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CLINICAL PERSPECTIVE

Hyperhidrosis: don't sweat it

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Abstract

Hyperhidrosis is an under-reported and under-treated condition that causes significant patient morbidity. Secondary causes require consideration, but the vast majority of cases are idiopathic. The condition is encountered by a range of clinicians, including neurologists, dermatologists and endocrinologists, and it pays to be familiar with the range of highly effective treatment options available for the treatment of both focal and generalised sweating disorders. We outline the treatment options and therapeutic approach to the most common hyperhidrosis phenotypes, with illustrative cases.

Physiology and pathophysiology of sweating

Eccrine sweat glands, the most prevalent sweat gland type with a particularly high density in the palms and axillae, produce watery salt-rich solutions which thermoregulate. Eccrine sweat glands are the main sweat gland type implicated in hyperhidrosis. Being under sympathetic control, thermoregulation is primarily controlled by the hypothalamus, and control is transmitted via first-order to second-order neurons located in the anterior column of the spinal cord. Then, third-order effector neurons located in the thoracolumbar sympathetic chain release acetylcholine to activate muscarinic receptors on the sweat glands.[1] The basal activity of this system increases with higher temperature, exercise or emotional triggers such as anxiety. The eccrine glands are enlarged in hyperhidrosis but otherwise are ultrastructurally normal.[2] Biopsies from the sympathetic chain in primary hyperhidrosis demonstrates hypermyelination, with increased expression of neuregulin-1, an important regulator of axonal myelination, perhaps indicating an increased level of sympathetic tone.[3]

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The problem

Defined as excessive sweating beyond that required for normal thermoregulation, hyperhidrosis is estimated to affect ~5% of adults in the United States, with prevalence estimates up to 16% in certain populations.[4] The peak is in 18- to 39-year-olds, with genders affected equally but older patients having a different topographic pattern.[5] Less than half of patients seek care for this issue, and even fewer receive appropriate treatment.[5] Focal axillary hyperhidrosis is most common, followed by generalised hyperhidrosis.

Around 50% of persons with self-reported hyperhidrosis describe a reduced quality of life, and in some patients this approximates chronic diseases such as rheumatoid arthritis and multiple sclerosis.[6] Patients commonly report embarrassment related to the visible appearance of sweating or stained clothing, but sometimes also bromhidrosis, an unpleasant body odour. This is often exacerbated in the work setting whereby anxiety-provoking scenarios, such as giving presentations, temporarily worsen sweating. Focal palmar hyperhidrosis can make it difficult to grip objects such as a steering wheel and affect the ability to write and could create electrical hazards in some professions. Personal and social impacts are significant, and many avoid social situations and relationships. Those with partners report anxiety about how their sweating is perceived, restricting physical touch and intimacy. Comorbid mood disorders, particularly generalised anxiety, social

anxiety and depression, are much more prevalent in hyperhidrosis cohorts.[7]

In addition, excessive sweating predisposes to skin breakdown and irritation, as well as bacterial, fungal and viral skin. Non-infective skin conditions such as atopic dermatitis are also more common.[8]

Primary versus secondary hyperhidrosis

Hyperhidrosis is classified as either primary or secondary. Most presentations of hyperhidrosis relate to patients with primary hyperhidrosis. Primary hyperhidrosis refers to excessive sweating that is not driven by another medical condition and therefore is idiopathic. It most commonly presents focally, with the axillae the most commonly affected region, followed by the palms. Onset is typically in adolescence or early adulthood. A family history is common, with up to 60% of sufferers reporting a first-degree relative in palmar hyperhidrosis cohorts.[9] Despite many demonstrating an autosomal dominant pattern of inheritance, no clear single monogenetic cause has been identified.[4]

Secondary hyperhidrosis is self-explanatory, and although it is much less common, it is important to recognise cases to guide appropriate treatment. Secondary hyperhidrosis is more likely to be generalised and have an onset after the age of 25 years, and further investigation may be warranted for an underlying cause. An important clue is nocturnal sweating. The causes are broad (Table 1).

