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Hyperhidrosis: Pathophysiology, Clinical Evaluation, and Current and Emerging Treatment Approaches

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Abstract: ***Hyperhidrosis is a chronic disorder in which sweating exceeds the amount needed for temperature regulation. It may be primary (focal and without an identifiable cause) or secondary to another disease, a medicine, or a systemic disorder. Although it is not life-threatening, it can cause skin complications, psychological distress, and limitations in education, work, and social life. This narrative review summarizes the classification, epidemiology, pathophysiology, clinical evaluation, and management of hyperhidrosis, with emphasis on pharmacological treatment. Sources included clinical guidelines and consensus statements, systematic reviews, randomized trials, and regulatory documents. Primary focal hyperhidrosis most often affects the axillae, palms, soles, and craniofacial region and is thought to result from exaggerated cholinergic sympathetic stimulation of structurally normal eccrine glands. Diagnosis relies mainly on history and examination, supported by the Hyperhidrosis Disease Severity Scale (HDSS), gravimetry, and the starch-iodine test. Secondary causes should be investigated when sweating is generalized, nocturnal, of recent adult onset, or accompanied by systemic symptoms. Management is stepwise: general measures and aluminum chloride, topical anticholinergics, iontophoresis, botulinum toxin, oral anticholinergics, device-based treatments, and, rarely, sympathectomy. Sofpironium bromide gel is a recent addition for axillary disease. Evidence gaps remain for long-term outcomes, comparative effectiveness, palmoplantar and craniofacial disease, and cost-effectiveness. Treatment should be individualized according to site, severity, comorbidity, and patient preference.***

Keywords: Hyperhidrosis; excessive sweating; eccrine sweat glands; anticholinergic drugs; botulinum toxin; iontophoresis; sofpironium bromide; sympathectomy

1. Introduction

Sweating is a normal and essential process. Eccrine sweat glands release fluid onto the skin, and its evaporation removes heat from the body. Hyperhidrosis is defined as sweating that exceeds the level required for temperature regulation. It may be limited to specific areas (focal) or involve the whole body (generalized) [1, 2].

The condition is important for both clinical and social reasons. Persistent moisture can lead to skin maceration, bacterial and fungal infection, and dermatitis [2]. Socially, it interferes with everyday tasks such as writing, using a phone or keyboard, shaking hands, and choosing clothing. Many patients are never diagnosed or treated because of limited public awareness, stigma, and difficulty in accessing treatment [3, 4].

The topic is also relevant to pharmacy practice. Many treatments are medicines or medical products, including aluminum salts, anticholinergic drugs, botulinum toxin, and iontophoresis devices, and pharmacists are often the first professionals consulted about sweating. They also have a role in identifying drug-induced sweating and in counselling patients about adverse effects.

The aim of this review is to outline the classification, epidemiology, pathophysiology, and clinical evaluation of hyperhidrosis and to examine current and investigational treatments. It then proposes a stepwise approach for primary focal hyperhidrosis and identifies gaps in the evidence. The emphasis is on primary focal disease because it is the main target of symptomatic drug therapy [2, 5].

2. Classification of Hyperhidrosis

Hyperhidrosis is classified by cause (primary or secondary) and by distribution (focal or generalized).

1) **Primary focal hyperhidrosis** has no identifiable underlying disease. Sweating is restricted to certain regions, is usually bilateral and symmetrical, and often begins in childhood or adolescence. It typically lessens or stops during sleep, and a family history is common [6, 7].
2) **Secondary hyperhidrosis** results from another condition or from a medicine. It may be focal but is more often generalized. It usually begins in adulthood, may occur at night, and is often accompanied by features of the underlying disorder [1, 8].

Primary hyperhidrosis is further described by site. The axillae, palms, and soles are most often affected, followed by the craniofacial region. Less common patterns include groin and trunk involvement and gustatory sweating, which is triggered by eating and may follow nerve injury [2, 9]. Tables 1 and 2 summarize these distinctions.

