Botulinum toxin type A for treatment of hyperhidrosis

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Hyperhidrosis is defined as excessive sweating beyond that required to return the body temperature to normal. Focal hyperhidrosis commonly affects the axillae, palms, soles or face and often has a tremendous psychosocial and occupational impact on affected patients. To date, a variety of treatments have been used in the management of this condition, each with their own advantages and disadvantages. Botulinum toxin type A is licensed for the treatment of axillary hyperhidrosis but is now being used to treat several other types of focal hyperhidrosis. Botulinum toxins exert their effect by inhibiting the release of acetylcholine from autonomic cholinergic nerve terminals. Clinical trials investigating the use of botulinum toxin type A for axillary and palmar hyperhidrosis have shown a reduction in sweating and improvement in quality of life, with few reported side effects. This review discusses the use of botulinum toxin type A for the management of focal hyperhidrosis, relating to current evidence.

The introduction of botulinum toxins (BTs) to clinical medicine has been hugely successful and their potential therapeutic value is being explored in almost every branch of medicine. Many physicians are now of the opinion that not only are BTs useful treatments, but in many instances, they are the best treatment.

Hyperhidrosis is a pathologic condition in which sweating occurs in excess of that required for thermoregulation. Recently BT type A (BTA) was approved for the treatment of axillary hyperhidrosis and has also been used successfully to treat other types of focal hyperhidrosis. This article supports the use of BTA as a treatment for hyperhidrosis and discusses the current evidence for its use.

Background

Primary focal hyperhidrosis is defined as excessive, bilateral and relatively symmetric sweating occurring in at least one of the following sites:

- The axillae
- Palms
- Soles
- Craniofacial region

The frequency of the condition in is not well documented; however, a recent survey of the US population found a prevalence of 2.8% [1].

Etiology

Hyperhidrosis can be classified as primary (idiopathic, essential) or secondary to a number of medical conditions including; endocrine disease (hypoglycemia, hyperthyroidism), neurological disorders, drug use, the menopause, neoplastic disease, chronic infection, obesity and anxiety states [2]. Primary axillary hyperhidrosis is a chronic, idiopathic disorder which most commonly affects the axillae, palms, soles of the feet or the face. There is often a family history, and in these cases, onset of symptoms begins in the prepubertal age range [3].

The eccrine glands are responsible for focal hyperhidrosis. As well as their important thermoregulatory function, the eccrine glands also respond to emotional stimuli. The total number of sweat glands is somewhere between 2 and 4 million, distributed over nearly the entire body surface, but principally over the palms and soles and in the axillae. The sweat glands are innervated by sympathetic nerve fibers. Nerve cells from spinal cord segments T2 to T8 supply the skin of the upper limbs, those from T1 to T4 the face and eyelids, those from T4 to T12 the trunk and those from T10 to L2 the lower limbs [3]. Sweat is a clear, hypotonic, odorless fluid produced by clear and dark cells. In response to nerve impulses, acetylcholine is released from the presynaptic nerve endings and then binds to postsynaptic cholinergic receptors present in the basolateral membrane of the clear cells. This activates a complex causing efflux of electrolytes and creating hypotonic sweat [4]. The sweat glands are morphologically normal in the majority of hyperhidrotic patients – the neurologic response to stimuli in the hypothalamic sweat centers is considered the primary abnormality [5].

Keywords: botulinum toxin type A, focal hyperhidrosis, treatment

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Diagnosis

To establish a diagnosis, the following criteria have been recommended for primary focal hyperhidrosis: localized, visible, excessive sweating of at least 6 months duration without apparent cause and with at least two of the following characteristics [1]:

- Bilateral, relatively symmetric output
- Impairment of daily activities
- Frequency of at least one episode per week
- Age of onset less than 25 years
- Positive family history
- Cessation of focal sweating during sleep

Causes of secondary hyperhidrosis should be excluded by history and appropriate laboratory investigations. Sweat tests can be useful in providing an objective measure of hyperhidrosis before treatment. The area affected can be visualized with Minor's iodine starch test [6]. The extent of hyperhidrosis can also be measured gravimetrically as the rate of sweat production (in mg/min) [7]. In studies evaluating treatment for hyperhidrosis, patients have been excluded if they produced less than 50 mg sweat/axilla over 5 min [8].

