Adapted from Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004; 51(2):274–86*

insight into the impact of hyperhidrosis on the patient's life (**Box 2**). The results can be used to tailor treatment and for insurance reimbursement or coverage documentation purposes.<sup>3</sup>

## TOPICAL OPTIONS FOR HYPERHIDROSIS TREATMENT

Because of the history of safety, cost-effectiveness, and ease of use and access of topical therapies, and because many patients

### Box 2

#### HDSS

*How would you rate the severity of your hyperhidrosis?*

1. My sweating is never noticeable and never interferes with my daily activities
2. My sweating is tolerable but sometimes interferes with my daily activities
3. My sweating is barely tolerable and frequently interferes with my daily activities
4. My sweating is intolerable and always interferes with my daily activities

*From Walling HW, Swick BL. Treatment options for hyperhidrosis. Am J Clin Dermatol 2011;12:285–96; with permission.*

obtain symptom relief from them, topical treatments are often the first line of treatment of primary focal hyperhidrosis (**Fig. 1**).<sup>3</sup> Topical antiperspirants are most effective for axillary sweating but may also be used for the palms of the hands, soles of the feet, and on the craniofacial area. Aluminum chloride is the most commonly used topical agent.<sup>3</sup>

## ALUMINUM SALTS

Aluminum chloride is the partially neutralized form used in cosmetic antiperspirants, whereas aluminum chloride hexahydrate is used in prescription products and is among the most effective antiperspirants available.<sup>11</sup> Newer over-the-counter (OTC) clinical-strength antiperspirants are also available and are discussed later in this article.

With regard to mechanism of action, several studies have shown that aluminum salts cause an obstruction of the distal eccrine sweat gland ducts.<sup>12</sup> The mechanism underlying this obstruction is thought to be that the metal ions precipitate with mucopolysaccharides, damaging epithelial cells along the lumen of the duct and forming a plug that blocks sweat output (**Fig. 2**).<sup>11</sup> Sweat may still be produced, as shown by the appearance of miliaria (prickly heat) during heat stress, with sweat building up behind the obstruction created by the metallic salt.<sup>12</sup> However, normal sweat gland function returns with epidermal renewal, so retreatment/topical reapplication is required, with frequency depending on the product.<sup>11</sup> However, long-term histologic studies of eccrine glands in patients on chronic aluminum salt treatment have shown destruction of some secretory cells, accounting for the clinical finding of reduced severity of hyperhidrosis over time, as reflected by the need for less-frequent treatments.<sup>12</sup> Other metallic salts such as zirconium,

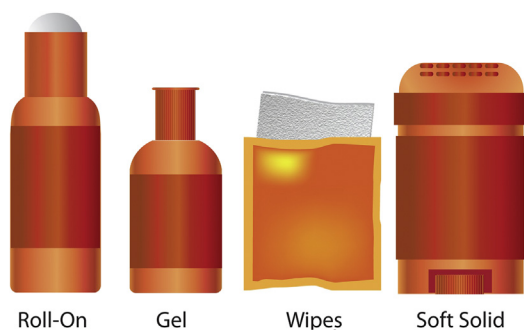
vanadium, and indium are thought to work by the same mechanism.<sup>11</sup> Some of these salts are more effective than aluminum salts, but aluminum salts have been used for more than 80 years and are inexpensive, easily available, and nontoxic, so they remain the common active ingredient of most preparations.<sup>11</sup>

Less severe cases of hyperhidrosis may respond to OTC aluminum chloride antiperspirants. More severe cases may require prescription-strength aluminum chloride (20% solution).<sup>3</sup> Most patients with hyperhidrosis note a reduction or cessation of sweating at night. In order for the plugs to form most efficiently, to limit skin irritation, increase efficacy, and limit damage to clothing, antiperspirants should be applied at nighttime, before bed, to dry skin. Clinical efficacy is often noted in 1 to 2 weeks.<sup>3</sup> However, compliance with nighttime application can be limited by the products having traditionally been part of the morning grooming routine. Fragrances may also interfere with sleep and patients may not think that the product is working during the day because there are no awareness signals that the product is still present in the morning.

