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Diagnosis and management of hyperhidrosis

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SUMMARY POINTS

The prevalence of hyperhidrosis is estimated at 1%, but it is probably much higher owing to low levels of reporting to primary care
Onset tends to be at puberty, when axillary apocrine glands start to function, making axillary hyperhidrosis the most common type
Although prevalence is equal among the sexes, women are more likely to present to primary practice
Initial treatment in primary care should include lifestyle and behavioural advice and topical agents
If this approach does not work, refer to a dermatologist
Sympathectomy is reserved for people in whom conservative measures are ineffective or poorly tolerated, and who accept the risk of compensatory hyperhidrosis

Primary hyperhidrosis is characterised by sweating in excess of that needed for normal thermoregulation.[1] The condition often goes unreported because of embarrassment,[2] and management is hindered by a poor evidence base and lack of clinical guidelines. Anxiety about social situations and relationships, and problems with daily living, such as an inability to hold a pen at work, can affect quality of life.[3] Hyperhidrosis may be associated with bromhidrosis (unpleasant odour) from the byproducts of bacteria that colonise sweaty areas.[4 5] Subjective perceptions of the condition's impact on the person's life, and therefore its severity, can make confirmation of diagnosis and effective management challenging.[6] This review aims to provide an update on identifying this condition, instigating appropriate management, and when to refer to a specialist.

SOURCES AND SELECTION CRITERIA

We searched Medline, Embase, and the Cochrane database. Terms used alone and cross referenced were hyperhidrosis, botulin, iontophoresis, tumescent liposuction, oral therapy, topical therapy, and sympathectomy. We considered reviews, meta-analyses, randomised and non-randomised controlled trials, and large case series (owing to the lack of large volume trials). When possible, we used trials published within the past 10 years. The evidence for many treatments used in primary hyperhidrosis is poor, non-randomised, non-blinded, and with low subject numbers; we tried to clarify this in the text.

What is hyperhidrosis and who gets it?

Hyperhidrosis is classified as primary or secondary. Idiopathic focal sweating in an otherwise healthy person is classed as primary hyperhidrosis. Generalised sweating associated with any of the conditions or drugs listed in box 1 is classed as secondary.[7]

The reported prevalence of primary hyperhidrosis ranges from 1% to 2.8%.[2 8] In one large American national survey, only 38% of patients with primary pattern of symptoms had consulted a health professional.[2] It can present at any age, with an estimated prevalence of 1.6% in teenagers. It is uncommon in elderly people, suggesting spontaneous regression.[9]

Children tend to present with palmoplantar hyperhidrosis. Axillary hyperhidrosis is more common after the onset of puberty, and is almost certainly linked to the development of sweat glands. The axillae are most commonly affected (73%) followed by hands (45.9%), feet (41.1%), scalp (22.8%), and groin (9.3%).[1]

An epidemiological study of 508 patients in North America noted a higher preponderance in women (62.8% *v* 37.2%).[1] However, many other reviews quote equal ratios among the sexes, so this may represent higher presentation rates in women. The mean age of onset was 14 years old, with a 15 year delay in presentation to primary care. Most patients were white (87.9%).

A positive family history is reported in 65% of cases, suggesting a genetic association.[10]

What is the underlying pathophysiology of primary hyperhidrosis?

The pathophysiology remains unclear. Patients have a normal density of sweat glands but seem to overproduce sebum.[7] Most sweat glands are of the eccrine type, producing a thin fluid that is hypotonic to plasma that is involved in thermoregulation. They are most dense in the palms, soles, and axillae and can produce up to 10 L of sweat a day during stress, hot weather, or extreme physical effort.[9] Apocrine glands are histologically identical to eccrine glands but connect to hair follicles rather than directly on to the skin.

Normal sweating of the palms and soles begins soon after birth, whereas axillary sweating does not begin until puberty. This is related to the development of apocrine glands,[11] which increase in size and number until the age of 18 years, at which point they comprise up to 45% of all axillary glands.[12] Primary hyperhidrosis is associated with environmental and emotional triggers such as anxiety or stress, heat, exercise, tobacco, alcohol, and hot spices.[1 13] The glands are innervated by the sympathetic nervous system. Acetylcholine is the primary neurotransmitter. Spinal cord segments T2-8 supply the skin of the upper limbs, T1-4 the face and eyelids, T4-12 the trunk, and T10-L2 the lower limbs.[14]

How is primary hyperhidrosis diagnosed?