Table 1: Comparison of primary focal and secondary hyperhidrosis

Feature	Primary focal hyperhidrosis	Secondary hyperhidrosis
Typical onset	Childhood to early adulthood	Any age; often adult
Distribution	Focal, bilateral, symmetrical (axillae, palms, soles, face)	Often generalized; may be focal
Night sweating	Uncommon	Common
Family history	Frequent	Variable
Associated symptoms	Usually none	Fever, weight loss, palpitations, tremor, flushing

Underlying cause	None identified	Endocrine, infectious, neurologic, malignant, or drug-related
Core management	Symptom-directed treatment	Treat the cause or adjust the drug.

Sources: [1, 6-8].

Table 2: Common sites of primary focal hyperhidrosis

Site	Clinical features
Axillary	Most frequently treated; visible clothing stains; the most extensive treatment evidence
Palmar	Wet hands interfere with writing and physical contact.
Plantar	Often coexists with palmar disease, wet footwear, odor, and infection risk.
Craniofacial	Face and scalp: highly visible; treatment evidence more limited
Other focal sites	Groin, trunk, and gustatory sweating; less common; management individualized

Sources: [2, 9].

3. Epidemiology and Quality-of-Life Impact

3.1 Prevalence

Prevalence estimates depend on the definition used and the method of survey. A large United States survey estimated that about 4.8% of the population has hyperhidrosis, with the axillae the most commonly affected site [3, 4]. A Japanese survey, cited in a phase 3 trial report, found primary axillary hyperhidrosis in about 5.75% of respondents [10]. Because definitions and questionnaires differ, these figures are approximate. Most cases are primary and begin early in life [2, 5].

3.2 Effects on daily life and mental health

Qualitative research shows that hyperhidrosis affects many areas of life. Patients describe changing clothes repeatedly, avoiding certain fabrics and colors, difficulty with handwriting and electronic devices, and reluctance to make physical contact such as handshakes [11]. A review of 49 studies concluded that primary hyperhidrosis affects psychological, physical, and social functioning [3].

School and work are also affected. Wet hands can damage paper and equipment, and jobs that need fine manual skill or frequent personal contact may be especially difficult. Some patients restrict social activities, avoid intimacy, or limit their career choices [3, 11].

A comparison of people with and without hyperhidrosis found more anxiety and depression in the hyperhidrosis group [12]. Such data cannot show the direction of the relationship. Anxiety can aggravate sweating, and sweating can increase anxiety, creating a cycle. Clinicians should therefore ask about psychological well-being and refer patients when appropriate [3, 12].

4. Pathophysiology

4.1 Eccrine sweat glands and thermoregulation

The skin contains millions of eccrine sweat glands, with the highest density on the palms, soles, and axillae. Each gland has a secretory coil in the dermis and a duct that opens onto the skin surface. The coil produces a fluid similar to plasma, and the duct reabsorbs part of the sodium and chloride before the sweat reaches the surface [13].

Thermoregulatory sweating is coordinated by the hypothalamus, which responds to rising core and skin temperature. Signals travel through the sympathetic nervous system. Unusually for sympathetic fibers, those supplying eccrine glands are cholinergic. They release acetylcholine, which acts on muscarinic receptors (mainly the M3 subtype) on the secretory cells [13, 14]. This explains why antimuscarinic drugs reduce sweating and why they also cause typical anticholinergic adverse effects such as dry mouth and blurred vision.

The palms, soles, and, to a lesser extent, the axillae also respond strongly to emotional stimuli. This emotional sweating is considered especially relevant to primary focal hyperhidrosis [14].

4.2 Proposed mechanisms in primary hyperhidrosis

The precise mechanism of primary hyperhidrosis is unknown. Affected glands generally appear normal in number and structure, which suggests that the abnormality lies in how the glands are stimulated rather than in the glands themselves [1,14]. Proposed contributors include the following.