Impact of disease

The condition often has tremendous psychosocial and occupational impacts for affected patients. Stained clothing can be socially embarrassing. Furthermore, skin maceration and subsequent microbial infection lead to discomfort and body odor and can impede social contact.

Treatment

To date, a variety of treatments have been used in the management of this condition including both non-operative and operative options (**Box 1**).

Nonsurgical interventions comprise topical agents, systemic agents, iontopheresis and intradermal injection of BT.

Box 1. Treatment options for hyperhidrosis.

Nonoperative options:

- Topical treatments
- Systemic oral anticholinergics
- Iontopheresis
- Botulinum toxin

Operative options:

- Local surgery
- Liposuction/ curettage
- Sympathectomy

Topical treatments

Topical agents remain the simplest choice and are usually offered first. Aluminium chloride is the most widely used and appears to work either by mechanically obstructing the eccrine sweat gland pore or by causing atrophy of the secretary cells [9]. Varying success rates in the treatment of axillary hyperhidrosis have been reported [10–13] and treatment is usually limited by the fact that 50% of patients who use aluminium chloride experience some degree of axillary irritation.

Systemic anticholinergic agents

Oral anticholinergic drugs (glycopyronium bromide and paropantheline bromide) can be used to treat hyperhidrosis but unpleasant side effects such as blurred vision, dry mouth and urinary retention preclude their use except for very brief periods [9]. Other drugs that have been used with varying success include phenoybenzamine (an α-adrenergic blocking agent), diazepam, indomethacin, clonidine (a centrally active α-adrenergic autoreceptor stimulant) and propoxyphene hydrochloride (a narcotic and weak ganglionic blocking agent) [14].

Iontophoresis

Iontophoresis is the introduction of an ionized substance through intact skin by the application of a direct electric current with the objective of coagulating eccrine sweat glands [2]. Good results can be achieved and complications are mild but patients require multiple treatments. Surgical options include gland excision, liposuction or sympathectomy.

Local surgery

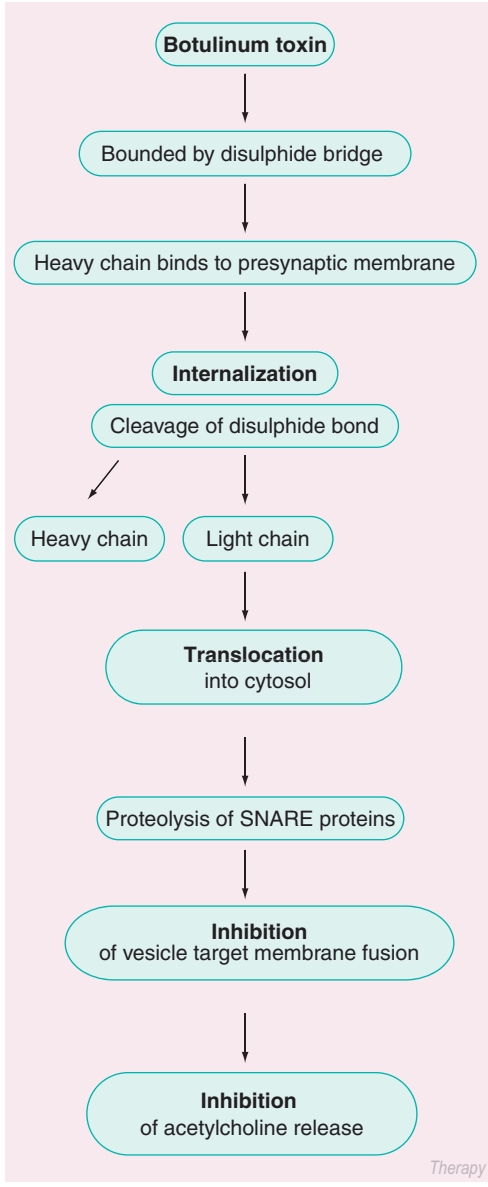
Many local surgical techniques have been proposed and include excision of subcutaneous tissue alone, *en bloc* removal of skin and subcutaneous tissue or skin excision with excision of underlying and adjacent subcutaneous tissue [15]. Procedure-related complications may include hematoma, infection, scarring, contractures and subsequent restriction of arm movement. Information on long-term outcome is limited with complication rates between 4 and 6% [16,17].

Subcutaneous curettage and liposuction are associated with fewer side effects and have been shown to be effective [18,19].