A comprehensive history must be taken to ensure that sweating is focal and not generalised (which indicates secondary hyperhidrosis) and the patient examined to detect any of the causes listed in box 1. Box 2 provides recommendations for diagnostic criteria from a multispecialty working group.[15] "Excessive sweating" is hard to define, but a level that has an unacceptable impact on quality of life is a good indication.[6] In primary care, the diagnosis may be guided by age (less than 25 years old according to working group criteria)—reviews suggest a peak of onset at 15-18 years, the age at which sweat glands become active.[9]

To make a diagnosis of primary hyperhidrosis, sweating should be focal and symmetrical. Record all areas affected and any specific triggers. Note a positive family history as well as any drugs. Record how often patients have problems, and how often excessive sweating prevents them from doing certain activities, because this will allow the effects of treatment to be assessed.

Indications that a patient has secondary hyperhidrosis include generalised sweating, predominantly night-time sweating (haematological cancer or infection, such as tuberculosis), use of drugs with related side effects, history of illicit drug use, weight loss (cancer), palpitations (thyrotoxicosis), or feeling systemically unwell. Measure full blood count, renal and liver function, erythrocyte sedimentation rate, thyroid function tests, and random glucose to rule out other disease. If any of the underlying causes in box 1 are suspected, patients should be investigated and referred on appropriately.

Tests such as gravimetry or the starch-iodine (Minor's) test are used as objective outcome measures in the research setting only.[16] In Minor's test, an iodine solution is applied followed by cornstarch. The sweat glands appear as small blue-black dots, indicating the area for treatment, but the test does not quantify sweat production.[16] Gravimetry measures the weight of liquid produced in one area in a given period. Axillary hyperhidrosis is defined as more than 50 mg of sweat a minute, but it is difficult to control for environmental and patient variability, so gravimetry is not used as a formal diagnostic test.[17]

In our hospital, the validated dermatology life quality index (DLQI) is used in initial assessment of the impact of sweating and to monitor the response to treatment.[18 19] Each answer is scored 0-3, resulting in a maximum of score of 30 and a minimum of 0. The higher the score, the greater the impact on quality of life.[19] The hyperhidrosis disease severity score is used to monitor treatment response in the research setting and is also used to decide point of entry into a treatment algorithm.[17 20]

What are the treatment options for primary hyperhidrosis in primary care?

The National Institute for Health and Care Excellence (NICE) has recently published recommendations for initial treatment in primary care.[21] They suggest avoiding spicy foods or alcohol, stressful situations, and identifiable emotional triggers.[13 22 23] Other recommendations include using antiperspirant spray rather than deodorant, wearing loose fitting clothes made of natural fibres, and using dress shields to absorb sweat. No formal outcome studies have investigated the impact of these measures on quality of life, and most are based on patient feedback.

What topical treatments are available for primary hyperhidrosis?

Aluminium chloride preparations are the most widely used first line agent (table). Aluminium ions are taken up by cells lining the sweat ducts, causing an osmotic influx of water. Swelling is thought to occlude the duct exit site, preventing sweat being deposited on to the skin. In all trials of this drug, the effects were not permanent. No formal trials have looked at how long the effects of aluminium chloride last after treatment is discontinued.[21] All forms (powder, roll-on, spray) are licensed in the United Kingdom for use anywhere on the body and are available online and over the counter without prescription. These products are designed for daily use initially (applied at night to dry skin) in conjunction with standard antiperspirant, then as required as symptoms improve. The main reported side effect is skin irritation. Other side effects depend on the preparation used and should be checked individually before starting treatment.

