Review paper

Hyperhidrosis: disease aetiology, classification and management in the light of modern treatment modalities

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Abstract

Hyperhidrosis is a disorder of sweat glands characterized by overproduction of sweat, which is inadequate to the thermoregulatory needs of the body system. Owing to the heavy social and economic burden of the disproportionate perspiration, current treatment methods still do not seem to be sufficient enough to reach patients' expectations. Therefore, the researchers continue a robust pursuit of novel therapy modalities such as topical treatment methods, oral agents, minimally-invasive medical approach and surgical techniques. In this review article authors summarise the disease outline with the emphasis on the new era of hyperhidrosis treatment methods.

Key words: hyperhidrosis diagnosis, glycopyrrolate, oxybutynin, sofpironium bromide, sympathectomy

Introduction

The aetiology of excessive perspiration can be either primary or secondary to the systemic diseases. Considering many differences in its clinical manifestations and management, it becomes necessary for clinicians to determine the origin of hyperhidrosis in order to incorporate individually tailored treatment options, and thus, achieve a therapeutic success [1].

Moreover, the symptoms of sweat overproduction contribute to the major deterioration of patients' quality of life. They strongly affect manifold areas of life, such as psychological, social and even economic areas, leading to the disruption of daily life activities. They constitute a heavy burden for patients leading to self-isolation and loss of self-consciousness. Furthermore, they can be aggravated by stress and emotions which creates a vicious circle. Recently, researchers have observed an association between hyperhidrosis and the overall greater risk of psychiatric diseases, including depression [2, 3].

Hyperhidrosis has also a direct effect on skin condition by interfering with its natural protective mechanisms. This results in a greater prevalence of dermatoses among affected patients, especially of fungal, bacterial and less often viral origin [4]. Therefore, excessive perspiration constitutes a complex problem that requires a diligent professional care supported by the novel hyperhidrosis treatment modalities.

Hyperhidrosis epidemiology

Disproportionate perspiration is sometimes the cause of patients' significant emotional distress and reluctance to inform physicians about their symptoms. For this reason, researchers emphasize the fact that the prevalence of hyperhidrosis is highly underreported. Nevertheless, the epidemiological studies conducted among large population in the United States of America and Canada estimated the global prevalence of primary hyperhidrosis equally at about 2.0–3.0% for men and women [5, 6]. Stefaniak *et al.* performed a research among Polish medical and dentistry students and discovered that the occurrence of hyperhidrosis reached up to 8.0% of the study group [7]. Such data discrepancies might result from the characteristic study group profile, because primary excessive sweat production is the most common in the population of patients aged 20–25 years. A typical onset of symptoms is usually observed in individuals aged 14–25 years and their intensity mostly reduces with time. Every hyperhidrosis manifestation in older patients, i.e. above 60 years old, should urge physicians to seek for secondary causes of the disease. Additionally, a correlation between the location of sweat overproduction and patients' age was observed. Adolescents and young adults demonstrated the hyperhidrosis symptoms more often on palms, whereas adults around axillary areas [1, 8].

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Regulatory mechanisms of the sweat production

Human organism consists of about 2–4 million sweat glands, which play a key role in dermal and thermoregulatory homeostasis of the body. Approximately 80% of them is represented by eccrine sweat glands, which are evenly distributed all over the body, except for local concentrations on palms and soles. They are the main source of water evaporation out of the body system and provide optimal body temperature due to the production of odourless, transparent secretion of watery consistency. The remaining part consists of the apocrine sweat glands, which are responsible for thick excretion of an unpleasant odour. They are distributed focally predominantly around axillae, groins and external genital organs. Additionally, some researchers distinguish the apocrine sweat glands in the axillae region, which combine both patterns of sweat secretion [9].