Sympathectomy

Endoscopic transthoracic sympathectomy has superseded the traditional open access to the thorax as it is less invasive with fewer side effects.

Figure 1. Mechanism of action of botulinum toxins.



SNARE: Soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment receptor.

Access to the thoracic cavity is gained through an incision in the third intercostal space in the anterior axillary line. Surgical technique varies widely as the sympathetic trunk or ganglion can be divided with scissors, excised, ablated, clipped or cauterized. The level of the procedure also varies from T2 only, T2 to T3, or T2 to T4 [20]. Axillary hyperhidrosis does not appear to respond to the procedure as well as palmer hyperhidrosis. Immediate success rates vary between 91 and 99%; however, patient satisfaction declines over time especially for axillary hyperhidrosis [21–31]. This is mostly due to side effects of treatment and potential complications which include Horner's syndrome, brachial plexus injuries, pneumothorax, compensatory hyperhidrosis, gustatory sweating and recurrence [9]. Compensatory sweating can affect up to 50% of patients and gustatory sweating can affect as many as a third [32].

Botulinum toxin type A

BTs are a family of neurotoxins produced by the anaerobic bacterium *Clostridium botulinum*. There are eight serotypes (A, B, Cα, Cβ, E, F and G) which produce seven serologically distinct exotoxins. The different serotypes are structurally and functionally similar; however, specific differences in neuronal acceptor binding sites, intracellular enzymatic sites and species sensitivities suggest that each serotype is its own unique pharmacologic entity. BTs exert their effect by inhibiting the release of acetylcholine from both skeletal and autonomic cholinergic nerve terminals. The toxin must enter the nerve ending to exert its effect in a three-step process (**Figure 1**):

- Internalization
- Translocation
- Inhibition of neurotransmitter release

BT is synthesized as a single-chain polypeptide composed of a heavy and a light chain bonded by a disulfide bridge. The heavy chain is responsible for binding, whereas the light chain provides intracellular toxic moiety. The heavy chain binds to the presynaptic membrane at as-yet unidentified receptors and BT is internalized inside endocytic vesicles. After internalization, the disulfide bond is cleaved by an unknown mechanism. At low pH, BT changes confirmation and inserts itself into the lipid layer of the vesicle membrane and translocates the light chain into the cystosol. Inside the cystosol, the light chain catalyzes the proteolysis of one of the three soluble *N*-ethylmaleimide-sensitive fusion protein (NSF) attachment receptor (SNARE) proteins (Snap-25, Vamp or Synataxin). Each of the seven BT serotypes cleaves a specific peptide:

- A and E cleave Snap-25
- B, D, F and G cleave Vamp
- C cleaves both Synataxin and Snap-25

Once cleaved by a BT, the SNARE proteins cannot become part of the complex-mediating vesicle-target membrane fusion. At cholinergic nerve terminals, this specific proteolytic

cleavage mediated by BTs in the synaptic cytosol prevents the release of acetylecholine and hence transmission of the nerve impulse [4,33].

The mode of measuring the strength of this toxin is via paralytic activity in the mouse. One unit (U) is defined as that amount of toxin which will provide a lethal dose for 50% (LD_{50}) of a standardized mouse model when injected intraperitoneally [34].

BTA is available in two preparations; in the USA, it is available as Botox® (Allergan) and in Europe as Botox or Dysport® (Ipsen Biopharm). In terms of efficacy, one unit of botox is estimated to be equal to 3 to 5 U of dysport. When injected intradermally into the forehead of a normal control, 0.1 to 1.0 U of botox produces a 1.0 to 1.5 cm^2 anhidrotic area [35]. When used for hyperhidrosis, a 5 to 10 U injection of botox produces an anhidrotic area of 1.2 to 1.9 cm^2 within 6 days [36]. After 6 months, the anhidrotic skin area decreases, suggesting partial recovery of sweat gland function [37]. The extent of the anhidrotic effect of BTA is dose dependant, with a minimum dose of 2.5 U/cm^2 of dysport (c. 0.625 U of botox) needed to obtain an effect on sweat production [37]. To block sweat gland activity completely, 20 U/cm^2 of dysport (c. 5 U of botox) needed.

Botox was first approved by the US Food and Drug Administration (FDA) in December 1989 to treat the eye muscle disorders blepharospasm and strabismus. In 2002, it was approved to treat cervical dystonia and frown lines. It is now approved for the treatment of primary axillary hyperhidrosis that cannot be managed by topical agents.