Box 1 | Differential diagnosis of generalised excessive sweating[7]

Infective: Acute viral or bacterial infections; chronic infections, such as tuberculosis, malaria, brucellosis

Drugs: For example, alcohol, cocaine, heroin (including withdrawal), ciprofloxacin, aciclovir, esomeprazole, sertraline, and other antidepressants

Endocrine: Diabetes, hyperthyroidism, menopause, pregnancy, carcinoid syndrome, hyperpituitarism, pheochromocytoma, acromegaly

Neurological disorders: Stroke, spinal cord injuries, gustatory sweating after parotidectomy, Parkinson's disease

Other: Lymphoma and other myeloproliferative disorders, congestive heart failure, anxiety, obesity

Box 2 | Multi-specialty working group recommended criteria for diagnosing hyperhidrosis[15]

Focal, visible, excessive sweating of at least six months' duration without apparent cause with at least two of the following characteristics:

- Bilateral and relatively symmetrical
- Impairs daily activities
- At least one episode a week
- Age of onset less than 25 years
- Positive family history
- Cessation of focal sweating during sleep

Suggested stepwise management of primary hyperhidrosis, summarised from published recommendations*[15 17 28]

Type of hyperhidrosis	Management steps				
	First	Second†	Third†	Fourth	Fifth
Axillary hyperhidrosis	Topical aluminium chloride at increasing doses as tolerated	Botulin A injections	Systemic anticholinergic treatment at increasing doses as tolerated	Iontophoresis using tap water ±topical anticholinergics	Thoracoscopic sympathectomy
Palmar hyperhidrosis	Topical aluminium chloride at increasing doses as tolerated	Iontophoresis using tap water ±topical anticholinergics	Systemic anticholinergic treatment at increasing doses as tolerated	Thoracoscopic sympathectomy	
Plantar hyperhidrosis	Topical aluminium chloride at increasing doses as tolerated	Iontophoresis using tap water ±topical anticholinergics	Systemic anticholinergic treatment at increasing doses as tolerated		
Craniofacial hyperhidrosis	Topical aluminium chloride at increasing doses as tolerated; topical glycopyrrolate	Systemic anticholinergic treatment at increasing doses as tolerated	Thoracoscopic sympathectomy		

*Other potential treatments based on low level evidence not included.
†There may be crossover between steps 2 and 3 for patients, depending on combinations of symptoms or patient preference.

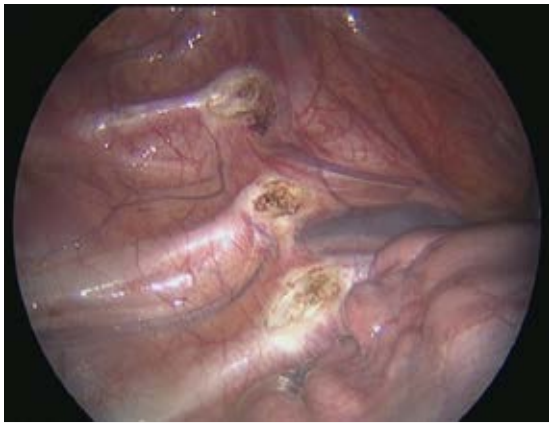

Image showing cauterisation of the sympathetic chain as it runs down the back of the chest cavity, over the heads of the ribs at the level of T2-4

A randomised unblinded trial of 20 patients with plantar hyperhidrosis compared 12.5% aluminium chloride hexahydrate with a 30% preparation over six weeks.[24] Both preparations significantly decreased sweat production measured by Minor's test, a "sniff test," and pH measurements; patient diaries were used to record side effects. No differences in tolerability were seen, which agrees with earlier findings (although these studies were equally small).[3] The trial found that the response was maximal by six weeks, suggesting that a higher aluminium chloride concentration should be tried if no benefit is seen by this point. This could be done in primary care or after referral to a dermatologist.

Glycopyrrolate is an anticholinergic drug that can be applied topically, although it is currently unlicensed for this method of application in the UK. Evidence for efficacy is restricted to small placebo controlled trials, which have shown satisfactory results in the form of patient reported outcomes for facial and axillary hyperhidrosis using the DLQI score. Larger scale trials are needed before it is used in regular practice.[25 26]

When should you refer to secondary care?

Once lifestyle advice and topical aluminium chloride have been trialled for at least six weeks (based on trial findings), refer patients who have not benefited or are still distressed by the severity of their symptoms to a dermatologist (table).

What treatments are available for primary hyperhidrosis after specialist referral?