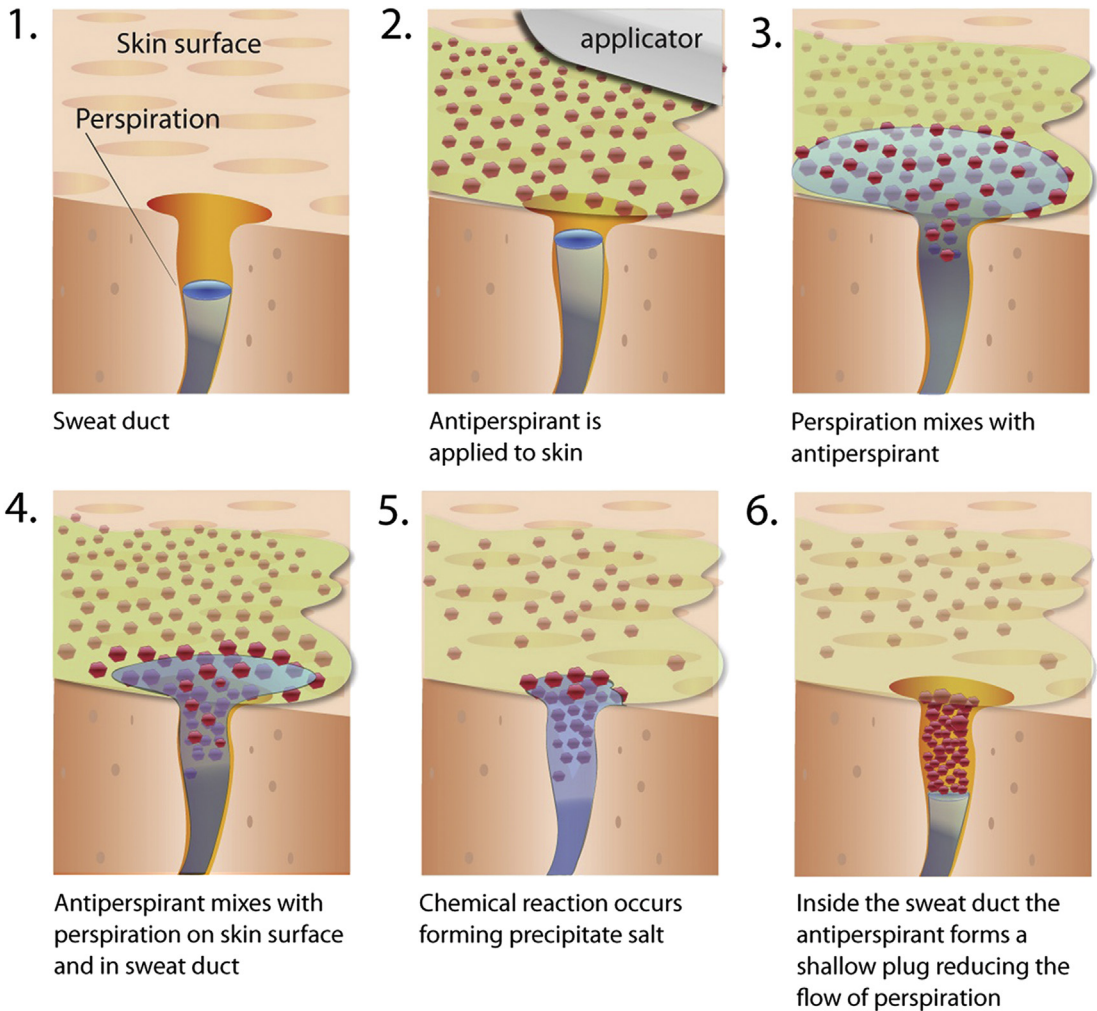
In a study involving 691 patients with axillary hyperhidrosis treated with aluminum chloride, 82% of the group reported dryness or a tolerable amount of sweating, and, in longer follow-up, 87% reported satisfaction with the treatment.<sup>11</sup> In that study, various concentrations were evaluated, and the investigators concluded that a 15% solution was as effective as 20% solution and was better tolerated.<sup>11</sup>