One concern with the use of BTA is the possibility of blocking antibodies leading to nonresponse of subsequent injections [38]. The factors that predispose patients to the development of antibodies are unknown, but experience has shown that risk is increased with repeated dosages above 300 U [39,40]. Some of these patients have benefited from different preparations of BTA or other serotypes of BT. Several trials have shown the effectiveness of BT type B (BTB) in the treatment of cervical dystonia for all patient groups, including those who no longer respond to BTA [41–43]. BTB is now a licensed treatment for cervical dystonia. It has also been shown to be a safe and effective treatment for primary axillary hyperhidrosis [44].

Botulinum toxin A for axillary hyperhidrosis

BTA has been shown to be an effective treatment for axillary hyperhidrosis. There have been numerous trials investigating the effects of this type of treatment, although comparison between studies can be difficult due to differences in the type of BTA, dose, number of injections, duration of observations, and choice of outcome [45]. Currently botox is the only BTA licensed for axillary hyperhidrosis.

The benefit of BTA on reducing axillary hyperhidrosis has been demonstrated by several open studies and two multicenter, double-blind placebo-controlled trials [7,8]. The largest study was conducted by Naumann and colleagues [7]. From a total of 320 patients, 242 were randomized to receive 50 U BTA (botox) per axilla and 78 to placebo. The percentage of responders (patients with >50% reduction from baseline of spontaneous axillary sweating) at 4 weeks was 94 in the BTA group compared with 36 of the placebo group. At 16 weeks response rates were 82 and 21% respectively. Patient satisfaction was high throughout in the BTA group.

Longer-term follow-up over 16 months was evaluated in an extension to this study [46]. It was found that repeated intradermal injections of BTA over 16 months is a safe and effective treatment for primary axillary hyperhidrosis. After 4 months, participants could receive up to three further treatments over 12 months. A high response rate was seen following each treatment and the mean time between first and second treatments was 7 months. Retreatment was not required by 28% of patients during the study.

In another multicenter trial [7], 145 patients were randomized to receive either 200 U of BTA (Dysport) or placebo. A significant reduction in sweat production from baseline was demonstrated at 2 weeks post-treatment in the BTA group compared with placebo. The effect was maintained up to 24 weeks and treatment was well tolerated. The onset of effect of BTA is usually rapid. Many patients report complete dryness within 24 h and the remainder within 3 days of injection [48].

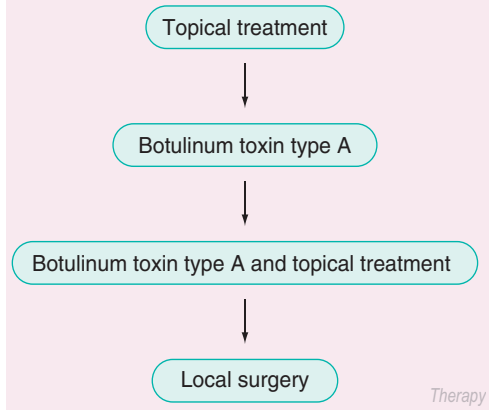
The average duration of anhidrosis in the axillae is 4 to 6 months [35], but reported response times vary from 4 to 10 months, depending on dosage and technique [45]. Patients should be retreated when the sweating returns to a level of concern to the patient, although retreatment within 16 weeks is not recommended [14]. There appears to be a dose–response relationship, with higher doses of BTA producing longer remissions of up to 7 to 15 months [36,37]. However, this may be outweighed by higher costs and the risk of antibody formation [34].

In addition to measuring changes in sweat production as an outcome of treatment, investigators have also studied the effect of BTA on patient satisfaction and quality of life (QoL). Hyperhidrosis has been found to have a significant effect on QoL as assessed by Naumann and colleagues using the Hyperhidrosis Impact Questionnaire [48]. Significant improvement was seen following treatment with BTA. The most dramatic changes were seen in the degree of limitation of being in public places and on meeting people for the first time. The Dermatology Life Quality Index (DLQI) is a validated tool for measuring the impact of cutaneous disease on the QoL of patients and allows comparison with other dermatologic conditions. It has also been used to assess the change in QoL in patients treated with BTA. One study has shown a statistically significant improvement in DLQI for patients treated with BTA for hyperhidrosis of the axillae, palms and forehead [35]. This was associated with high overall patient satisfaction ratings for these areas. Similar results were produced by Campanati and colleagues – all 41 patients in the study experienced a decrease in QoL as measured by the DLQI [49].