Table 1 Causes of secondary hyperhidrosis

Causes of secondary hyperhidrosis	
Medications	Antidepressants, especially SSRIs and TCAs
	Antipsychotics
	Acetylcholinesterase inhibitors e.g. pyridostigmine and donepezil
	Opioids, e.g. methadone
	Oestrogen modulators, e.g. tamoxifen and aromatase inhibitors
	Androgen deprivation therapy
	Immunosuppressants, e.g. cyclosporine
Endocrinopathies	Diabetes
	Hyperthyroidism
	Acromegaly
	Phaeochromocytoma
	Carcinoid syndrome
Neurological conditions	Parkinson disease
	Post-stroke†
	Frey syndrome†
	Ross and Harlequin syndrome†
	Spinal cord injury†
Other systemic conditions	Malignancies, especially lymphoma
	Chronic infections, e.g. tuberculosis
	Inflammatory arthropathies
	Cardiac or respiratory failure
	Menopause

†Associated with focal hyperhidrosis.
SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Management options for hyperhidrosis

Management consists of topical, oral or device-based therapies before consideration of injectable, ablative or surgical options (Table 2). Various methodologies exist to quantify the degree of affliction. Gravimetry allows a more precise characterisation of the degree of sweating but is largely used in interventional studies. The more simple four-point hyperhidrosis disease severity scale (Data S1) can be used by the treating physician to document the subjective qualitative degree of impairment and track response to treatment.[10]

Topical therapies

Topical therapies are considered first-line for the management of focal hyperhidrosis due to their ease of use, tolerability and efficacy. As the surface area of abnormal sweating increases, the practicality of using topical therapies diminishes, and therefore topical therapies are less commonly used in generalised hyperhidrosis.

The most common antiperspirants contain aluminium salts, typically aluminium chloride or hexahydrate. Over-the-counter antiperspirants contain 1%–2% aluminium chloride, but clinical-strength antiperspirants used for the management of hyperhidrosis contain 15%–25% aluminium chloride. When used appropriately, response rates of up to 98% have been reported for axillary hyperhidrosis, with a slightly lower response rates in palmoplantar hyperhidrosis.[11]

Aluminium salts react with mucopolysaccharides within the duct of eccrine sweat glands, forming an occlusive plug that prevents the excretion of sweat. To optimise the efficacy of aluminium salts, these products should be applied at night when sweat production is at its nadir. The duration of effect relates to the timing of epidermal renewal, and therefore repeated application is required, with most subjects requiring daily or second daily applications. A response is typically seen after 1–2 weeks of treatment.

Minor skin irritation is common, which may limit tolerability. Up to 70% of users report at least mild pruritis after application, which typically becomes less severe with

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Table 2 Treatment options available for hyperhidrosis

Treatment options for hyperhidrosis				
	Options	Uses	Efficacy	Side effects
Topical	Aluminium salts	Focal HH	98%[11]	Skin irritation
	Glycopyrrolate		63%[13]	Dry mouth, mydriasis
Oral	Anticholinergics	Focal or generalised HH	76%[14]	Dry mouth, drowsiness, constipation, urinary retention
	Propranolol		Anecdotal	Hypotension, bradycardia, bronchospasm
	Clonidine		Anecdotal	Hypotension
Iontophoresis		Focal HH	90%[15]	Skin irritation
Botulinum toxin		Focal HH	90%–98%[16,17]	Bleeding, infection, flu-like reaction, muscle weakness
Surgical	ETS	Focal HH	90%–100%[19]	Pneumothorax, Horner's syndrome, recurrent HH, compensatory HH very common

ETS, endoscopic thoracic sympathectomy; HH, hyperhidrosis.

ongoing use. Systemic absorption of aluminium salts is very low, and there is currently no clear epidemiological evidence linking aluminium-containing antiperspirants to an increased risk of diseases such as Alzheimer dementia or breast cancer.[12]

An alternate topical therapy for focal hyperhidrosis is glycopyrrolate, an anticholinergic muscarinic antagonist that inhibits terminal sympathetic signals. Glycopyrrolate can be applied through impregnated wipes (e.g. Qbrexza) or compounded into topical creams. An open-label study of glycopyrrolate-impregnated wipes found improvement in sweating in 63% of cases.[13] Typical anticholinergic side effects such as dry mouth and mydriasis are common. Patients must take care to clean their hands carefully after use to prevent inadvertent transfer through touching the eye, resulting in mydriasis.