The innervation of the sweat glands comes from the sympathetic nervous system, which is controlled by the central nervous system. Perspiration results from the activation of the supraoptic nucleus, localized in the anterior region of the hypothalamus and is triggered by certain stimuli (mainly emotional and thermal ones and physical exercise). It is hypothesized that the overproduction of sweat might result from the dysfunction of the autonomic system nerve fibres. What is more, this concept is supported by the histopathological findings of the overactive sweat glands, which demonstrate abnormalities neither in their structure, nor in their amount around the affected body area [9, 10].

Hyperhidrosis – classification and clinical manifestations

Hyperhidrosis can be classified as either primary or secondary to the systemic causes. Clinical manifestations of both types vary in terms of patients' age, family disease history, symptoms' onset, localization and triggering factors [1].

Primary hyperhidrosis

The aetiology of primary hyperhidrosis is idiopathic, with the highest incidence among young patients without any comorbidities. Furthermore, in about 30–50% of cases, a positive family history of the disease can be observed, which suggests a potential genetic background of the hyperhidrosis. Excessive perspiration usually manifests as a solitary focus or multiple symmetrically localized foci. The most frequently affected areas of the body are axillae (about 50%), soles (about 30%), palms (about 25%), and face (about 20%) [1, 11]. The symptoms that patients commonly complain about are sweaty stains on clothing, shoes or touched objects (for example paper sheets), visible sweat drops on the forehead, wet handshakes or sensation of body odour. The primary type of sweat overproduction occurs episodically and can be triggered by emotions and stress. In addition, the symptoms emerge during daytime and disappear over sleep [5, 11].

Apart from that, clinicians distinguish also other rare variants of primary hyperhidrosis. Hexsel's hyperhidrosis is characterized by excessive perspiration in the groin region, which can expand to anterior thigh surface, pubis, external genital organs and gluteal fissure. There are very few case reports describing localized unilateral hyperhidrosis, however, the genesis of the disease is still unknown [12, 13]. The Ross syndrome is a rare peripheral autonomic nerve fibre damage or degeneration of unknown mechanism, characterized by the triad of symptoms: uni- or bilateral segmental anhidrosis, Adie's tonic pupils and the absence of deep tendon reflexes. The subsequent localised compensatory hyperhidrosis constitutes the patients' major concern, although, other dysautonomia manifestations might appear (such as orthostatic hypotension, arrhythmia, dyspnoea, headache, gastroesophageal reflux and psychiatric disorders) [14, 15].

Secondary hyperhidrosis

On the other hand, secondary hyperhidrosis usually affects older patients and may result from fever, physiological processes like pregnancy or menopause as well as comorbid systemic diseases, drug adverse reactions or complications of medical procedures (for example after thoracic sympathectomy). In contrast to the primary type of the disease, secondary hyperhidrosis most often manifests itself as a generalized overproduction of sweat. The symptoms can also appear as asymmetrically localized foci. Moreover, the disease is not associated with any familial inheritance and may characteristically manifest itself during sleep as the night sweats [1].

Various systemic disorders can impair the thermoregulatory homeostasis of the body. Therefore, the exclusion of potential secondary causes of hyperhidrosis is an essential step in its diagnostic process. The most common triggering factors involve: proliferative diseases, endocrinopathies, cardiac, infectious, nervous system diseases, metabolic and psychiatric disorders [11, 16]. Excessive perspiration can also develop from adverse reactions after intake of a wide range of ubiquitous drugs like opioid analgesics and cyclooxygenase inhibitors, antibiotics and antivirals, cardiac and hypotensive medicaments, antidepressants and mood stabilizers, anticholinergic agents, antipyretics, hypoglycaemic agents or topically used formulas (for example glucocorticosteroids, isotretinoin) [17] (Table 1).

