

The use of Botulinum Toxin for focal hyperhidrosis – life changing and not only cosmetic

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Abstract

Focal hyperhidrosis is the excessive sweating from one part of the body most often the axillae, palms, soles and face. This condition is known to carry a high social and psychological burden with studies showing that patients with this condition end up avoiding leisure and social activities with sometimes even affects on their occupation. The aim of this literature review is to evaluate the different types of focal hyperhidrosis and how they can be treated. It seeks to compare Botulinum toxin treatment to other treatment options available for focal hyperhidrosis in terms of cost, efficacy and side effects. Research on Botulinum toxin and available serotypes are being done to help improve hyperhidrosis treatment by reducing side effects and improving efficacy. It also focuses on the effects of this condition on the patient's lifestyle and how debilitating this condition can be. This kind of treatment is sometimes regarded as a cosmetic procedure since medical professionals consider hyperhidrosis as benign. However, research has shown that effective treatment of hyperhidrosis with botulinum toxin improves patient's quality of life (QoL) significantly.

MeSH Terms

botulinum toxin, quality of life, hyperhidrosis, cost benefit, efficacy treatment, botulinum toxin type a, botulinum toxin type b.

Introduction

Focal hyperhidrosis was found to affect 3% of the population in the United States suffer from hyperhidrosis most of which suffer from axillary hyperhidrosis. It affects mostly people between age 25 and 34 and affects more females and males. Due to this significant prevalence, recent developments in treatment especially with Botulinum toxin and lack of research and studies on focal hyperhidrosis here in Malta, it was important to review available literature on focal hyperhidrosis.¹

Hyperhidrosis on the other hand is defined as a disorder of excessive sweating beyond what is necessary for thermoregulation. Eccrine glands are those responsible mainly for hyperhidrosis and they are densely found at the soles of the feet, forehead, palms and cheeks thus leading to focal hyperhidrosis. Apocrine glands which are mainly focused at the axillary and urogenital regions are regulated by a hormonal process and are thus not usually responsible for hyperhidrosis. However it is difficult to quantify excessive sweating and usually diagnosis is based on dysfunctional sweating, that is, how much the condition affects the patient's quality of life (QoL).² In order to establish a standard with regards to the extent that hyperhidrosis is affecting a particular patient, a scale known as **Hyperhidrosis Disease Severity Scale (HDSS)** can be used. In this scale, the doctor scores the patient according to how much the disease is affecting the patient with a score of 1 showing least impact and 4 showing the worst.³ This same scale was used in studies done in the United States which showed that the majority of those with axillary hyperhidrosis had a score of 3 or 4 in the HDSS scale. At least 1.3 million

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individuals in the United States have severe focal hyperhidrosis that might require management with Botox to control. Table 1 shows the HDSS scoring sheet used to grade the severity of hyperhidrosis.^{1,4-5}

Table 1: Hyperhidrosis Disease Severity Scale (HDSS)²

“How would you rate the severity of your Hyperhidrosis?”	Score
My sweating is never noticeable and never interferes with my daily activities	Score 1
My sweating is tolerable but sometimes interferes with my daily activities	Score 2
My sweating is barely tolerable and frequently interferes with my daily activities	Score 3
My sweating is intolerable and always interferes with my daily activities	Score 4

Apart from the HDSS score, there are also **diagnostic criteria** that help to diagnose focal idiopathic hyperhidrosis. These criteria state that there needs to be focal, visible, excessive sweating for a period of at least 6 months without apparent reason and with at least two of the following characteristics:

1. Bilateral and relatively symmetrical sweating
2. Frequency of at least 1 episode per week
3. Impairment of daily activities
4. Age of onset less than 25 years
5. Positive family history
6. Cessation of sweating during sleep.

Hyperhidrosis is mainly subdivided into two, **generalized and focal hyperhidrosis**, with the former one affecting the sweat glands of the entire skin surface area while the latter affecting certain areas. Generalized hyperhidrosis is usually secondary to drugs, such as, anti-depressants but can also be caused by endocrine conditions, such as, hyperthyroidism, chronic infections and neoplastic conditions, for example, Hodgkin’s Lymphoma.⁶ The focus of this review is on focal hyperhidrosis since it is the one that can be treated with BTX.