Iontophoresis is a process in which an electric field drives the flow of ions in a medium. The mode of action in hyperhidrosis is unclear, although understanding is evolving.[27] Despite a relatively weak evidence base and a lack of long term data, many guidelines recommend its use.[17] Each palm or sole is placed in a small tray filled with tap water, through which a current of 15-20 mA is run. Treatment lasts for 30 minutes. Manufacturers supply their own recommended regimen. When patients think that the level of sweating is controlled, maintenance treatment is once a week or less. Side effects include a burning sensation, erythema, and small vesicle formation.[28]

As with all treatments for primary hyperhidrosis (except for sympathectomy, see below), iontophoresis requires ongoing maintenance. Once patients are established on an effective regimen, they can buy a machine to use at home. However, quality and safety vary according to the machine's site of manufacture and stringency of European standard markings, so patients who wish to trial home treatment should be guided by their dermatologist and warned of these risks. In a study of home iontophoresis,[29] 85% of patients reported ongoing improvement in symptoms, although 62% thought that home iontophoresis was "much less effective" than hospital treatment.

Some well defined but small double blind randomised controlled trials have shown a significant improvement with a solution mixed with botulin toxin compared with standard iontophoresis solution.[30 31] Less encouraging results have been shown for glycopyrrolate (0.05%) solution versus tap water, although in the UK it is licensed for use with iontophoresis, unlike botulin.[32]

Are any oral treatments available for primary hyperhidrosis?

Oral anticholinergic drugs are not currently licensed for UK use in primary hyperhidrosis, although they may be trialled in secondary care at the clinician's discretion. They act by competitive inhibition of acetylcholine at the muscarinic receptor. They are contraindicated in patients with myasthenia gravis, pyloric stenosis, and ileus, and they should be used with caution in those with gastro-oesophageal reflux, glaucoma, bladder outflow obstruction, and heart failure.[33]

In a well run but unblinded prospective trial of 35 patients with plantar hyperhidrosis, oxybutynin was taken in progressively higher doses—starting at 2.5 mg once daily, then increased to twice daily after one week and 5 mg twice daily at six weeks if tolerated. At the end of treatment, 70% of patients noted moderately or greatly improved quality of life, with 60% showing improvement at other anatomical sites.[34] At higher doses, 6% had urinary retention and 26% had severe dry mouth, known side effects of these drugs. Similar results were noted in a similar trial of oxybutynin versus placebo in palmar hyperhidrosis.[35]

In a small retrospective analysis of 24 patients treated with glycopyrrolate 2 mg twice daily, effective symptomatic relief was noted in 75% of patients, although a third had unacceptable side effects.[36] Glycopyrrolate can be considered as a second line treatment in moderate to severe palmar, plantar, or axillary hyperhidrosis (at the clinician's discretion).[33]

Finally, methantheline bromide has been shown to be effective in small randomised trials of patients with axillary hyperhidrosis, with little improvement for those with palmar disease.[37 38]

What is the role of botulin toxin?

Botulin toxin may be considered at different points in the treatment pathway, depending on which site is affected. In axillary hyperhidrosis, many guidelines avoid iontophoresis, so botulin is used when topical agents have not worked. In primary plantar hyperhidrosis, several algorithms place botulin alongside iontophoresis. Botulin A toxin (BTX-A) is the most commonly used and is administered on an outpatient basis by a variety of clinicians, including dermatologists, plastic surgeons, and vascular surgeons. The toxin inhibits acetylcholine release temporarily but more effectively than topical agents. The evidence base for its use is good, and several recent well performed studies confirm a 75-100% reduction in sweat after application and improvements in emotional and physical wellbeing.[39 40]

Effects are reported to last for six to nine months, and although reported levels of patient satisfaction are high,[41] treatment is potentially lifelong, raising concerns about cost effectiveness. Side effects are transient (bruising, flu-like symptoms, dry eyes, indigestion, and minor localised haemorrhage), and several well performed systematic reviews have confirmed the long term safety profile of botulin in the treatment of axillary hyperhidrosis.[28 42 43] Compensatory sweating has been reported after administration.[40 44] BTX-A has been tested in single blinded studies against placebo, saline injection, and local anaesthetics, and in well powered studies that have shown significantly improved satisfaction scores in patients with axillary hyperhidrosis. Comparison studies of different preparations have shown similar efficacy,[45] but again numbers were small.