BTA appears to be a well-tolerated treatment for axillary hyperhidrosis apart from some discomfort at injection sites. There have been no adverse events to date. A perceived increase in nonaxillary sweating has been reported [8]. This may be the result of a heightened awareness of sweat production at other sites or may reflect a central upregulation of the autonomic regulation system [8].

A summary of current recommendations for treatment of axillary hyperhidrosis is shown in **Figure 2.**

Figure 2. Treatment of axillary hyperhidrosis



Botulinum toxin A for palmar hyperhidrosis

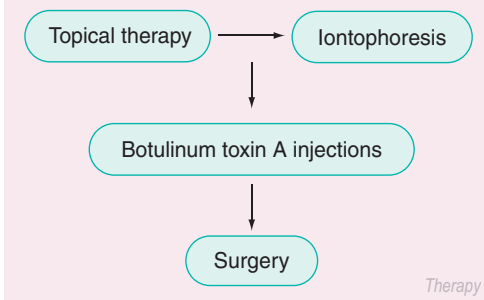
There is less consistency in the treatment of palmar hyperhidrosis with BTA than axillary hyperhidrosis. There is currently no license for the treatment of palmar hyperhidrosis with BT.

There has been a variation in the dose of BT used for palmar hyperhidrosis, ranging from 30 to 100 U/hand [50–53]. Saadia and colleagues conducted a randomized, single-blind, two-dose study to establish the effectiveness of BTA in reducing palmar hyperhidrosis and establish the most effective dose [54]. A total of 24 patients received either a low (50 U) or high dose (100 U) of BTA injected intradermally in 20 sites in each palm. Using the iodine–starch test, a significant decrease in sweating was seen within the first month with both doses. Results lasted up to 6 months in two-thirds of the patients in both groups. There appears to be a broader range of responses to palmar treatment varying from 3 to 12 months, with an average of 6 months [55–57]. Some of the reasons suggested for this include [45]:

- A problem of backflow from the injection sites
- A smaller diffusion distance in thicker palmer skin
- A higher number of cholinergic nerve endings in the palmer skin
- A differential recovery rate between the nerves of the palm and those in the axilla

It has been reported that patients who receive this treatment develop a transient period of weakness and instability of the lumbric muscles which usually reverses spontaneously [45]. However, the evidence is conflicting. Lowe and colleagues investigated the use of botox versus placebo in 19 patients and concluded that patients experienced significant improvements in palmar hyperhidrosis without a concomitant decrease in grip or dexterity, or the occurrence of serious adverse events [58]. However, in the study by Saadia and colleagues, although handgrip strength was not affected, finger pinch strength decreased 2 weeks after injection by 23 ± 27% with 50 U and 40 ± 21% with 100 U [54]. Pinch strength improved gradually however 6 months after treatment it was still 7 to 11% lower than at baseline. Thus, they conclude that low dosages of BTA for palmar hyperhidrosis may reduce side effects because there was a trend towards milder finger weakness in patients receiving the low dose (50 U/hand). For this reason, some recommend that treatments should be staggered to make it easier for the patient [45].

Figure 3. Treatment of palmar hyperhidrosis.



Another drawback to treating palmar hyperhidrosis with BTA is pain during injections. Simple topical anesthesia such as ice or Lidocaine/Prilocaine cream (EMLA®) can be used but few can tolerate the discomfort. Most patients will require regional nerve block anesthesia before undergoing palmar injections [59]. Blocking of the ulnar and median nerves at the wrist using 1% lidocaine is recommended [60]. The use of regional nerve blocks is not associated with reduced efficacy of BTA for palmar hyperhidrosis [61]. There have been recent reports of botox delivery by iontophoresis [64]. This has important therapeutic potential for patients with focal hyperhidrosis as they may be spared from painful injections. A summary of current recommendations for treatment of palmar hyperhidrosis is shown in **Figure 3**.

Other types of focal hyperhidrosis treated with botulinum toxin A

Table 1 shows the dose range and duration of effect of BTA for different forms of focal hyperhidrosis.