- **Exaggerated sympathetic outflow.** Central or autonomic pathways may drive eccrine glands more strongly than normal, particularly in response to emotional triggers [1, 14].
- **Altered gland responsiveness or neurotransmitter handling.** Differences in acetylcholine release, clearance, or receptor response have been suggested, but the evidence is limited [1].
- **Genetic predisposition.** Many patients report affected relatives. A study of families with palmar hyperhidrosis found a pattern consistent with genetic transmission, but specific causative genes have not been firmly established [15].

These mechanisms remain working hypotheses. The consistent response to anticholinergic drugs and botulinum toxin supports a central role for cholinergic signalling at the gland, whatever the upstream cause [14].

4.3 Secondary causes

In secondary hyperhidrosis, sweating results from another process that increases heat production, stimulates the autonomic nervous system, or alters central control. The main categories are listed in Table 3 [1, 8, 16, 17].

Table 3: Common causes of secondary hyperhidrosis

Category	Examples	Clinical clues
Endocrine and metabolic	Hyperthyroidism, diabetes mellitus (including hypoglycemia), menopause, pheochromocytoma, acromegaly	Heat intolerance, palpitations, flushing, hormonal symptoms
Infectious	Tuberculosis, HIV infection, endocarditis, brucellosis, other chronic infections	Fever, weight loss, night sweats
Neurologic	Parkinson's disease, stroke, spinal cord injury, autonomic neuropathy, gustatory sweating	Distribution may follow the lesion.
Malignancy	Lymphoma, carcinoid syndrome, other tumors	Night sweats, weight loss, fatigue
Drug-induced	Antidepressants, opioids, cholinergic drugs, some hormonal therapies, withdrawal states	Onset related to starting or changing a medicine
Other	Anxiety disorders, pregnancy, obesity, alcohol use	Contribute to or aggravate sweating

Sources: [1, 8, 16, 17]. Specific drug examples should be checked against current references.

Drug-induced sweating is particularly relevant to pharmacists. A review of prescribed and over-the-counter medicines, alcohol, and recreational substances can often identify a reversible cause [1, 8].

5. Clinical Evaluation and Diagnosis

5.1 History and physical examination

Evaluation aims to define the pattern, severity, and impact of sweating and to judge whether a secondary cause is likely. The history should cover [1, 6, 17]:

- Age and circumstances of onset;
- Distribution (focal or generalized) and symmetry;
- Triggers such as heat, emotion, or food, and whether sweating occurs during sleep;
- Duration, frequency, and effect on daily life;
- Family history;
- All medicines, including supplements;
- Systemic symptoms such as fever, weight loss, palpitations, tremor, headache, or flushing;
- Previous treatments and their results.

Examination should look for visible sweating, maceration, infection, odor, and signs of systemic disease such as goiter, tremor, lymph node enlargement, or neurological abnormality [1, 6].

5.2 Distinguishing primary from secondary hyperhidrosis

A widely cited consensus defines primary focal hyperhidrosis as visible, excessive focal sweating for at least six months without an apparent cause, plus at least two of the following: bilateral and relatively symmetrical sweating, interference with daily activities, at least one episode per week, onset before about 25 years of age, a positive family history, and absence of sweating during sleep [6]. Features that point away from a primary cause include sudden onset in adulthood, generalized or asymmetric sweating, prominent night sweats, and systemic symptoms [1, 17].

5.3 Severity assessment: the Hyperhidrosis Disease Severity Scale

The Hyperhidrosis Disease Severity Scale (HDSS) is a single-question, four-point, patient-reported scale of how much sweating interferes with daily activities. A score of 1 means sweating is never noticeable and never interferes; 2 means it is tolerable but sometimes interferes; 3 means it is barely tolerable and frequently interferes; and 4 means it is intolerable and always interferes. Scores of 3 and 4 are generally regarded as severe disease and are commonly used to guide treatment choice [2, 7, 17]. Because the scale is brief, it is useful both at diagnosis and for monitoring response.

5.4 Objective assessment

Objective tests are not needed for most patients. They are useful in research for confirming borderline cases, for mapping areas to be injected, and for measuring response [1, 6, 7]. Table 4 summarizes the main methods.