Secondary hyperhidrosis may also rarely manifest itself as a localized excessive perspiration, especially in the face area. It can be induced by intake of spicy meals, impairment of the sympathetic nervous system associated with pathology of the parotid gland (known as the Frey syndrome) or as a compensatory reaction after endoscopic thoracic sympathectomy [1]. Auriculotemporal syndrome

Table 1. The most common triggering factors of the secondary hyperhidrosis [11, 16, 17]

Physiological causes	
Menopause Pregnancy Fever	
Diseases	
Proliferative diseases	Myelodysplastic disorder Hodgkin's lymphoma
Endocrinopathies	Hyperthyroidism Pheochromocytoma Diabetes and hypoglycaemia Carcinoid syndrome Hypopituitarism and pituitary tumours Acromegaly
Cardiac diseases	Heart failure Endocarditis
Infectious diseases	Influenza HIV infection Tuberculosis Encephalitis
Nervous system diseases	Pituitary stroke Post-traumatic spinal cord injuries Parkinson's disease Familial dysautonomia Polyneuropathies
Metabolic disorders	Obesity
Psychiatric disorders	Alcoholism Generalized panic disorder Social phobia
Drug adverse reactions	
Opioid analgesics	Morphine, oxycodone, fentanyl, tramadol
Cyclooxygenase inhibitors	Naproxen, nabumetone
Antibiotics and antivirals	Ceftriaxone, ciprofloxacin, acyclovir
Cardiac and hypotensive medicaments	Amlodipine, nifedipine, verapamil, carvedilol, metoprolol, enalapril, lisinopril, losartan, hydralazine, propafenone
Antidepressants and mood stabilizers	Tricyclic antidepressants, neuroleptics
Hypoglycaemic agents	Insulin, glipizide
Topically used formulas	Glucocorticosteroids, isotretinoin

(also recognized as the Frey syndrome) is a relatively common postoperative injury of the nerve fibres after the parotidectomy procedure, although, rare cases following neck dissection, face lifting or mechanical trauma were reported. Due to aberrant parasympathetic sweat gland reinnervation, mastication or salivary stimuli trigger facial gustatory excessive perspiration with concomitant local flushing, burning, itching of the skin and neuralgia [18].

Hyperhidrosis diagnosis

Medical history and clinical presentation of the disease constitute a fundamental element of the hyperhidrosis diagnosis. The severity of the disease can be evaluated using a 4-score questionnaire Hyperhidrosis Disease Severity Scale (HDSS) based on patients' subjective perception of the daily routine disruption with the 4th level indicating the most exacerbated form of the sweat overproduction. Moreover, it is a valuable tool in clinicians' daily practice which helps to assess the efficacy of the therapy by monitoring its score reduction, which results in symptom alleviation by about 50% (1-point), and by nearly 80% (2-points) [19].

In case of concerns about the relevance of the diagnosis, clinicians can use the gravimetric method as an objective quantitative measurement of perspiration. It is an easy and quick technique, which involves wiping the area of excessive sweat production with a gauze, and thereafter, determining the difference in its weight. Furthermore, it is possible to verify the location of the overactive sweat glands by performing a starch-iodine test (also known as the Minor's test). Due to the chemical reaction between the iodine, starch and sweat, the excessive perspiration area colour turns purple, which enables its visualisation and implementation of targeted treatment methods. Other noteworthy methods for objective hyperhidrosis assessment involve dynamic sudorometry, thermoregulatory sweat test and skin conductance [17, 20, 21].

In order to distinguish between the primary and secondary type of hyperhidrosis the following factors should be taken into evaluation: symptom location and foci symmetry, frequency, duration, severity, occurrence at night, the onset of the disease, family history, the influence on daily life activities and other aspects pointing towards the presence of underlying systemic diseases. Furthermore, exclusion of the secondary causes of the excessive perspiration by performing laboratory tests is an obligatory step in every hyperhidrosis' diagnostic process. The prerequisite for primary hyperhidrosis diagnosis is the focal overproduction of sweat without any perceptible cause lasting for at least 6 months and co-occurrence of at least 4 following additional criteria: bilateral symmetrical excessive perspiration, minimal frequency of symptoms occurence of at least once per week, their occurrence limited to daytime, disruption of daily life activities, age onset before 25 years or positive family history [8, 11, 22].

