SYNOPSIS OF THERAPEUTIC OPTIONS IN HYPERHIDROSIS

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Summary

Hyperhidrosis is a disease characterized by excessive sweating, which can become a burden to patients, interfering with daily social and proffesional activities, as well as inducing a sense of shame and low self-esteem. It can be primary (idiopathic) or secondary to an underlying disease, and it can be generalized, involving the entire area of the body, or focal, restricted to certain anatomic regions, most often axillary, palmar or plantar. Patients rarely seek medical attention for this affliction due in part to the fact that they are sometimes unaware that the condition is treatable. There are various therapeutic options available for hyperhidrosis, conventional as well as novel therapies, which present a varying degree of success. This article strives to present treatment options available for hyperhidrosis and assess their efficiency according to various studies from medical literature.

Keywords: *hyperhidrosis, oxybutynin, iontophoresis, botulinum toxin, microwave therapy, retro dermal curettage.*

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Introduction

Hyperhidrosis affects 1–3% of the population and has a higher incidence among adolescents and young adults. Also, it has an even distribution among sexes [1-2]. This affliction has a significant negative impact on the quality of life of patients, being a disturbing factor to a patient's social, professional, psychological, and physical well-being. Patients often experience embarrassment and experience discomfort due to dampening of clothing items which require frequent changing. In addition, patients have difficulty in undertaking various activities, mainly due to palmar hyperhidrosis, such as handling papers, documents and touch screen devices. However, many patients do not realize they have a treatable medical condition, therefore hyperhidrosis remains widely underdiagnosed and undertreated [3]. American studies, such as *Strutton et al.* [4], report that only 38% of patients had discussed their sweating with a healthcare professional.

Numerous therapeutic options are utilized with varying degrees of success. These therapeutic options differ according to the degree invasiveness, treatment efficiency, side-effects and patient satisfaction. Apart from conventional treatment options, new methods have also been reported, such as laser technology or micro-wave and ultrasound therapy, which are currently tested and applied with promising results [5-6]. However, all conventional or new therapeutic options for hyperhidrosis require regular supervision by a dermatologist in order to evaluate treatment evolution.

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There are sufficient published reports concerning therapeutic results of singular methods for hyperhidrosis, conventional or newly proposed, but only a few provide an overview or a comparative image of all therapeutic options in use [7-9]. In addition, from our knowledge, there are not any reports in Romania concerning this disease, at least for the last decade. Therefore, the present paper will focus on presenting the current therapeutic options for hyperhidrosis by comparing their efficiency, the benefits of each treatment, possible side-effects, with a specific accent on adapting each therapy to individual patient requirements. Beside classical methods applied at the moment, there are also indicated some novel therapeutic methods that are of most interest for achieving maximum symptomatic improvement with minimum side-effects.

Definitions, Diagnosis and Assessment

Hyperhidrosis is an affliction which is defined as abnormally abundant sweat, well over the level necessary for body heat thermo-regulation [10, 11]. Hyperhidrosis is caused by an excessive function of the sudomotor sweat control system which, in turn, translates into hyperactive sweat glands [1]. Sweat glands are divided in three categories, according to structure, area of anatomic distribution, function, secretory products, and mechanism of excretion [9]:

– Eccrine
– Apocrine
– Apoeccrine

Eccrine sweat glands are distributed in varying densities across the surface of the skin, with the exceptions of such areas as: lips, external acoustic meatus, prepuce, glans penis, labia minora and clitoris [1]. They are 10 times smaller the apocrine sweat glands and open directly on the skin surface. Eccrine sweat is a dilute salt solution. The secretion activity rate is controlled by neural and hormonal mechanisms. At peak capacity, eccrine glands produce over 3 liters of sweat per hour [1].

Apocrine sweat glands are located in limited areas of the body, mainly in the axillary region, the perineum, around the nipples, and are present in modified versions in the external acoustic meatus and eyelids [11]. Their activity begins at puberty. Before puberty apocrine glands are small and inactive. Once puberty is reached, they grow in size, and in adults, apocrine glands are significantly larger than eccrine glands. They secrete small quantities of oily substance, which includes lipids, cholesterol and steroids. The excretory duct does not open directly onto the skin surface but rather into the pilary canal of the hair follicle. Apocrine sweat is initially odorless. However, it is degraded by the resident bacteria on the skin and is responsible for the characteristic odor of each individual [11-14].