Palmar hyperhidrosis is less responsive to aluminum chloride therapy than axillary hyperhidrosis<sup>13</sup> and successful treatment may require active ingredient concentrations up to 30%.<sup>14</sup>

Skin irritation is a common limiting factor in the treatment of hyperhidrosis with aluminum chloride. A study of 38 patients with axillary hyperhidrosis reported treatment-limiting irritation in 26% of patients.<sup>15</sup> The most common adverse effects of aluminum chloride treatment are itching and stinging immediately after application, and ongoing skin irritation.<sup>11</sup> In one series of 691 patients, pruritus was minor and short in duration in 70% of study participants, moderate in 21%, and severe in 9%, whereas skin irritation was moderate in 36% and severe in 14%. During maintenance treatment, less itching and skin irritation were seen.<sup>11</sup> In many cases, skin irritation is mild and can be controlled with the application of 1% hydrocortisone cream the morning after treatment.<sup>16</sup> Damage to fabrics can occur, so patients should be counseled against wearing expensive nightwear.<sup>14</sup>



**Fig. 1.** Topical treatments are often the first line of treatment of primary focal hyperhidrosis. (Courtesy of Albert Ganss, International Hyperhidrosis Society, Quakertown, PA; with permission.)



**Fig. 2.** The metal ions precipitate with mucopolysaccharides, damaging epithelial cells along the lumen of the duct and forming a plug that blocks sweat output. (Courtesy of Albert Ganss, International Hyperhidrosis Society, Quakertown, PA; with permission.)

Available by prescription, 20% aluminum hexahydrate in anhydrous ethanol (Drysol, Person and Covey, Inc, Glendale, CA) is a commonly used agent.<sup>5</sup> Concentrations of 10% to 15% and up to 30% are used in compounded formulations to treat axillary and palmoplantar hyperhidrosis, respectively.<sup>14</sup>

Following a recommended regimen may enhance efficacy and reduce the incidence of adverse effects.<sup>13</sup> Aluminum chloride should remain on the skin for 6 to 8 hours to be effective. Overnight application best takes advantage of low sweat output during sleep because diffusion of the aluminum ions into the sweat gland may be negatively affected if the gland is actively excreting sweat.<sup>11</sup> As mentioned earlier, patients need to be educated that, despite nighttime application, the product continues to work during the

day and that adjustment of the morning grooming routine is necessary. Those patients who may want to use a fragranced product as part of morning grooming can be instructed to use a nonmedicated deodorant in the morning after a bath or shower.

If the patient regularly shaves the axillary region, it is best to wait 24 to 48 hours after shaving before applying the medication to decrease irritation.<sup>13</sup> Irritating hydrochloric acid forms in the presence of water, so prewashing is not advised; drying the axillae with a blow dryer may reduce irritation.<sup>13</sup> In the morning, the medication should be washed off before daytime sweating begins.<sup>13</sup> Irritated skin can be treated with topical hydrocortisone cream for up to 2 weeks if irritation persists.<sup>5</sup> If irritation persists beyond that point, a dermatology consult should be obtained. Nightly

treatments are recommended until an effect is noted, and then the interval between treatments can be lengthened.<sup>5</sup>

In another study, 4% salicylic acid in a hydro-alcoholic gel base was used as the vehicle for aluminum chloride hexahydrate in 238 patients with hyperhidrosis involving the axillae, feet, hands, and groin.<sup>17</sup> The rationale for using this combination included possible enhancement of aluminum chloride absorption, possible additional antiperspirant effects of salicylic acid, and potentially less skin irritation afforded by the hydroalcoholic gel. The percentage of aluminum chloride varied with the site treated: 10% to 25% for the axillae and 30% to 40% for the palms and soles. For patients with axillary disease, 94% reported excellent to good results. Excellent to good results were reported by 60% and 84% of patients with palmar or plantar involvement, respectively. Patients who had previously failed to respond to aluminum chloride in absolute alcohol or who could not tolerate it seemed to improve with use of the salicylic acid gel vehicle. The researchers suggested further study on this treatment option.<sup>16</sup>