Hyperhidrosis current and emerging topical treatment methods

Due to the heavy social and economic burden of the disproportionate perspiration, current treatment methods still seem to be insufficient to meet patients' expectations. Therefore, the researchers continue a robust pursuit of novel therapy modalities combining the most desirable

Table 2. Modern treatment modalities of primary hyperhidrosis [23–62]

Pharmacological	Medical procedures	Surgical
Aluminium chloride antiperspirants Glycopyrrolate Sofpironium bromide* Oxybutynin Oxybutynin and pilocarpine combination* Botulinum toxin	Iontophoresis Microwave thermolysis radiofrequency therapy Ultrasound technology Laser treatment	Local skin excision Liposuction-curettage Sympathectomy

**Emerging therapies.*

features i.e. complete symptoms' alleviation, elimination of the adverse reactions, convenient application and long-term effect duration. Topical treatment methods constitute the first-line therapy, followed by a wide range of alternative modalities such as oral agents, minimally invasive medical approach and surgical techniques (Table 2). Nevertheless, lifestyle changes are necessary and involve the avoidance of: factors provoking sweat overproduction, spicy meals or alcohol consumption and occlusive clothing or footwear [23].

Antiperspirants containing variable concentrations (from 5.0% to 25.0%) of the aluminium salts are a baseline treatment option of the mild and moderate sweat overproduction. Gels and powders which are rich in metal salts precipitate and temporarily obstruct the eccrine glands orifices until the stratum corneum exfoliates. The therapy involves a regular antiperspirant application on the cleaned and dried skin for the time period not shorter than 6 to 8 h, therefore nightly use is usually recommended. The amelioration of the disproportionate perspiration is usually observed after 1–2 weeks. Many trials and clinical experience endorsed the following method for the hyperhidrosis treatment in the axillary, palmar, plantar and craniofacial regions [23, 24]. Data from the research evaluating the overall aluminium salts efficacy in 691 patients indicated the effective disease control among about 80% of the study group. However, the therapy results may vary across the affected regions indicating the highest symptom reduction rate in the axillae and the lowest on palms [25, 26]. Skin irritation is the most common drug adverse reaction, which can be avoided by less frequent drug application or by the topical administration of the hydrocortisone ointments and emollients. Furthermore, recent concerns about the influence of the persistent aluminium exposure from the antiperspirants on the greater prevalence of the breast cancer and the Alzheimer's disease have not been confirmed in the latest reports. Therefore, aluminium chloride antiperspirants remain a cost-effective and safe topical treatment method of the focal hyperhidrosis [23, 27].

Glycopyrrolate is an anticholinergic agent, currently available as a 0.5–4% concentrated topical formulation recommended for the craniofacial and gustatory sweating treatment. The substance transdermal mechanism of action enables skin penetration and competitive inhibition of the muscarinic acetylcholine receptors responsible for the sweat glands overactivity. Simultaneously, the abundance and diffusion of the active drug is insufficient for the induction of the systemic response, which significantly reduces the possible adverse reactions. Further safety analysis showed no phototoxic, genotoxic or carcinogenic effect of the topical glycopyrrolate, and therefore, proved its suitability for chronic usage [26, 28].

In 2018, the United States Food and Drug Administration (FDA) approved an innovative treatment option of the primary axillary hyperhidrosis in the form of a cloth pre-moistened with the 2.4% concentration of glycopyrronium bromide. The method is dedicated to patients above 9 years old and provides a convenient drug application. Two randomized, double-blind, vehicle-controlled phase III trials ATMOS-1 and ATMOS-2 demonstrated high efficacy and safety profile of the therapy, followed by an acceptable level of the adverse effects and the consequent sporadic treatment discontinuation. In the supplementary studies, the researchers observed the prevalence of mild to moderate cholinergic-derived side effects among 2–25% patients, of which the most commonly reported were xerostomia, blurred vision, mydriasis, urinary hesitation, nasal dryness and xerophthalmia [29, 30].