Apoeccrine sweat glands are a mixed type of sweat glands. They evolve during puberty from eccrine sweat glands and represent approximately 50% of the sweat glands in the axillary region [15]. They continuously secrete a watery sweat, which has similar sodium and potassium levels as those present in eccrine sweat. This type of sweat gland has a higher response rate to cholinergic and adrenergic stimuli than that of an eccrine gland, and the secretion rate is overall higher compared to other types of sweat glands [12].

Hyperhidrosis is *primary* (idiopathic) or *secondary* to other diseases. It can be *generalized* (which causes are indicated in Table 1), involving the entire surface area of the skin, or *focal*, involving restricted areas of the body, primarily axillary, palmar, plantar or facial region [16]. *Secondary hyperhidrosis* can be either generalized or focal and is the result of an underlying disease of endocrine, neurological or infectious origin [15]. Hyperhidrosis can be further classified in regards to anatomical area of distribution: unilateral or bilateral and symmetrical.

Primary hyperhidrosis is idiopathic and focal. It is an affliction of the eccrine sweat glands and is associated with a high sympathetic activity. It has no particular predilection for either sex. Most often it affects population aged 25 to 64 [17]. Axillary hyperhidrosis is the most common type, present in up to 80% of cases, followed by palmar and plantar hyperhidrosis [1-2]. The Japanese population has been observed to have a higher

incidence frequency, being afflicted up to 20 times more often than other ethnic groups [18]. Genetic predisposition is present in 30-50% of cases, with an autosomal dominant inheritance pattern, incomplete penetrance and variable phenotype [18].

Diagnostic criteria include excessive sweating for at least 6 months with 4 or more of the following criteria [19]:

– Primary involvement of regions with a high density of eccrine glands.
– Bilateral and symmetrical distribution.
– Absence of clinical signs during sleep.
– Weekly episodes.
– Onset at 25 years of age or younger.
– Positive family history.
– Impairment of daily activities.

In order to assess the severity of hyperhidrosis several types of subjective measurements have been devised. Among those that are utilized often are DLQI (*Dermatological Life Quality Index*) and HDSS (*Hyperhidrosis Disease Severity Scale*) [20].

Table 1. Causes of generalized hyperhidrosis [7]

Endocrine diseases	- Menopause[1] - Hyperthyroidism[1] - Diabetes[2] - Hypoglycaemia[2] - Pheochromocytoma[3] - Hyperpituitarism[3] - Carcinoid syndrome[3]
Medications[1]	- propranolol - tricyclic antidepressants - cholinesterase inhibitors - selective serotonin reuptake inhibitors - opioids
Febrile infective illness[2]	- malaria - tuberculosis - endocarditis - HIV (seropositive patients)
Congestive heart failure[2]	
Neurological disorders[2]	- Parkinson disease - peripheral neuropathies - brain lesions (e.g. malformation of corpus callosum)
Malignancy[3]	

1 - uncommon
2 - very uncommon
3 - rare

DLQI is a general questionnaire utilized frequently in dermatology for assessing the emotional impact that diseases have on patients.

HDSS (Table 2) is a questionnaire created specifically for patients with hyperhidrosis [20]. This measurement device presents four degrees of quantifying the severity of the impact the disease has on the patient, on the emotional state and the impairment of daily activities. It varies from a degree of affliction which does not impair the patient's daily and social activities and presents a level of sweating which is not noticeable or uncomfortable up to a level at which the daily activities are severely impaired and the level of sweat is intolerable.

Table 2. Hyperhidrosis Disease Severity Scale (HDSS) proposed by [20]

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

Although the patient's assessment of his condition is important in the course of treatment, an objective assessment of hyperhidrosis is also necessary, especially in the case of focal hyperhidrosis.