Focal hyperhidrosis is further sub-divided in three other groups, primary idiopathic, gustatory sweating and neurological. Table 2 shows the different types of focal hyperhidrosis sub divided into these categories. Axillary hyperhidrosis is the

most common type of focal hyperhidrosis. In a national survey done in the United States of people having focal hyperhidrosis, half of them had axillary hyperhidrosis. This is followed by focal hyperhidrosis in the soles and in the palms.¹

Table 2: Types of focal hyperhidrosis^{5,7}

Primary Idiopathic	Axillary
	Palmar
	Plantar
	Craniofacial
Gustatory sweating	Frey’s syndrome
	Certain foods such as, citric acid, coffee, chocolate, peanut butter and spicy food
Neurological	Neuropathies
	Spinal Injury or disease

Method

We performed a search using PubMed and Google Scholar to find studies or systematic reviews relevant to focal hyperhidrosis especially if including treatment with Botulinum toxin. Search terms and phrases used were the various combinations of botulinum toxin, quality of life, focal hyperhidrosis, cost benefit and efficacy, treatments for hyperhidrosis, botulinum toxin type a, botulinum toxin type b and guidelines for focal hyperhidrosis. The search was conducted between August and September 2016. We made sure that the majority of the studies considered were recent (ideally after 2008) and that non-original articles were excluded. Preferred studies used in this review compared Botulinum toxin to other treatments and/or included patient’s quality of life before and after treatment with Botulinum toxin.

Results

Research has shown that Botulinum toxin (BTX) works by targeting the presynaptic cholinergic neuromuscular junctions that innervate the eccrine glands in that area, hindering the release of acetylcholine thus inhibiting contraction and release of sweat from the sweat secreting cells in the eccrine sweat gland. Figure 1 shows the target site of BTX to stop sweat production compared to other treatments for focal hyperhidrosis. BTX usually takes around 1-14 days to work. After around 4 to 17 months, new neuromuscular junctions form and the patient might need another

injection of BTX to avoid developing the symptoms again.⁸⁻⁹ BTX injection for hyperhidrosis also has its own side effects. A common side effect is myalgia at the site of injection. This may cause the patient to refuse more BTX injections to avoid such pain. However, in a study done in 2007, it was found that this side effect can be avoided by injecting Botox constituted with lidocaine. This double blind study showed that the use of lidocaine with BTX-A reduces pain at the injection site without affecting its effectiveness.¹⁰ Botulinum toxin treatment for palmar hyperhidrosis is also known to cause reversible minor weakness of palmar muscles with reduced handgrip.¹¹ Other side effects include myalgia, itching and increased compensatory sweating of the face.⁹⁻¹⁰ BTX therapy is contraindicated for patients who are pregnant or lactating, suffering from neuromuscular disorders, have an organic cause of hyperhidrosis or are taking medications that are known to interfere with neuromuscular transmission. BTX must only be administered by a specialized physician trained in the administration of Botulinum toxin.⁵

Treatment of focal hyperhidrosis with Botulinum toxin compared to other treatments available –costs and benefits.

BTX treatment is to be discussed in the context of the other available therapies.

Aluminium chloride hexahydrate applied topically to the affected area is currently the first line treatment for most forms of focal hyperhidrosis. This chemical works by blocking the epidermal duct of the eccrine sweat glands. It is thought that this causes direct damage to the eccrine sweat gland, specifically to the glandular secretory cells causing them to atrophy. Their effect extends also to the epidermal cells of the duct which undergo necrosis. This therapy is known to cause skin irritation in about 50% of patients thought to be caused by the formation of hydrochloric acid when this topical treatment makes contact with water. New formulations with aluminium chlorhydroxide in purified water try to avoid this side effect. Alternatively, local hydrocortisone 1% is applied with this topical treatment to relieve this burning and painful sensation. However the main disadvantage of this treatment is the short duration of effect. Within 48 hours, its effectiveness diminishes and within one week, the patient's condition goes back to how it was before treatment

started, making BTX treatment a better option for those who want a more long term solution. However unlike BTX, this treatment is low cost and convenient so it is for this reason that aluminium chloride salts are chosen as first line treatment especially for mild cases of hyperhidrosis.^{9,12} The cost of a single injection of BTX A 50 Units which is used per axilla range from €81 to €87 (powder only) compared to an average of €3.50 for the liquid form of aluminium chloride hexahydrate or €8 for the more convenient spray form.¹³