The promising results of the latest phase II randomized, controlled, double-blind clinical trial might result in an introduction of a new anticholinergic gel formula – sofpironium bromide, a derivate of the glycopyrrolate – for the primary axillary hyperhidrosis treatment. The researchers performed an evaluation of the 5%, 10% and 15% active drug concentrations, which provided a clinically valuable response and a statically significant reduction of the excessive perspiration. Moreover, due to the developed retrometabolic drug design, the adverse effects were limited to those of a mild and moderate severity. Hence, topical sofpironium bromide modalities might be an efficacious hyperhidrosis treatment option in the foreseeable future [28, 31].

Oxybutynin in the transdermal formula proved to be a successful therapy of the overactive bladder in adults due to its anticholinergic effect. Two small pilot studies investigated the use of 3% and 10% oxybutynin gel for the focal hyperhidrosis management. Both demonstrated meaningful symptom reduction and patients' life quality enhancement. Although considerable systemic side

effects were infrequent or absent, a consecutive investigation upon the safety, efficacy and drug dosage of the method is necessary [32, 33].

Finally, a pioneering pharmaceutical enrichment of the botulin toxin A skin absorption in a liposomal cream demonstrated satisfactory results of a possible clinical application for the non-invasive excessive axillary perspiration therapy [34].

Hyperhidrosis systemic treatment methods

According to the experts' recommendations, oral therapies should be reserved for the patients non-responding to the topical treatment or multifocal hyperhidrosis. Systemic anticholinergic agents comprise the most common choice in the clinical practice regardless of the risk of their constitutional adverse reactions, which forces approximately 1/3 of the patients to cease the therapy. Additionally, there are some data available for the use of propranolol and clonidine in the anxiety-triggered sweat overproduction [23, 35].

Glycopyrrolate is a widely prescribed oral medicament with a fixed starting-point dosage of 1–2 mg daily. The inability of the glycopyrrolate to penetrate the hematoencephalic barrier is a favourable feature that limits the severity of the central nervous system-derived adverse reactions, and hence, allows for the possible dose augmentation to accomplish a satisfactory therapeutic effect [36, 37]. The alternative treatment involves 2.5 to 5 mg dose of oxybutynin that can be gradually increased up to 15 mg per day if the treatment is well tolerated. Reports of the oxybutynin efficacy found a 70% excessive perspiration reduction among subjects with palmar and axillary hyperhidrosis [38]. Nevertheless, the major side effects are the systemic adverse reactions which commonly involve xerostomia, xerophthalmia and blurred vision, constipation, hyperthermia, orthostatic hypotension, tachycardia, urinary retention, headache and dizziness [39]. Due to the anticholinergic mechanism of action, the following treatment is contraindicated in patients with myasthenia gravis, pyloric stenosis, paralytic ileus, closed-angle glaucoma or bladder outlet obstruction and other diseases requiring the use of the anti-Parkinson's remedies, phenothiazines and tricyclic antidepressants [23].

Interestingly, the latest development of an innovative compound containing a set dose of oxybutynin and pilocarpine (7.5 mg/7.5 mg) might redefine the role of the systemic anticholinergic agents in the clinical practice. In comparison to oxybutynin, its equivalent therapeutic effect was associated with a lower prevalence of xerostomia among the patients with axillary and palmar hyperhidrosis [40].

The use of medical devices and minimally invasive methods in the hyperhidrosis therapy

Iontophoresis is a widespread first-line treatment of the plantar and palmar disproportionate sweating. The regionally limited application arises from the requirement of the intact skin submersion in liquid, which enables the transduction of a galvanic current. Multiple mechanisms of action are proposed to be accountable for the perspiration inhibition, mainly the formation of the hyperkeratotic plug, change in the sweat electrochemical gradient, disruption of the autonomic nerves' transmission or the sweat pH value alterations [41, 42]. The therapy offers high anhidrotic efficacy and verified safety profile when applied for 3–4 weeks for 20–30 min at a current of 15–20 mA and the reported symptoms alleviation was perceivable after 6–15 treatment sessions. However, chronic use is required for the therapeutic effect maintenance which may trigger erythema and can be the source of patients' frustration [43, 44]. Recent method development allows for the enhancement of the therapeutic effect by combining iontophoresis with the simultaneous application of aluminium chloride, anticholinergic agents and botulinum toxin [45–47]. Nonetheless, the modality in contraindicated in pregnancy, epilepsy or in patients with implanted medical devices and pacemakers [23].