Table 4: Assessment methods in hyperhidrosis

Method	Principle	Use and limitations
History and examination	Clinical pattern and diagnostic criteria	Basis of diagnosis: no equipment needed
HDSS	Four-point patient-reported impact scale	Quick and widely used; subjective
Gravimetry	Pre-weighed filter paper is applied to the skin for a set time and re-weighed.	Quantitative; used mainly in trials. About 50 mg per axilla over 5 minutes is a commonly used entry threshold [18]; thresholds vary.
Starch-iodine (minor) test	Iodine and starch applied to skin turn dark blue-violet where sweat is present.	Maps the affected area, for example, before botulinum toxin injection; qualitative
Quality-of-life questionnaires (e.g., Dermatology Life Quality Index, DLQI)	Patient-reported impact	Useful for monitoring and research
Laboratory tests	Targeted to suspected causes (e.g., thyroid function, glucose, blood count)	Used when secondary hyperhidrosis is suspected

Sources: [1, 6, 7, 17, 18].

5.5 When to investigate for underlying disease

Investigation is appropriate when sweating is generalized, of recent adult onset, mainly nocturnal or asymmetric, or accompanied by weight loss, fever, palpitations, tremor, flushing, or neurological symptoms [1, 8, 17]. A reasonable first set of tests often includes a full blood count, glucose or glycated hemoglobin (HbA1c), and thyroid function, with further tests guided by the clinical picture [1, 17]. In contrast, a young patient with typical focal, symmetrical sweating of

the axillae, palms, or soles and a normal examination rarely needs extensive testing [6, 17].

6. Management of Hyperhidrosis

Treatment depends on the site and severity of sweating, patient preference, previous response, and availability. Most guidance recommends a stepwise approach, starting with simple, low-risk measures and progressing to more intensive options [2, 7, 19, 20]. The evidence is uneven: a systematic review found that many trials were small and short and used differing outcome measures, which limits comparison between treatments [21].

6.1 General and Supportive Measures

General measures do not cure hyperhidrosis but can reduce its impact [2, 17].

- **Clothing and footwear:** Loose, breathable fabrics promote evaporation, and dark or patterned clothing can hide marks. Rotating shoes and wearing absorbent socks may help prevent plantar disease.
- **Hygiene:** Regular washing and thorough drying reduce bacterial growth and odor. Secondary skin infection needs specific treatment.
- **Absorbent products:** Underarm pads, insoles, and absorbent powders offer practical relief.
- **Trigger avoidance:** Some patients report that heat, caffeine, alcohol, or spicy food worsens sweating, although evidence that avoiding them helps is limited.
- **Psychological support:** Counselling or relaxation techniques may help when anxiety and sweating reinforce each other, but they do not treat the underlying condition [12].

6.2 Topical Therapy

1) **Aluminum chloride hexahydrate:** Aluminum salts are the traditional first-line treatment for mild to moderate focal hyperhidrosis [7, 17, 19]. They are thought to block sweat gland ducts and to alter the gland epithelium. Prescription preparations (commonly about 10–20% in an alcohol or aqueous base) are applied to dry skin at night, daily at first and then less often as control improves, and washed off in the morning. The main adverse effect is skin irritation, including stinging, burning, and itching, which limits use, especially in the axillae. Less frequent application, a shorter contact time, or a brief course of a topical corticosteroid may help. The salts can also stain clothing. Evidence is better for axillary than for palmar or plantar disease, and the quality of randomized evidence is modest [17, 19, 21].
2) **Topical glycopyrronium (glycopyrrolate):** Topical anticholinergics are reviewed in [22]. Glycopyrronium is a quaternary ammonium antimuscarinic that blocks acetylcholine at the sweat gland. A 2.4% glycopyrronium tosylate pre-moistened cloth applied once daily to the axillae was evaluated in two large randomized trials (ATMOS-1 and ATMOS-2), which showed greater reductions in sweat production and in patient-reported sweating severity than the vehicle [23]. It was approved in the United States in 2018 for primary axillary hyperhidrosis in patients aged 9 years and older. Reported adverse effects include dry mouth, mydriasis, application-site pain, and other local reactions [22]. Systemic absorption has been reported to be lower than with oral glycopyrrolate [22]. Eye contact should be avoided and hands washed after use. As with other anticholinergics, use is cautioned or contraindicated in conditions such as narrow-angle glaucoma and urinary retention; the product label should be consulted.
3) Compounded topical glycopyrrolate (often 0.5–2%) has been used for palmar and craniofacial disease. A small study reported benefit in facial hyperhidrosis [24], and a review describes a growing but heterogeneous evidence base [22]. Concentration, formulation, and quality vary between compounded products.
4) **Other topical agents:** Other topical anticholinergics, topical botulinum toxin preparations, and newer antimuscarinic soft drugs have been investigated, but the evidence is limited or at an early stage [5, 22].