A double blind randomised trial of 10 patients treated with two kinds of BTX-A (onabotulinumtoxinA and abobotulinumtoxinA) found comparable results using Minor's test and gravimetry.[46] Another double blinded trial of 46 patients with axillary hyperhidrosis compared Botox and Xeomin preparations using patient reported outcomes. Both treatments were equally effective, with only minor and well tolerated side effects reported.[47] In a single blinded, randomised study, the efficacy of BTX-A and botulin toxin B (BTX-B) was compared in 10 patients with axillary hyperhidrosis. All patients reported a reduction in sweat production, but gravimetry results were better for BTX-B.[48] A higher powered non-blinded comparison of the two preparations compared self reported outcomes in 84 patients (58 axillary hyperhidrosis AH, 26 palmar hyperhidrosis). BTX-A was used in the axillae, and a mix of the two injected into the palms. All patients were satisfied with the results, with significant improvements in DLQI score suggesting BTX-B can be used in this setting also.[49]

Because the availability and licensing of preparations varies internationally, we have not included information on botulin dosage. All licensed preparations provide recommended dosages, but a range of dosing regimens is described in the literature and depends on the patient's age and area covered.[11]

Botulin can be used in the palmar and plantar sites, but treatment is more painful in these areas than in the axillae. There have been small scale reports of several methods that might improve tolerance of these treatments. They are mostly unblinded, and no randomised controlled trials have compared techniques. Methods include application of ice packs for 15 minutes followed by topical 2.5% lidocaine cream for up to an hour before the procedure.[41] More robust, double blinded prospective studies of botulin with local anaesthetic have shown promise,[50 51] as has a small (40 patients) unblinded comparison of dichlorotetrafluoroethane spray compared with ice pack application.[52] Administration under peripheral nerve blockade was also effective during treatment of palmar hyperhidrosis.[53] Of concern, a recent single case report described small muscle wasting and weakness of the hands after use of botulin toxin within manufacturer guidelines.[54] Other studies have noted transient weakness in thumb-index finger grip after treatment, but no grip weakness.[55]

Are there any surgical options for treating primary hyperhidrosis?

Endoscopic thoracosympathectomy is the most commonly used surgical option, potentially providing permanent relief. It is reserved for those in whom other less invasive interventions have failed. Patients should be well informed about the irreversible nature of the surgery and the permanence of side effects, such as compensatory hyperhidrosis. Formally introduced in the 1980s, there is a large and reliable body of retrospective and prospective trial evidence on overall patient satisfaction, with reports of operative success ranging from 92% to 100%.[17] It is usually performed as a day case procedure under general anaesthesia by a subspecialist vascular surgeon. During the operation the sympathetic chain is divided, or clipped, within the pleural cavity (figure). Patients must be counselled carefully about the risk of complications, including pleuritic chest pain, pneumothorax or need for a chest drain, recurrent symptoms requiring reoperation, and Horner's syndrome.[56] Overall complication rates excluding compensatory hyperhidrosis (see below) have been quoted as 5.8-9.7%, although complications that need intervention are much lower (1.9-2.7%).[56 57]

Of particular concern to patients is compensatory hyperhidrosis elsewhere on the body. Although the development of this complication is unpredictable, the Society of Thoracic Surgeons consensus document recommends excluding patients with widespread hyperhidrosis from surgery.[58] It may be a physiological response to a reduced surface area for body cooling, with activity being increased in those areas left untreated.[59]

In a retrospective review of 170 patients who had undergone surgery, 85% of patients reported compensatory hyperhidrosis at one year.[60] In a recent series of 51 patients undergoing sympathectomy under a single surgeon at the T2-3 levels, 97.4% reported some degree of compensatory hyperhidrosis. The back was the most common site (42.1%), followed by chest (35.5%), abdomen (7.9%), face (5.3%), axillae (2.6%), thighs (2.6%), and feet (1.3%).[56]

A case report looking at the use of Botox to treat compensatory hyperhidrosis showed positive results, but there have been no controlled trials.[45]

Several prospective randomised studies have compared outcomes according to level of sympathectomy. A review of data on more than 6000 patients confirmed heterogeneity of population, techniques, and assessment tools among clinical trials.[61] Results, and therefore recommendations, vary.[57 59] A more recent and robust systematic review and meta-analysis focusing on palmar hyperhidrosis concluded that T3 and T3-4 sympathectomy provided the best clinical results, with T3 alone reducing the risk of compensatory hyperhidrosis.[62]

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