There are various diagnostic methods that assess the severity and extent of hyperhidrosis:

– One of these methods is the *iodine starch test* which allows direct visualization of affected areas [9]. A mixture of 0.5 to 1g of iodine crystals are applied to the affected areas, followed by 500 g of soluble starch. Areas with abnormally high secretion rates will present a black colour following the test.
– Another diagnostic method is the *Minor test*, which relies on the same principle as the previous test with the added benefit of a quantitative assessment through gravimetric analysis [21]. The area will be shaved, cleaned and dried prior to the test. Iodine solution, 3.5% in alcohol, will be applied followed by a dusting of starch

flour. The analyzed area will present a violet colour, indicative of excessive sweating. In order to assess the amount of sweat secreted, filter paper will be applied to the specific area for a predetermined period of time (1–5 minutes). The paper will be weighed before and after exposure, the difference in weight signifying the amount of sweat produced in the given time (mg/min) [9]. Axillary hyperhidrosis is defined as a rate of secretion which exceeds 50 mg/min [22].

Consequences of Hyperhidrosis

Apart from the discomfort this disease causes patient, hyperhidrosis may lead to other dermatological diseases. Due to the humid state of the skin, skin infections may develop. Intertriginous areas, particularly in axillary hyperhidrosis are predisposed to irritative dermatitis and infection. Palmar hyperhidrosis can lead to dyshidrotic eczema (*pompholyx*). Plantar hyperhidrosis can be lead to unpleasant odor, dyshidrotic eczema, pitted keratolysis, skin maceration, tinea pedis and onychomycosis [15].

Another consequence of hyperhidrosis is the possible development of bromhidrosis. This is a chronic affliction which presents with abnormally unpleasant body odor [1]. It is secondary to an excessive secretion of eccrine or apocrine sweat glands, the secretion becoming malodorous following bacterial breakdown. Bromhidrosis of apocrine origin is the most common form, patients with this type of affliction having apocrine glands in greater numbers and with larger proportions. The sweat secretion of these glands is subjected to bacterial breakdown and produces ammonia and short chain fatty acids which are responsible for the characteristic unpleasant odor [23-24].

Bromhidrosis occurs most often in the axillary region and is often unnoticed by the patient but rather by family members. In some cases, patients who complain of malodorous axillary sweat do not clinically present this problem. The false perception of unpleasant odor may be a symptom of psychiatric nature, such as paranoia or phobia, or is secondary to a lesion of the central nervous system. In addition, intranasal foreign bodies or chronic fungal infection of the sinuses may also cause the erroneous perception of unpleasant axillary sweat [25].

Antibacterial soaps and commercial antiperspirants can be used to control axillary bromhidrosis. Frequent baths, changing undergarments, hair removal and topical application of aluminum salts are also efficient methods.

Therapeutic options

The therapeutic options of hyperhidrosis are summarized in the Table 3 and are described and discussed below. The selection of a specific treatment depends on severity of the diagnosed hyperhidrosis, on other possible associated diseases and also on possible benefits or risks of the selected variant, that must be discussed with the patient.

1. **Topical treatment**

Topical treatment is the first choice in hyperhidrosis. Topical agents include: boric acid, topical anticholinergic agents, tannic acid solution 2–5%, resorcinol, potassium permanganate, formaldehyde, glutaraldehyde, methenamine [26]. However, these agents have limited efficacy and their use is limited due to adverse reactions

Table 3. The algorithm of hyperhidrosis treatment

Algorithm: Treatment of Hyperhidrosis					
	First line	**Second line**	**Third line**	**Fourth line**	**Final options**
Axillary	Topical Antiperspirant	Iontophoresis	Botulinum Toxin	Retrodermal curettage	Endoscopic thoracic sympathectomy
Palmar					

such as staining of garments, irritative reactions on application areas and skin staining.

Aluminum salt solutions are the most often utilized form of antiperspirant [27]. Aluminum chloride is an efficient antiperspirant which blocks the pores of sweat glands. Metal ions precipitate mucopolysaccharides, damaging epithelial cells along to duct of the sweat gland and thus creating a plug which will in turn block sweat secretion along with atrophy of the eccrine acini [28]. Sweat glands continue their secretion which, in case of thermic stress, may lead to *miliaria* due to the accumulation of sweat behind the blockage created by the metallic salts [28]. However, sweat glands resume their secretion along with epidermal regeneration, which will necessitate further application of the antiperspirant once or twice a week.