6.3 Iontophoresis

1) **Mechanism:** In iontophoresis, the hands or feet are placed in shallow trays of tap water through which a low-intensity direct current is passed. The mechanism is uncertain. Suggested explanations include temporary blockage of the sweat duct and altered ductal or gland function [25, 26].
2) **Indications and use:** Iontophoresis is mainly used for palmar and plantar hyperhidrosis and is a standard first- or second-line option at these sites. Axillary use is possible with special pads but is less convenient. Treatment sessions are given several times a week until sweating is controlled, followed by maintenance sessions. Home devices are available after initial training [19, 26].
3) **Evidence:** Studies are mostly small. A controlled study of tap water iontophoresis in palmoplantar hyperhidrosis reported a significant reduction in sweating [25]. Adding an anticholinergic such as glycopyrrolate to the water has been tried, but the added benefit is not firmly established [26].
4) **Adverse effects and limitations:** Mild tingling, erythema, dryness, irritation, and occasional vesicles are common. The treatment is generally avoided in pregnancy and in patients with pacemakers, other implanted electrical devices, or metal implants in the treated area [26]. Practical limitations include the time commitment, the need for continued maintenance, and variable access to devices [19, 26].

6.4 Botulinum toxin therapy

1) **Mechanism:** Botulinum toxin type A blocks the release of acetylcholine from nerve terminals by cleaving SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) proteins needed for vesicle fusion. Injected into the skin, it interrupts cholinergic signaling to eccrine glands and reduces sweat production [19, 27].
2) **Evidence and duration:** Randomized, placebo-controlled trials have shown substantial reductions in axillary sweating after intradermal injection [27, 28]. In a 52-week trial of 322 patients, the median duration of effect was about 200 days with either 50 U or 75 U per axilla, compared with about 96 days with placebo [28]. In practice, relief generally lasts several months, after which

treatment must be repeated. Benefit has also been described for palmar, plantar, and craniofacial disease, but the evidence is less extensive [19, 21]. In the United States, regulatory approval covers severe primary axillary hyperhidrosis only, and insurance coverage for other sites may be limited [16].

3) **Practical use:** The toxin is injected intradermally at evenly spaced sites, often after the area has been outlined with the starch-iodine test. Local anesthesia, cooling, or nerve blocks are often used for palmar injections because of pain.
4) **Adverse effects and contraindications:** Injection-site pain and bruising are common. In the palms, temporary weakness of hand muscles can occur if the toxin spreads to deeper tissue. Compensatory sweating at other sites has been reported in a minority of patients [27]. Contraindications include infection at the injection site, hypersensitivity to the product, and neuromuscular junction disorders such as myasthenia gravis. Use in pregnancy and lactation is generally avoided because data are limited [16, 19].
5) **Suitable sites:** Evidence is strongest for the axillae. At the palms and soles, pain, cost, and the need for repeated treatment limit use, and botulinum toxin is usually reserved for patients who have not responded to, or cannot tolerate, other options [19, 21].

6.5 Systemic pharmacotherapy

Systemic treatment is mainly considered for generalized or multifocal disease, or for focal disease not controlled by topical measures or procedures. It is not curative and usually must be continued or repeated [19, 20].