Another treatment which is available for focal hyperhidrosis is **tap water iontophoresis**. In this treatment, the patient has to put the affected areas with focal hyperhidrosis, usually the palms of the hand or the soles of the foot, in small containers with tap water and a pulsed direct current with a high frequency of 5-10 kHz is passed through the water. The treatment usually takes around half an hour and needs to be repeated three to four times a week or until adequate results are achieved. This treatment is only possible for flat surfaces affected by focal hyperhidrosis, namely the soles and palms. However it can be considered as a cheap and effective treatment for highly motivated patients. It is usually considered for palmar and plantar hyperhidrosis when topical treatment with aluminium chloride hexahydrate fails. Side effects of iontophoresis range from burning discomfort and skin irritation to burns and cutaneous necrosis if not used properly.¹⁴ Costs for tap water iontophoresis are fairly reasonable. In the UK according to NHS, iontophoresis kits that one can use at home cost between €280 and €560.¹⁵ In some studies, **addition of BTX-A to iontophoresis** was attempted and it was found that focal hyperhidrosis improved drastically without any pain which is usually reported with BTX injections. Compensatory hyperhidrosis was also reported in one study post-treatment with tap water iontophoresis which wasn't the case for BTX-A iontophoresis done in the same study.¹⁶ However, in a recent study published about 2 years ago, injection administration provided more long term reduction in sweat production than when it was administered with iontophoresis. In this randomized, controlled trial, it was found that after 6 months, 50% of patients treated with Botulinum injections still had significant reduction in focal hyperhidrosis compared to 32% with BTX iontophoresis.¹⁷

Systemic anticholinergics, such as,

oxybutynin or glycopyrrolate are also sometimes considered for focal hyperhidrosis since these inhibit sweating through competitive blocking of muscarinic receptors. However, these have a lot of systemic side effects with the most common one being dry mouth. In a study done by V. Bajaj and J. Langtry, it was found that although 75% of patients reported improvement with glycopyrronium bromide for hyperhidrosis (9 generalized and 15 focal hyperhidrosis), 79% of them reported dry mouth and 50% dropped out from the study. Given the side effects, this type of treatment can be therefore considered if topical treatment fails and Botulinum treatment is either not available or cannot be afforded by the patient.¹⁸ In other studies showed that decreased sweating at high environmental temperatures may cause fever and heat stroke. Diarrhoea may herald incomplete intestinal obstruction. Other adverse effects include blurred vision, urinary retention, dry mouth, vomiting, drowsiness and palpitations. Glycopyrronium bromide tablets are contraindicated in medical conditions that preclude antimuscarinic therapy (NICE 2013).¹⁹⁻²¹ Just like with BTX, glycopyrronium bromide can be administered to the affected area via iontophoresis and in a recent study, it was found that 81.8% patients treated with this method had a significant improvement in their condition.²² However, glycopyrronium bromide used for iontophoresis is quite expensive. Robinul powder for solution for iontophoresis costs €298 compared to €144 for 100 units of BTX used for iontophoresis.¹³ Topical anticholinergics can also be used for the treatment of focal hyperhidrosis. It was found that daily topical application of 0.5% glycopyrrolate is effective in controlling craniofacial hyperhidrosis. However, symptoms tend to recur after two days without treating.²³

Different **surgical treatments** for axillary and palmar hyperhidrosis exist and these usually offer a more permanent solution to focal hyperhidrosis. **Local surgery** includes **subcutaneous curettage** to excise sweat glands and this kind of operation is usually reserved for severe axillary hyperhidrosis unresponsive to topical and BTX treatments. This surgery is known to have high complication rates and morbidity with reduced arm movement, scars, infections and haematomas. **Suction curettage** is another type of local surgery to control hyperhidrosis. In suction curettage the surgeon

places a cannula between the dermis and the hypodermis of the affected area to destroy sweat glands in this area through liposuction. This offers much less side effects than local direct excision; particularly less scars. However, this also carries its own side effects, such as bleeding, infection and even damage to the brachial plexus when used to treat axillary hyperhidrosis.⁹ The most invasive surgeries available for focal hyperhidrosis are those that cause **sympathetic denervation – sympathectomy or ganglionectomy and sympathotomy**. In sympathectomy or ganglionectomy, the sympathetic chain is transected endoscopically at a level above or below T2 ganglion or the ganglion itself is destroyed while in sympathotomy, the rami connecting to T2 ganglion are transected.²⁴ Cost of such surgeries are considerably higher than Botox treatment. In a study it was shown that while the baseline cost of BTX treatment for focal hyperhidrosis is €389 with an annual cost of around €853, that of an uncomplicated endoscopic thoracic sympathectomy is €9389 with costs going up to €11390 if complications occur.²⁵ These kinds of operations often carry the risk of side effects, mainly sexual dysfunction and sometimes even compensatory sweating with the incidence of such complications varying from 14% to 90%. Other major complications associated with such operations include vascular injury and pneumothorax. They are therefore not common and usually reserved for patients who didn't respond to topical, BTX treatments and even oral anticholinergics.²⁶