Aluminum chloride (20–25% aluminum chloride in 70% alcohol) is a popular first line treatment in clinical hyperhidrosis, especially for palms and axillae [8]. This usually provides effective control for mild to moderate hyperhidrosis. However, its continued use is often limited by rashes, stinging sensations and irritation. Therefore, it should not be used on recently shaved, irritated or broken skin.

Products which contain 10–20% aluminum chloride hexahydrate are an efficient treatment for axillary hyperhidrosis. A study conducted by *Goh* [29], found that in the case of 20% aluminum chloride, hyperhidrosis is reduced for 48 hours after application, although the effects disappear in 48 hours after cessation of treatment.

Products containing 25% aluminum chloride hexahydrate are used for palmar and plantar hyperhidrosis [30-31]. Initially, a concentration of 10% is a safe starting point for topical treatment in order to avoid localized skin irritations and burning sensations. Some patients may require higher doses, up to 35% if it is well tolerated and there has been no previous response with lower doses. The treatment will be applied in the axillary region each night, but the side effects are rarely tolerated at this strength in the axilla. Associated skin irritation can be controlled with 1% hydrocortisone [7]. Some studies have shown that there is no added benefit from applying an occlusive dressing [30]. In the case of palmar hyperhidrosis, this type of therapy has proved less efficient.

A study by *Benohanian et al* [32], has reviewed the effects of changing the vehicle for aluminum chloride from an alcohol solution to 4% salicylic acid in a hydro alcoholic gel base. Salicylic acid was chosen for its beneficial properties regarding the enhancement of aluminum chloride absorption and reduction of skin dryness and irritations. The study was conducted on 238 patients with axillar, palmar and plantar hyperhidrosis and excellent results were reported in 94% (axilla), 60% (hands) and 84% (feet) of patients. The patients who had previously utilized aluminum chloride in alcohol solution reported an improvement in their disease burden with this formulation.

2. **Systemic therapy**

Systemic therapy includes anticholinergic agents such as propantheline bromide, glycopyrrolate, oxybutynin and benztropine [33-34].

Among these, *oxybutynin*, which is an antimuscarinic agent, is considered and utilized as second line therapy in hyperhidrosis, by proving its efficacy in focal hyperhidrosis as well in generalized hyperhidrosis [10, 35]. The most common side effect, present in almost all cases, is xerostomia. The use of oxybutynin is contraindicated for patients with urinary retention, impaired motility of gastrointestinal tract or glaucoma [36]. Treatment regimen used for oxybutynin usually begins with a dose of 2.5 mg/day in the first week of treatment and can be increased up to 10mg/day after 3 weeks or until an improvement is observed [37]. Selective serotonin reuptake inhibitor (SSRI) induced hyperhidrosis also responds well to oxybutynin.

A case report [36] of successful treatment of hyperhidrosis with the anticholinergic drug oxybutynin indicate a woman with a history of hyperhidrosis that has been treated with oxybutynin for urge incontinence and who noticed resolution of her hyperhidrosis that continued through a 6-month follow-up period.

Glycopyrrolate and *propantheline bromide* have also been used, although the doses required for systemic therapy often result in unpleasant side-effects such as xerostomia, tachycardia, urinary

retention and constipation, similar to those reported in the case of oxybutynin [38-39]. A retrospective study of 24 patients conducted by *Bajaj et al* [40] reviewed the use of oral glycopyrrolate with a response in 79% of patients. However, the treatment was not agreeable to patients due to the side-effects and as such was limited and eventually discontinued.

Propantheline bromide and oxybutynin are the most accessible regarding price, as opposed to glycopyrrolate which is an effective alternative, but as an expensive treatment is limiting for patients.

3. **Iontophoresis**

Iontophoresis is a procedure which entails the transdermic passing of a galvanic current [3, 41-42]. Moistened pads are applied to the skin. A direct electric current is passed through the solution. Although the exact mechanism of action at the sweat gland is unknown, the intent is to block, in a reversible manner, the ion channel which will in turn lead to a blockage of sweat glands in the treated area [29]. It can be utilized in patients who have had no satisfactory results with topical agents. Iontophoresis appears to be safe in normal patients and its only common side-effect is mild irritation that responds well to hydrocortisone cream [21].