1) **Oral anticholinergics:** Oxybutynin and glycopyrrolate are the most commonly used agents. In a randomized, placebo-controlled trial, oxybutynin improved palmar and axillary hyperhidrosis [29]. A multicenter trial of 62 adults, most with generalized disease, used low-dose oxybutynin titrated from 2.5 mg to a maximum of 7.5 mg daily. At least one-point HDSS improvement occurred in 60% of treated patients and 27% of those given a placebo, and dry mouth affected 43% and 11%, respectively [30]. Oral glycopyrronium bromide has been reported to help patients in an observational report [31]. Doses used in practice should be taken from current product information and local guidance.
2) **Adverse effects:** Effects are dose-related and reflect muscarinic blockade: dry mouth (the most frequent), blurred vision, constipation, urinary hesitancy or retention, tachycardia, and heat intolerance. Oxybutynin, a tertiary amine, can cross the blood–brain barrier and may cause drowsiness, dizziness, or cognitive effects, particularly in older adults. Glycopyrrolate is a quaternary amine that crosses the barrier less readily, but it is not free of systemic effects [29, 30].
3) **Contraindications, cautions, and monitoring:** Oral anticholinergics should be avoided or used with great caution in narrow-angle glaucoma, urinary retention, gastrointestinal obstruction or severe motility disorders, myasthenia gravis, and significant arrhythmia. Older adults are more vulnerable to cognitive and urinary effects, and the cumulative anticholinergic burden from other drugs (for example, tricyclic antidepressants, some antihistamines, and antipsychotics) should be reviewed. Patients should be reviewed after starting treatment for benefit and tolerability, including vision, bowel and bladder function, and mental state. Because sweating is reduced, heat exposure and vigorous exercise carry a risk of overheating [19].
4) **Other systemic options:** Clonidine, beta-blockers, benzodiazepines (mainly for anxiety-triggered sweating), and other anticholinergics such as propantheline have been used in individual patients. Evidence is largely limited to small studies and case reports, and adverse effects such as hypotension, sedation, or dependence limit their use [16, 19].

6.6 Device-based and procedural treatments

1) **Microwave thermolysis:** This technique delivers microwave energy to the axillary skin to heat and damage sweat glands at the junction of the dermis and subcutaneous fat, while cooling the skin surface. In a randomized, sham-controlled trial of 120 adults with primary axillary hyperhidrosis, treatment produced greater sweat reduction than sham treatment, and the study was funded by the device manufacturer [32]. Common effects are temporary swelling, soreness, and altered sensation. Because gland destruction is intended to be lasting, it may suit patients who want an alternative to repeated injections, although long-term data and cost-effectiveness need further study [19, 32].
2) **Laser and other energy-based therapies:** Lasers, radiofrequency devices, and microneedle radiofrequency have been used for axillary hyperhidrosis. They aim to damage sweat glands thermally. Studies are often small, uncontrolled, or heterogeneous, so these methods are options for selected patients rather than established first-line treatment [19, 21].
3) **Local surgical approaches:** For axillary disease, sweat gland excision, curettage, liposuction, or combinations of these remove or damage the glands. They can be effective but may cause scarring, hematoma, infection, altered sensation, and impaired wound healing. They are usually reserved for localized, refractory axillary disease [19].
4) **Endoscopic thoracic sympathectomy (ETS):** In ETS, sympathetic chain tissue at the upper thoracic level is interrupted by clipping, cutting, or ablation through small thoracoscopic incisions. A consensus document from the Society of Thoracic Surgeons concluded that ETS is the best-supported treatment for primary hyperhidrosis of the hands, axillae, and face, and suggested that the level of interruption be chosen according to the pattern of sweating: for example, the top of the third or fourth rib for palmar-only disease and the third rib for craniofacial disease [33]. This is an expert consensus rather than a formal guideline [33]. Reviews of non-surgical and surgical care place ETS late in the treatment sequence, after less invasive options have failed [2, 19]
5) **Compensatory hyperhidrosis and other adverse effects:** The most important adverse effect of ETS is compensatory hyperhidrosis, which is new or increased sweating in areas such as the trunk, back, abdomen, and thighs. It is frequent, can be severe, and is often permanent. The consensus document noted that interruption at a lower level may carry less compensatory