A study done by I. Hoorens and K. Ongenae which prepared guidelines for the different types of focal hyperhidrosis listed BTX therapy as second line treatment for most focal hyperhidrosis. It can also be used as first line for moderate to severe conditions in which the patients' lifestyle is severely affected or their lifestyle doesn't allow them to continuously use aluminium chloride hexahydrate sprays or iontophoresis. Unlike most treatments, BTX injections usually only need to be applied once and take months before the patient goes back to pre-treatment stage. It helps to treat the condition locally without having to resort to systemic drugs, such as, anticholinergics or surgery that carry major side effects, with the risk of compensatory sweating.⁹ BTX injections are also considered first line in **gustatory sweating usually caused by Frey's Syndrome**. This syndrome

occurs in different extents in patients who undergo parotidectomy due to aberrant regeneration of transected parasympathetic fibers between the otic ganglion and subcutaneous vessels. An intracutaneous injection of BTX-A helps to effectively control this condition with long lasting results.²⁷ The same can be said for **forehead**

hyperhidrosis with studies showing BTX-A to be the most effective treatment for this kind of hyperhidrosis with a reduction in sweating of approximately 75% for a period of around 5 months.²⁸ Figure 1 shows the target site of action for each treatment mentioned in this section.

Figure 1: Target site of action of BTX (BTX) compared to other treatments for focal hyperhidrosis. Source of diagram from Hoorens I, Ongenaes K. Primary focal hyperhidrosis: Current treatment options and a step-by-step approach⁹

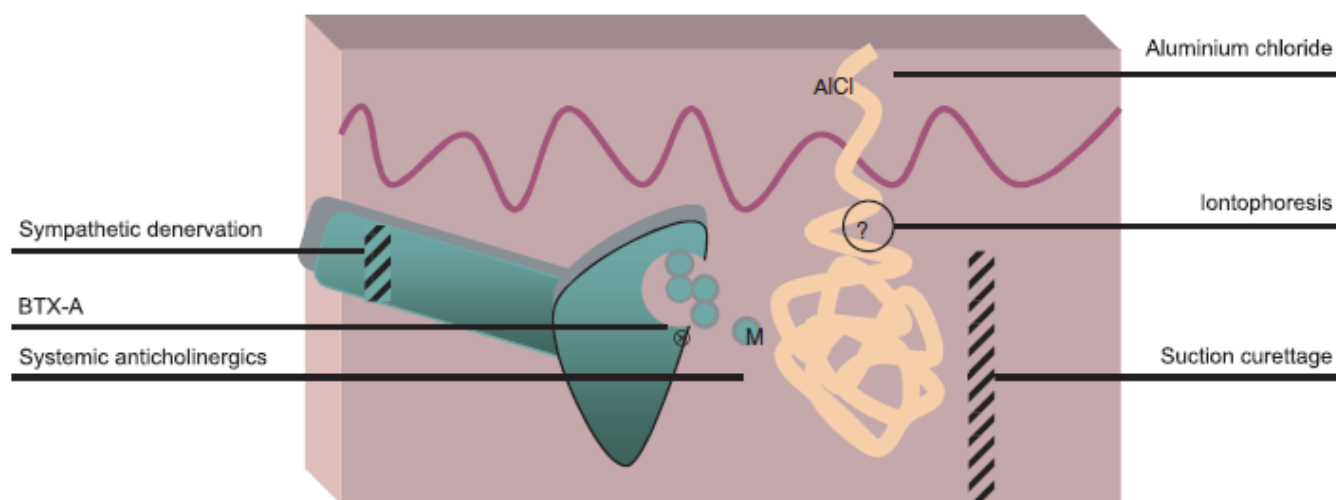


Table 3 summarizes the treatment of the common forms of focal hyperhidrosis organised as step-by-step approach and evidence obtained mainly using randomised trials, case control studies and non-randomized controlled cohorts. It shows that BTX-A treatment can be considered even first line in severe cases of focal hyperhidrosis while second or third line in mild presentations after topical treatment fails.