Iontophoresis with plain tap water or saline solution (either alone or with anticholinergic drugs) is a treatment often utilized for idiopathic hyperhidrosis and is efficient in palmar and plantar regions [21]. Iontophoresis devices are commercially available and can be purchased for home use. However, this type of treatment requires long-term use in order to sustain the desired effect and most patients report re-appearance of symptoms within weeks after discontinuation, therefore they find iontophoresis time-consuming and inefficient [39]. In addition, iontophoresis does not lend itself to the treatment of axillary hyperhidrosis and is an impractical choice due to the local anatomy.

Iontophoresis with anticholinergic agents seems to yield superior results than tap water iontophoresis, with a faster onset of effects and a longer period of sweat reduction. This type of method is preferred, given that systemic anticholinergic treatment can cause side-effects such as glaucoma, urinary retention and constipation [43-46]. However, mild systemic side-effects have been noted, such as sore or dry throat [47].

Dolianitis et al [47] have studied the efficiency of iontophoresis with glycopyrrolate and have concluded that the positive outcome was due to local as well as systemic effects, with patients reporting only mild side-effects. *Karakoc et al* [41] conducted a study of 112 patients treated with iontophoresis for palmar hyperhidrosis. A significant reduction in sweat intensity was observed, with 81.2% of patients being satisfied with the outcome of their treatment. The study also observed an interesting result, 65 patients reporting a simultaneous improvement of plantar hyperhidrosis even though this was not the target area. This outcome led to a hypothesis, the authors suggesting that a biofeedback mechanism is involved in the therapeutic action of iontophoresis.

Iontophoresis has also proven efficient in the percutaneous delivery of botulinum toxin (BTX-A). In the case of this therapeutic combination, sweat reduction has proven to last up to 16 weeks [48].

Iontophoresis is contraindicated in pregnant women, patients with a pacemaker and metal implants.

4. **Botulinum toxin**

Botulinum toxin is a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. Botulinum toxin inhibits reversibly the release of neurotransmitter acetylcholine to the presynaptic membrane. This in turn leads to a blockage of the signal to the neuromuscular junction, or in the case of hyperhidrosis treatment, to the sweat glands.

This type of treatment is efficient in the case of axillary and palmar hyperhidrosis [49-54]. Before the botulinum injection a Minor iodine-starch test is performed in order to clearly visualize the hyperhidrotic area. The area will also be marked with a grid pattern in order to facilitate a uniform distribution of the toxin [55]. Topical application of lidocaine cream can be used to reduce the pain of injection. In the case of axillary hyperhidrosis, application of 1 U/cm^2

seems to be efficient, and yields results that last for 6 to 8 months.

Botulinum toxins A and B are two of the seven antigenically distinct serotypes of toxin produced by *C. botulinum*. Both botulinum toxin A and B have been proven to be equally efficient in the treatment of axillary hyperhidrosis, although patients have reported greater incidence of pain, as well as characteristic side-effects in the case of botulinum toxin B [56].

Glaser et al [57] have conducted a study regarding the use of botulinum toxin A injection for the treatment of axillary hyperhidrosis. Patients were given a subsequent injection based on their self-assessment with the HDSS questionnaire and on gravimetric sweat measurements. The patients required one or two injections per year, and 80% reported a reduction in disease burden 4 weeks after treatment. After gravimetric analysis of the efficiency of the treatment, a reduction of over 75% in sweat production was reported in over 78% of patients 4 weeks after treatment [57].

The main inconvenient of botulinum toxin A is pain during injections. It may be applied a Cryo-treatment and application of anesthetizing cream but these are considered mildly effective or ineffective. Intravenous regional anesthesia (*Bier's block*) is effective but requires cardiac monitoring, and carries the risks of cardiovascular and central nervous system toxicity [58]. Refrigerant sprays with *dichlorotetrafluoroethane* have been used with some success [58].

Side-effects of botulinum toxin injection include: small hematomas, dry skin, and transient weakness of small hand muscles for up to 2 weeks due to the diffusion of the toxin. It is advisable to avoid injection in the thenar eminence, otherwise patients may experience a reduction in finger grip strength and dexterity. Superficial injections may also reduce the risk of secondary muscle weakness [58].