Oral therapies

These are considered first-line for generalised hyperhidrosis, can be quite effective in craniofacial hyperhidrosis, and are usually second-line for axillary and palmoplantar hyperhidrosis. The most commonly used are muscarinic antagonists including glycopyrrolate and oxybutynin. A systematic review of oxybutynin-treated patients reported a response rate of 76%.[14] Anticholinergic side effects are more common with systemic than topical administration and are dose-related, and older patients may be more sensitive.

Propranolol, a non-selective β-adrenergic receptor inhibitor, is ideal for those who report episodic worsening in stressful situations and can be taken regularly or as the need arises. We also find propranolol useful for the management of craniofacial sweating, although caution should be exercised in patients with bradycardia, low blood pressure, asthma and predisposition to hypoglycaemia. Clonidine, a centrally acting α2-receptor agonist is a less commonly used sympathetic modulator, can also be considered in craniofacial hyperhidrosis.

Iontophoresis

Iontophoresis, a device-based therapy, uses low-level DC electrical current to pass ions through the surface of the skin, usually via a water bath. For practical reasons, this is primarily used for palmar and plantar hyperhidrosis. Up to 90% of patients with palmar hyperhidrosis respond to iontophoresis.[15] Most patients experience tingling in the submerged skin during treatment, and any cuts should be covered with petroleum jelly to reduce discomfort. Tap water contains dissolved salts and is typically sufficient but occasionally, a half teaspoon of bicarbonate soda is needed. Treatment is for 20–30 min every second day initially, then tapered down to twice weekly or weekly treatments as per the patient's response. The mechanism is debated, but the main hypotheses are that ionic transfer either forms plugs in sweat glands, similar to the mechanism of topical aluminium salts, or electrical activity downregulates sympathetic nerve endings in the treated skin.[15] Iontophoresis can also be used to promote drug delivery to the skin, and therefore glycopyrrolate or oxybutynin can also be added to the water bath to increase efficacy.

Botulinum toxin injections

Botulinum toxin is second- or third-line option for the management of focal hyperhidrosis when the response to topical or device-based therapies has been inadequate. It is typically used for axillary, palmar, plantar and craniofacial hyperhidrosis. Injections are given at the dermal-subcutaneous junction to maximise the exposure to eccrine sweat glands. Up to 96% of patients are satisfied with the response to axillary injections.[16] Response rates are slightly lower for palmar hyperhidrosis and

palmar injections are uncomfortable, so the authors prefer to perform this procedure with sedation. The average duration of effect is around 6–9 months.[17] Compensatory sweating in other body segments is an uncommon complication of this technique.[16] Diffusion of toxin to nearby muscle can result in weakness and is more problematic with palmar and craniofacial rather than axillary injections. Mild subjective hand weakness after treatment usually resolves within a few weeks.[17] The risk of bleeding and infection is typically low with subcutaneous botulinum toxin injections.

Ablative therapies

Ablative therapies rely on targeted and irreversible thermolysis of the eccrine sweat glands by microwave radiation or a focussed laser, creating localised heat at the dermal-subcutaneous junction. The most commonly available device is miraDry, which utilises microwave radiation and is licenced for use in axillary hyperhidrosis. Response rates of up to 90% are reported after 12 months.[18] The procedure is uncomfortable, requiring skin anaesthesia prior to treatment, with pain and swelling expected for a few days after the treatment. Axillary hair density is also often reduced after treatment. It is not suitable for palmoplantar hyperhidrosis.

Surgical therapies

The primary surgical option is endoscopic thoracic sympathectomy (ETS), used mainly for refractory palmar hyperhidrosis. The procedure aims to interrupt the supply of sympathetic inputs to the target organ. For palmar hyperhidrosis, the procedure involves creating a lesion to the sympathetic ganglia at the level of ribs 2–4, either through cauterisation or clipping. Immediate response rates approach 90%–100%; however, recurrent hyperhidrosis in the treated area is seen in up to 10% of patients on later follow-up. Compensatory hyperhidrosis in other areas is very common, occurring in 80% of patients.[19] This can be particularly difficult to treat and for some patients causes more disability than the pre-surgical hyperhidrotic condition. Therefore, patients should be carefully counselled prior to proceeding to ETS, particularly for plantar hyperhidrosis due to the urological and sexual dysfunction that often follows lumbar sympathectomy.