Plantar hyperhidrosis

BTA has been found to be an effective treatment for plantar hyperhidrosis. In one study of ten patients, 50 U of BTA was injected into the sole of each foot [62]. A total of 7 patients were symptom free for up to 5 months and were satisfied with their treatment. One patient experienced a temporary localized hematoma. Regional nerve blocks (a medial ankle block of the tibial nerve and a lateral ankle block of the sural nerve) can also be used when treating plantar hyperhidrosis [63].

Frontal hyperhidrosis

Frontal hyperhidrosis has also been effectively treated with BTA. Effects have been shown to last for up to 5 months [65]. Side effects include painful injections and transient weakness of forehead muscles without ptosis.

Localized unilateral hyperhidrosis

Localized unilateral hyperhidrosis (LUH) is a rare condition of unknown etiology. It usually occurs on the forehead or forearm and is restricted to an area smaller than 10 cm^2 [66]. The major difference from primary hyperhidrosis is that LUH has no typical triggering factor and occurs even during sleep [4]. A dose of 30 U of BTA has been shown to induce complete anhidrosis to an area of LUH in one patient [67].

Frey's syndrome

Frey's syndrome comprises pathologic sweating of the preauricular area and flushing after gustatory stimulation. It is a common complication after surgical intervention or injury in the region of the parotid gland [68]. It is thought to be caused by misdirected resprouting of postsynaptic salivomotor parasympathetic fibers that have lost their glandular target organ.

BTA has also been shown to be effective in treating focal hyperhidrosis associated with Frey's syndrome and some recommend this option as first-line treatment [69,70]. Doses of botox used for this condition range from 16 to 80 U [71].

Table 1. Dose range and duration of effect of botulinum toxin A for focal hyperhidrosis.

Site	Dose range	Duration of effect
Axillae	50–200 U Botox®/axilla (recommended dose 50 U/axilla) 125–400 U Dysport®/axilla	4–10 months Average 4–6 months
Palm	30–100 U/palm	2–12 months
Sole of foot	50–100 U/foot	5 months
Forehead	1–86 U	5 months
Frey's syndrome	16–80 U	12–24 months

Ross' syndrome

This syndrome is characterized by the triad of unilateral tonic pupils, generalized areflexia (Homes–Adie syndrome) and progressive segmental anhidrosis with a compensatory band of excessive perspiration. BTA has been suggested to treat the areas of compensatory hyperhidrosis [4].

Highlights

- Botulinum toxin (BT) type A (BTA) is currently only licensed for the treatment of axillary hyperhidrosis.
- Several large trials have shown that BTA is a safe and effective treatment for axillary hyperhidrosis, with significant improvement in quality of life (QoL) for sufferers.
- Mean duration of effect of BTA for axillary hyperhidrosis is 6 months.
- BTA has been shown to be an effective treatment for palmar hyperhidrosis although the duration of effect is less reliable (2 to 12 months).
- BTA has been used successfully for other forms of focal hyperhidrosis including plantar and frontal hyperhidrosis, Frey's syndrome, localized unilateral hyperhidrosis and Ross' syndrome. However, further studies are required using larger numbers of patients to gather evidence for these conditions.
- BTA treatment is well tolerated by patients with minimal side effects.
- Some investigators have reported development of neutralizing antibodies to BTA, particularly with repeated use of large doses.
- BT type B is now being used successfully in the treatment of hyperhidrosis and it is possible that other serotypes of BT may be developed for usage in the future.

Expert commentary & outlook

BTA is an effective treatment for hyperhidrosis. It has been shown to reduce sweating in many types of focal hyperhidrosis using objective evaluation (gravimetric and Minor's iodine starch test) and subjective evaluation (DLQI and Hyperhidrosis Impact Questionnaire). BTA is generally well tolerated although it can be associated with some side effects. Although a well established and licensed treatment for axillary hyperhidrosis, further studies are required to gather evidence for the use of BTA in treating other types of focal hyperhidrosis. Controlled trials are required to assess optimum doses and duration of effect. Care must also be taken to monitor the long-term effects of BT and remember the risk of antibody formation with long-term use. With this in mind, it is possible that other serotypes of BT may be further developed. The use of BTB is increasing but further studies are required to evaluate outcome and duration of treatment, comparison with BTA and dose ranging in controlled studies. These new toxins will provide clinicians with an alternative option in the management of patients and in addition, provide hope for those who may not respond to or find a reduced effect with BTA.

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