### TOPICAL GLYCOPYRROLATE

Glycopyrrolate is an anticholinergic agent that is used off-label systemically for the treatment of hyperhidrosis. Topical glycopyrrolate may also be effective for focal hyperhidrosis. A topical application of 0.5% or 1% glycopyrrolate was studied in 16 patients with Frey syndrome (gustatory hyperhidrosis) and was effective and free of adverse effects.<sup>18</sup> In another study of 25 patients with craniofacial sweating, all the patients had half their foreheads treated with 2% glycopyrrolate and the other half treated with placebo. This split-face study found that 96% of the patients were satisfied with the effectiveness; whereas 1 patient did not tolerate the regimen because of headache. Improvement was transient, lasting 1 to 2 days for most patients.<sup>19</sup> Topical glycopyrrolate may also be considered as a treatment option for large areas of sweating (ie, post-ETS compensatory sweating) with side effects being mydriasis and accommodation failure,<sup>20</sup> and urinary retention.<sup>21</sup> In another uncontrolled study in which 35 patients with axillary hyperhidrosis who previously failed treatment with topical aluminum chloride applied a topical formulation of 1% glycopyrrolate in cetomacrogol cream BP once daily for 1 month found less favorable results.<sup>22</sup> Only 9 patients had a greater than 50% reduction in the Dermatology Life Quality Index score, and only 2 patients desired to continue treatment at the end of the study. The investigators of the study commented that

their clinical experience with this formulation of topical glycopyrrolate was more favorable in patients with craniofacial hyperhidrosis.

Topical glycopyrrolate is not commercially available worldwide, but can be compounded. A commercial product is not available in the United States.

Topical agents such as glutaraldehyde, formaldehyde, and tannic acid are currently seldom used because of irritancy, skin discoloration, and the availability of alternatives.<sup>3</sup>

### CLINICAL-STRENGTH OTC PRODUCTS

A new generation of OTC antiperspirants includes aluminum zirconium trichlorohydrate and may be an option for nonaxillary as well as axillary hyperhidrosis. These products provide more sweat-reduction benefits than traditional OTC products with less reported irritation to the skin than prescription topical therapies.<sup>23</sup> In a study of 20 male participants published in 2012, researchers found that sweat reduction caused by the use of an OTC clinical-strength antiperspirant product was more effective (an average of 34% better) than typical prescription topical (6.5%) aluminum chloride treatments with less skin irritation. OTC clinical-strength antiperspirants are typically based on partially neutralized salts such as aluminum zirconium trichlorohydrate gly. These materials reduce the amount of HCl (which is blamed for skin irritation) produced on the skin by as much as 80%, create a more superficial duct blockage than aluminum chloride, and allow daily or twice-daily application without significant skin irritation (which patients tend to find appealing and which fits into patients' traditional grooming routines). Although blockages are more superficial than may occur with stronger aluminum chloride solutions, there are several literature reports indicating that the blockage lasts more than 7 days, so it is possible to achieve high sweat-reduction values provided the active agent is effectively delivered to the opening of the eccrine gland daily.<sup>24</sup> Thus OTC clinical-strength soft-solid antiperspirants may be considered as an alternative treatment to aluminum chloride antiperspirants for the treatment of excessive sweating.

Because of information on the Internet, some patients ask about the association of aluminum use and Alzheimer disease and breast cancer. The Alzheimer's Association, the American Cancer Society, the Susan B. Komen Cancer Foundation, and the National Cancer Institute have statements on their respective Web sites indicating that there is no research to support claims that antiperspirant use is linked to either Alzheimer or breast cancer risk or incidence.

In conclusion, when used correctly, topical treatments for primary focal hyperhidrosis can provide significant benefit and, with patient education on usage, skin irritation can be limited and tolerable for some patients. Topical agents may also be a useful adjunct to other treatments such as onabotulinumtoxinA and systemic therapies. Many insurance companies consider treatment of hyperhidrosis with iontophoresis or onabotulinumtoxinA medically necessary only when topical aluminum chloride or other extrastrength antiperspirants are ineffective, result in a severe irritation, or produce other complications. Appropriate use of topical treatments is important for almost all patients with hyperhidrosis.

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