Surgical resection of axillary skin or local liposuction treatment are other, albeit uncommon, surgical treatment options for refractory sweating.

Figure 1 Treatment map for botulinum injections for axillary hyperhidrosis.

Clinical vignettes

Not all hyperhidrosis syndromes have the same treatment approach, and the following are some examples.

Axillary hyperhidrosis

A 33-year-old female presented with excessive axillary hyperhidrosis since adolescence with episodic exacerbations. She often wears darker clothing to reduce the visibility, a common strategy. High-dose aluminium-containing antiperspirants were insufficient and locally irritating. The patient had the sweating area defined with a starch iodine test and received toxin injections under local topical anaesthetic (Fig. 1), with a good clinical response. *Re*-treatment was undertaken every 6–9 months. Anticholinergics could have been considered, but there was a strong family history of glaucoma, and a low resting blood pressure precluded antihypertensives. More permanent therapies such as thermal ablation could also be considered if available.

Palmoplantar hyperhidrosis

A 25-year-old salesperson presented with concerns over palmar sweating (Fig. 2). This caused anxiety when shaking hands with clients and made gripping the steering wheel more difficult when driving. High-dose aluminium antiperspirants had resulted in a suboptimal response, and iontophoresis was trialled, but, although effective for a time, it proved too inconvenient for frequency of administration. Palmar toxin injections are often uncomfortable, and therefore, methoxyflurane inhaled self-administration was used, although local nerve blocks or distraction therapies could also be

Figure 2 Excessive palmar sweating prior to treatment.

considered. A marked improvement in palmar sweating was noted. Mild hand grip weakness resolved after 2 weeks.

Generalised hyperhidrosis

A 60-year-old female had a generalised increase in sweating over the last 5 years over the trunk, face, neck and axillae. The onset of the sweating coincided with the beginning of perimenopausal flushing symptoms. Given the generalised distribution and late-life onset, a secondary cause was considered, and mild hyperthyroidism was identified. A previous history of breast cancer was noted, with no evidence of recurrence. Excessive sweating persisted after appropriate treatment for hyperthyroidism. Oral glycopyrrolate was begun at 1 mg twice a day, and an adequate response was obtained at 2 mg twice a day with only mild xerostomia.

Craniofacial hyperhidrosis

A 48-year-old male complained of profuse facial sweating with minimal exertion. He carried a cloth at all times to wipe away sweat. High-dose aluminium-containing antiperspirants resulted in mild forehead erythema. With oral therapies being first-line for this region, propranolol was trialled, with a good response in this case, even though localised toxin injections to the hairline can also give a dramatic response.

Managing hyperhidrosis in Australia

For the majority of patients hyperhidrosis is easily treatable. Focal hyperhidrosis, such as of the axillae or palms, responds to topical therapies in more than 95% of cases, with high levels of patient satisfaction. Patients often trial high-dose aluminium antiperspirants prior to presenting to their general practitioner. Patients that do not respond to initial trials of topical therapies should be referred on for specialist assessment, with more advanced therapies controlling sweating in nearly all patients. Hyperhidrosis is typically treated by neurologists or dermatologists, and treating physicians can be found on the International Hyperhidrosis Society clinician finder portal (https://www.sweathelp.org/physician-finder/search.html). The International Hyperhidrosis Society is also a useful repository for both patient and clinician education material.

In Australia, the majority of hyperhidrosis care is provided in the private sector, and this provides a significant financial barrier to care. More advanced therapies often incur out-of-pocket costs to patients. Device-based therapies such as iontophoresis are not subsidised by the federal government; however, those with private health care can usually access a rebate to cover a portion of the costs. Botulinum toxin treatments are Medicare and PBS subsidised for axillary hyperhidrosis only. Therefore, botulinum toxin injections for palmoplantar or craniofacial are not subsidised and remain costly to patients. Ablative and surgical procedures also incur significant out-of-pocket costs.

Conclusion

Hyperhidrosis is an under-recognised condition with significant morbidity. Once secondary causes are excluded, the disorder should not be viewed as just a nuisance, and various treatment options can help patients lead a normal life. When successful, many patients frequently describe the intervention as life-changing, proving rewarding for the treating clinician.

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