Laser treatment and Miradry are new treatments for focal hyperhidrosis that are currently being researched but still not widely available. **Laser treatment** enables physicians to target specific body structures accurately, limiting damage to surrounding tissue. Added advantages include decreased risk of infection and reduced bleeding. These procedures are relatively quick; they take less than an hour, and can be done on an outpatient basis. Studies have shown that underarm sweating is reduced significantly; by approximately 78% at six months' time. Another advantage is that treatment is permanent as the sweat glands do not regenerate. Side effects include bruising, swelling

and numbness, which take approximately one to two weeks to resolve.³⁰ **Miradry** is a new microwave therapy developed as a non-surgical treatment for hyperhidrosis. Microwaves are absorbed more in high-water-content tissue, and thus heating is localised. The target is the skin-adipose interface, because most of the eccrine glands in the skin are found there with a focal energy zone created at this interface. In a study done to show the efficacy of this treatment reported an average sweat reduction of 82% and patient satisfaction were high when assessed using HDSS scoring before and after the treatment. Advantages of this treatment are that it is permanent, safe and effective. Discomfort and oedema in the underarm area are expected within the three day period following the microwave therapy and this may take several days to resolve. Other adverse effects include altered sensation in the treatment area and partial loss of underarm hair, temporary lumpiness and bumps in the axilla, bruising at the injection sites due to local anaesthetic and redness from device suction.³¹

Table 3: Step by step treatment (medical and surgical) for the four most common types of focal hyperhidrosis divided according to severity; HDSS <2 as mild and HDSS 3-4 as severe. ACH = Aluminium chloride hexahydrate, BTX-A = Botulinum Toxin A treatment.^{9,29}

		Step 1	Step 2	Step 3	Step 4	Step 5
Axillary Hyperhidrosis	HDSS Score <2	Topical ACH	BTX-A 50-100U per axilla. Repeat ONCE if failed	Systemic anticholinergics	Suction Curettage or excision of sweat glands. Repeat if failed	Reconsider suction curettage. Sympathetic Denervation
	HDSS score 3-4	BTX-A 50-100U per axilla. Repeat ONCE if failed OR Topical 10-35% AC	BTX-A AND Topical ACH	Systemic anticholinergics	Suction Curettage or excision of sweat glands. Repeat if failed	Sympathetic Denervation
Palmar Hyperhidrosis	HDSS Score <2	Topical ACH	Iontophoresis either by tap water, anticholinergics or BTX-A	BTX-A 100-150U per palm. Repeat ONCE if failed	Systemic anticholinergics OR Topical together with BTX-A or iontophoresis	Sympathetic Denervation
	HDSS score 3-4	BTX-A 100-150U per palm. OR Topical ACH OR Iontophoresis	Repeat BTX-A 100-150U per palm	Systemic anticholinergics	Sympathetic Denervation	
Plantar Hyperhidrosis	HDSS Score <2	Topical ACH	Iontophoresis either by tap water, anticholinergics or BTX-A	BTX-A 150-200U per sole. Repeat ONCE if failed	Topical together with BTX-A or iontophoresis	Systemic anticholinergics
	HDSS score 3-4	BTX-A 150-200U per palm OR Topical ACH OR Iontophoresis	Repeat BTX-A 150-200U per palm.	Systemic anticholinergics		
Craniofacial hyperhidrosis	HDSS Score <2	BTX-A up to 100U - First line for Frey's Syndrome. Consider topical AC.	Systemic anticholinergics			
	HDSS score 3-4	BTX-A up to 100U- First line for Frey's Syndrome. Consider topical AC.	Systemic anticholinergics	Sympathetic Denervation		

Effects of treatment with Botulinum Toxin on the patient's quality of life

Medical professionals sometimes underestimate the morbidity of this condition failing to recognize the impact of this disease on patient's QoL. The condition itself causes a lot of anxiety together with physical discomfort, functional impairment and psychosocial issues. In survey done in the U.S. about the impact of axillary hyperhidrosis, almost half of the participants complained that they find it difficult to meet new people especially due to the fact that they continuously soil clothing, paperwork and shoes and avoid handshakes as their palms are always wet and cold. Some even complained finding it difficult to engage into intimate situations and romance. More than a quarter of the participants had to change or even stop sports and some even reporting spending less time working due to their condition. However the most worrying facts that came out of this study were that more than half of the participants reported feeling less confident than they would like due to their condition and 35.7% reported feeling depressed. The latter showed the most impairment (score of 3 or 4) according to the HDSS score. 38% of the participants decided to seek out help from a medical professional with regards to this issue and the rest failed to recognise this as a medical problem and blamed themselves instead. Excessive focal sweating is also sometimes responsible for secondary medical conditions, mainly bacterial and fungal overgrowth and eczematous dermatitis, adding insult to injury already caused by this condition.¹