sweating but may leave the hands moister [33]. Other reported effects include gustatory sweating, Horner syndrome, pneumothorax, and bleeding [34]. A review of surgical complications stresses careful patient selection and full discussion of side effects before surgery [34]. ETS should therefore be reserved for severe, well-characterized primary focal disease unresponsive to other treatment, after thorough counselling about compensatory sweating and the irreversibility of the procedure.

Table 5: Comparison of main treatment options for primary focal hyperhidrosis

Treatment	Main sites	Key adverse effects and cautions	Main limitation	Evidence base
Aluminum chloride	Axilla; also palms, soles, and face	Skin irritation; clothing stains	Irritation limits adherence.	Modest; widely used [17, 19, 21]
Topical glycopyrronium	Axilla (approved); other sites off-label	Dry mouth, mydriasis, local reactions	Anticholinergic cautions; cost	Randomized trials for axilla [22, 23]
Iontophoresis	Palms, soles	Tingling, irritation; avoid with pacemakers or metal implants.	Time and maintenance	Small studies [25, 26]
Botulinum toxin A	Axilla (approved); palms and others less supported	Pain, transient muscle weakness (palms)	Repeat injections; cost	Randomized trials for axilla [27, 28]
Oral anticholinergics	Generalized or multifocal	Dry mouth, urinary and visual effects, CNS effects	Tolerability	Randomized trials [29, 30]
Microwave thermolysis	Axilla	Swelling, soreness, sensory change	Cost; limited long-term data	Sham-controlled trial [32]
Local axillary surgery	Axilla	Scarring, hematoma, infection	Invasive	Limited quality [19]
Thoracic sympathectomy	Palms (also axilla, face)	Compensatory sweating, Horner syndrome, pneumothorax	Irreversible; last resort	Expert consensus [33, 34]

RCT = randomized controlled trial; CNS = central nervous system. Evidence descriptions are summaries and do not replace product labelling.

6.7 Emerging and investigational therapies

Sofpironium bromide: Sofpironium bromide is a topical antimuscarinic "soft drug" designed to act locally and then be broken down quickly into less active metabolites in order to limit systemic anticholinergic effects [10, 22]. In a phase 3, randomized, double-blind, vehicle-controlled trial in Japan (281 patients with primary axillary hyperhidrosis), 5% gel was applied for 6 weeks. A significantly larger proportion of treated patients reached the combined endpoint of HDSS 1 or 2 plus at least 50% gravimetric sweat reduction (53.9% versus 36.4% with vehicle). Adverse reactions, mostly application-site dermatitis or erythema, were more frequent with sofpironium, and no serious adverse events were reported [10]. The gel is approved in Japan. In the United States, sofpironium topical gel (12.45%, equivalent to 15% sofpironium bromide) was approved in June 2024 for primary axillary hyperhidrosis in patients aged 9 years and older, applied once daily; the approval was based on two phase 3 trials [35]. Reported adverse effects include application-site reactions and anticholinergic effects such as dry mouth and blurred vision [35]. Because the drug is new, long-term experience, comparison with glycopyrronium or botulinum toxin, and data from non-axillary sites are limited.

Other formulations and combinations: Reviews describe other topical anticholinergics under study, including oxybutynin and umeclidinium preparations, as well as topical or transdermal botulinum toxin delivery. Most evidence comes from small or early-phase studies [5, 22]. In practice, treatments are often combined, for example, aluminum salts with iontophoresis, but few good trials test such combinations [2, 21]. Future work should aim for formulations that penetrate skin well while limiting systemic absorption [5, 22].

7. Treatment Algorithm

A practical stepwise approach to **primary focal hyperhidrosis**, adapted from published guidance and reviews [2, 7, 19, 20], is outlined in Table 6. It should be modified according to individual circumstances, product availability, and local regulations.