5. **Surgical treatment**

Surgical treatment is the last therapeutic option for hyperhidrosis, if this is unresponsive to any previous treatments. Among these final options, sympathectomy is used when all other treatment strategies have failed [59]. Endoscopic thoracic sympathectomy (or TES – *Transthoracic endoscopic sympathectomy*) is a method performed bilaterally through which the thoracic ganglion is cut, cauterized or clamped. TES is efficient for upper body hyperhidrosis. This type of procedure leads to satisfactory results in the case of axillary (75%), facial (85%) and palmar hyperhidrosis (95%) [8]. However, most evidence that supports its efficiency comes from quality of life studies rather than randomized trials [60-62]. In some cases, without no convincing anatomical or physiological explanation, plantar hyperhidrosis has been shown to improve after bilateral thoracic sympathectomy [63]. TES is contraindicated if chest scars from previous surgeries are present or if the patient has a pulmonary disease. The frequent adverse reaction is compensatory hyperhidrosis, seen in 50-70% of patients who undergo this procedure [64] which can affect the plantar and facial region as well as the torso, and in severe cases, the buttocks and popliteal fossa [65-66]. Other possible side-effects include: cardiovascular complications, pneumothorax, haemothorax, Horner's syndrome, pleuritic chest pain and a possible recurrence of hyperhidrosis, although these affect only a minority of patients [66-68].

Another surgical treatment is *suction-curettage or retro dermal curettage* that is a minimally invasive procedure [69]. It entails performing an incision 2 to 3 cm caudally, in the posterior and inferior region of the hair bearing region of the axilla. The retro dermal plain is revealed through blunt dissection. The curette is placed against the skin and a scrapping motion will remove the sweat glands. The incision will be washed out and drained. The drain tube will be removed when the output is less than 10ml per day [69].

A similar procedure which achieves the same result is *retro dermal liposuction* which utilizes a cannula instead of a curette [70-71]. This type of surgical procedure yields high success rates, has few adverse reactions, is well tolerated by patients, requires short recuperation time, has a small rate of complications and has a satisfying esthetic outcome, however the cost may prove an impediment for patients [72].

6. **Novel therapies**

Laser technology is another therapeutic option in hyperhidrosis. It is used externally in order to

disrupt the glandular tissue. Laser therapy, particularly Nd:YAG laser, has been used by *Goldman et al* [5] to treat axillary hyperhidrosis in 17 patients and has proven to be a safe and efficient method. *Kunachak et al* [73] reports successful using of frequency doubled, Q-switched Nd:YAG laser (1,064 nm) in axillary bromhidrosis. Other several studies [74-75] have also shown the beneficial effect for a long-term cure with the 1,444 nm Nd:YAG laser that destroys the apocrine glands by subdermal coagulation, even there are some side effects like transient pain and limitation of mobility for 1 to 4 weeks postoperatively.

Other novel therapies have been recently emerging in the case of hyperhidrosis treatment such as *microwave-based devices and ultrasound device* [6]. They have been shown to yield a significant level of success. *Nestor et al* [76] have found that 94% of patient who underwent this type of treatment have had a 1-point decrease on the HDSS following this procedure, while 55% have shown a 2-point decrease or even greater.

Conclusions

Hyperhidrosis is an affliction which carries with it a significant psychological and emotional impact. The variety of therapeutic options proves there is much interest in managing this unpleasant and troublesome disease. There is a variety of therapeutic options available for the treatment of hyperhidrosis, each one having its merits and failings.

Most of the current therapeutic options are reversible, and therefore are only a temporary solution, which in time are shown to be a financial challenge.

In the case of axillary and palmar hyperhidrosis the fastest and most efficient option seems to be the injection of botulinum toxin, which presents few adverse reactions apart from local pain upon injection.

Microwave therapy seems to be an interesting and valid therapeutic option as it has proven to yield satisfying long-term results. However, it requires repeated applications which amount to a significant cost.

It must be specified that there are few randomized control trials which seek to compare one therapeutic option with another. Therefore, doctors usually prescribe and recommend treatments based on familiarity and availability rather than based on objective comparative evidence. Although the medical literature is at present time lacking in conclusive studies regarding comparisons between treatment modalities for hyperhidrosis, therapeutic solutions should be customized according to individual symptoms, patient preferences and financial ability, and primary anatomic areas of involvement.

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Conflict of interest
NONE DECLARED

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