Different studies on the BTX treatment and QoL after treatment have been done, most of these show positive results. In a recent study done in Sweden, a cohort of 84 patients suffering with focal hyperhidrosis were treated with BTX injections – Xeomin[®], which is BTX-A and a more novel Neurobloc[®] which is a BTX-B. Fifty-eight of these patients were suffering from axillary hyperhidrosis, and were treated with Xeomin[®], while the rest suffered from palmar hyperhidrosis and were treated with Xeomin[®] and Neurobloc[®]. After a 3 week follow up, all patient treated for axillary hyperhidrosis were satisfied and reported an improvement in QoL which was evaluated by a Dermatology Life Quality Index (DLQI). With regards to palmar hyperhidrosis patients, all except for 1 reported satisfactory results and improvement

in QoL, with the unsatisfied patient complaining of muscle weakness.³² A very recent study used HDSS as well as and Hospital Anxiety and Depression Scale (HADS) to assess both QoL and mental health related to primary hyperhidrosis. This study also showed significant improvement in both scales 2 weeks after treatment.³³ Another study delved into the social and occupational aspects of focal hyperhidrosis and how they improved after BTX therapy. It was found that 68% of patients found it difficult to meet people before they were treated and 58% of patients felt that their condition was limiting their performance at their job. Other complaints, such as having to shower twice or more daily, feeling less confident and changing leisure activities were reported. All of these were significantly reduced after treatment, with results observed within 1 week of treatment.³⁴

In other studies, QoL after BTX treatment was compared to that after other treatments for focal hyperhidrosis. In a study aimed to compare QoL and cost effectiveness of BTX treatment and endoscopic thoracic sympathectomy, QoL was also accessed using DLQI questionnaires. Patients were asked to fill the questionnaire before treatment and 4-6 weeks following treatment. This study showed that BTX treatment not only improved the patient's quality of life but also proved to be a much more cost effective treatment than surgery. Study also showed that cost-equivalence is reached after about 13 years and considering Botulinum toxin treatment carries less risk, such treatment is more suitable than surgery.²⁵ In another study, patients who were unresponsive to topical treatment with aluminium chloride for axillary hyperhidrosis were treated using Botulinum injections and followed up. After 14 weeks, it was found that 81.4% rated the treatment as excellent with a significant improvement in QoL. Most patients were satisfied and only a few (around 1.4%) chose to rate the procedure as fair, would not recommend it or didn't respond to the questionnaire given.³⁵

Discussion

BTX treatment has been shown to be one of the most cost effective and safe treatments for focal hyperhidrosis and has proven to improve quality of life significantly.⁹ It also provides long term treatment and can prove to be an ideal treatment for patients who do not wish to use anti-perspirants, oral treatments or tap water iontophoresis

repeatedly or their lifestyle doesn't allow them to treat themselves repeatedly every day. In this review, current treatments have been analysed and compared to BTX treatment. It was shown that BTX can be used as a second line treatment for most types of focal hyperhidrosis after cheaper topical treatments have failed, without having to resort immediately to surgery or systemic drugs. It can also be used as first line for certain focal hyperhidrosis mainly Frey's syndrome and frontal hyperhidrosis. As discussed above BTX treatment is not only cosmetic, as it also significantly improves the patient's QoL. This highlights the importance of its availability and should therefore be offered even by governmental secondary care hospitals.

Botulinum toxin treatment is still being improved and researched. In recent studies, new serotypes of Botulinum toxin are being used and sometimes combined with the more commonly used BTX-A. A combination of Xeomin[®] (BTX-A) and Neurobloc[®] (BTX-B) used for palmar hyperhidrosis has shown that sweating reduced significantly and only one patient complained of reversible muscular weakness. This study not only showed that QoL can be improved with BTX therapy, but also that a combination of both Xeomin[®] and Neurobloc[®] can help lower the risk of muscular side-effects that occurs more often when BTX-A is used on its own.³² Similar results was obtained in another study in which only 12.5% had mild side effects from such treatment and significant reduction in hyperhidrosis was noted from 4 weeks post treatment.³⁶

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