The expanding implementation of medical devices in the axillary hyperhidrosis treatment results in various modalities like microwave thermolysis, radiofrequency therapy, ultrasounds and laser treatment. Their fundamental therapeutic effect is based on the mechanical destruction of the eccrine sweat glands and confirmed by the follow-up histopathological analyses. Yet, the use of medical devices is not free from adverse effects, and importantly, entails significant expenses [44].

Furthermore, dermal-subcutaneous injections of the botulinum toxin (BTX) A and B formulations are a noteworthy treatment approach registered for the primary axillary hyperhidrosis. However, numerous clinical studies provided evidence for its therapeutic value in the off-label use for the focal disproportionate perspiration in the palms, soles, inguinal and craniofacial regions [48]. Although the fundamental Frey syndrome treatment approach is concentrated on the surgical prevention techniques, the BTX A intracutaneous injections in the facial area are reported to be an effective temporal method [49]. Furthermore, the BTX segmental administration, alongside with tap water iontophoresis, are two modalities for symptomatic treatment of the Ross syndrome [50, 51]. The BTX main mechanism of action involves chemical denervation of the sweat glands by acetylcholine release inhibition from the presynaptic neurons. Therefore, the method is contraindicated in case of myasthenia, Lambert-Eaton syndrome, pregnancy and cutaneous infections in the administration area [23]. The advantage of BTX over other hyperhidrosis treatment modalities is due to its high safety profile, significant perspiration reduction rate (around 80% for axillae and the lowest for soles – about 50%) and long-lasting anhidrotic effect (about 6–8 months) [52, 53]. Although the permanent hyperhidrosis control requires regular BTX injections, its repeated supply might prolong the therapeutic

effect to 7–9.5 months [54]. Moreover, BTX B may exhibit moderately stronger autonomic effect and less impaired motor function in contrast to BTX A [55]. The principal limitations involve transitional muscle weakness, overall high therapy cost and, most importantly, painful delivery. Therefore, considering the latest, clinicians seek for new resolutions of pain alleviation which include: cold ice packs, vibration, topical lidocaine with prilocaine analgesia, dilution of BTX in lidocaine solution with transdermal administration by jet nebulization or multiple punctures injections [56–59].

Hyperhidrosis surgical treatment methods

Surgical invasive treatment is considered as a therapeutic option in the most severe hyperhidrosis cases that are unresponsive to the conservative modalities. Retrodermal curettage involves mechanical removal of the sweat glands restricted to the axillary areas, and thus, permanent primary axillary hyperhidrosis symptoms alleviation. On the other hand, limited number of studies and discrepancies in surgical techniques contribute to the ambiguous evaluation of the long-term therapeutic efficacy [60].

Finally, thoracic or lumbar sympathectomy is an advanced surgical procedure requiring general anaesthesia. The disruption of the sympathetic trunk allows for the 95% complete regain of focal perspiration control confirmed by short- and long-term follow-up clinical studies. Furthermore, the method proved to ensure a significant increase in patients' quality of life. Nevertheless, in some cases compensatory sweating in the abdominal-lumbar areas, groins and thighs might constitute a major procedure adverse consequence [61, 62].

In conclusion, the individual approach considering the hyperhidrosis aetiology, location and severity is vital to adjust efficacious and patient-acceptable therapy from various available treatment modalities.

Conflict of interest

The authors declare no conflict of interest.

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