Table 6: Stepwise approach to primary focal hyperhidrosis

Step	Approach
Step 0	Take a history, examine, review medicines, and record severity with the HDSS. If secondary hyperhidrosis is suspected (Section 5.5), investigate and treat the cause or modify the offending drug.
Step 1	General measures and topical aluminum chloride, particularly for mild to moderate disease. Review after several weeks for response and skin tolerance.
Step 2	Site-directed second-line therapy if response is inadequate. Axilla: topical glycopyrronium or sofpironium (where available) or botulinum toxin. Palms and soles: iontophoresis, with topical anticholinergics as an option. Craniofacial: topical anticholinergic (often off-label or compounded) or, in selected cases, botulinum toxin with attention to facial muscle weakness.
Step 3	For severe or persistent disease: botulinum toxin (strongest evidence in the axilla) or oral anticholinergics (particularly for generalized, multifocal, or craniofacial disease), taking account of contraindications, age, comorbidity, and other medicines.
Step 4	For persistent axillary disease: microwave thermolysis or, where appropriate, other energy-based or local surgical methods.
Step 5	Endoscopic thoracic sympathectomy is only for severe, disabling disease that has failed other treatments, after counseling about compensatory sweating and irreversibility.
Throughout	Reassess with the HDSS, treat skin infections, address psychological distress, and discuss realistic expectations.

Sources: [2, 7, 19, 20, 33].

Secondary hyperhidrosis requires treatment of the underlying cause, for example, management of hyperthyroidism or infection, review of hormonal therapy, or changing or reducing a causative drug. Symptomatic measures from the algorithm may be used while the cause is addressed or if sweating persists [1, 8, 17].

8. Challenges and Future Perspectives

1) **Gaps in the evidence:** Many trials are small and short, and they use different definitions and outcome measures [21]. Evidence for palmar, plantar, and craniofacial disease is weaker than for axillary disease. Long-term follow-up is limited, particularly for newer agents, devices, and surgery. Head-to-head comparisons are scarce, and it is unclear which patient characteristics predict response to which treatment [2, 5, 21].
2) **Access, cost, and adherence:** Botulinum toxin, devices, and newer branded topical agents can be expensive, and insurance coverage varies by indication and site [3, 16]. Repeated injections, daily applications, and regular iontophoresis sessions require sustained effort, so adherence may decline over time Underdiagnosis and delayed care add to the burden [3, 4].
3) **Adverse effects:** Anticholinergic effects limit the dose and duration of oral treatment and may be poorly tolerated by older adults or patients with comorbidities [29, 30]. Topical agents can cause local irritation or anticholinergic effects [22], and surgery carries a risk of permanent compensatory sweating [33, 34]. Pharmacists can contribute by counseling, identifying interactions and additive anticholinergic burden, and monitoring tolerability.
4) **Personalized treatment:** Treatment choice should balance site, severity, age, comorbidity, other medicines, cost, patient preference, and psychological impact. Shared decision-making and validated measures such as the HDSS can support this [2, 7]. Research priorities include standardized outcome measures, comparative trials, formulations with low systemic absorption, and predictors of response [2, 5].

9. Conclusion

Hyperhidrosis is a common, chronic, and under-recognized condition that can substantially reduce quality of life. Primary focal hyperhidrosis is thought to reflect exaggerated cholinergic sympathetic stimulation of structurally normal eccrine glands, whereas secondary hyperhidrosis requires evaluation and management of an underlying disease or drug. Diagnosis is mainly clinical and is supported by the HDSS and, where needed, gravimetry and the starch-iodine test. Management is stepwise, from general measures and aluminum chloride through topical anticholinergics, iontophoresis, botulinum toxin, oral anticholinergics, and devices to, rarely, sympathectomy. Sofpironium bromide extends the topical options for axillary disease but has limited long-term data. Better comparative and long-term evidence, wider access, and individualized care remain key goals.

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