Botulinum Toxin for Axillary Hyperhidrosis

Ada Regina Trindade de Almeida, MD[a,*], Suelen Montagner, MD[b]

KEYWORDS

• Axillary hyperhidrosis • Excessive underarm sweating • Botox • Botulinum toxin • Neuromodulators

KEY POINTS

- Botulinum toxin has been proved to be safe and effective for the treatment of axillary hyperhidrosis.
- Although its pathophysiology continues to be controversial, the beneficial effect of type-A neuromodulators in temporarily inhibiting localized sweating supports a level A recommendation from evidence-based review.
- Before the procedure, the correct identification of the affected area is mandatory to avoid wastage of drug and neglect of target areas, and to enhance efficacy, as the hyperhidrotic location may not match the hairy axillary region.

INTRODUCTION

Axillary hyperhidrosis is a disease that affects the social and occupational lives of many people on all continents.[1,2] Axillary hyperhidrosis begins during the teenage years and equally affects men and women.[3] When associated with axillary malodor it is known as bromhidrosis.

The pathophysiology of primary focal hyperhidrosis is not well understood. It can result from hyperstimulation of eccrine and, possibly, apoeccrine sweat glands.[4]

Eccrine glands are distributed over almost the entire body surface[5] and are most numerous on the palms, soles, forehead, axillae, and cheeks.[6] Innervated by cholinergic postganglionic sympathetic nerve fibers, they excrete sweat and contribute to regulation of body temperature.[6,7] When comparing patients with excessive sweating with normal controls, histologic studies have not shown any morphologic alterations or increase in the number or size of the sweat glands.[8] However, preliminary findings of a recent study suggest that the eccrine gland's secretory clear cell exercises a main role in fluid transport (the only one equipped with cotransporter and aquaporin channels), and is likely the source of excessive sweating in this form of hyperhidrosis.[9]

Apocrine glands are stimulated by epinephrine and norepinephrine, and are specifically localized at the urogenital regions and the axillae.[9,10] These glands produce a viscid secretion that can become malodorous as a result of bacterial breakdown.[11]

Sato and colleagues[5,12] described apoeccrine glands in 1989 as having morphologic characteristics of both eccrine and apocrine types. According to these investigators, they correspond to 10% to 45% of all axillary glands and respond to cholinergic stimuli, and intensely so to epinephrine and isoproterenol infusion.[7] However, recent histologic studies have failed to show evidence of

Funding Sources: None.
Conflict of Interest: Dr A.R. Trindade de Almeida has been a consultant to Allergan, Inc and has participated in clinical trials for Allergan and Galderma; Dr S. Montagner has no conflicts of interest.
[a] Department of Dermatology, Hospital do Servidor Público Municipal de São Paulo (SP), Rua Turiaçu, 390, cjs 113-114, Perdizes, São Paulo, São Paulo 05005-000, Brazil; [b] Av. Eng. Carlos Stevenson, 885, Campinas, São Paulo 13092-132, Brazil
* Corresponding author.
E-mail address: artrindal@uol.com.br

Dermatol Clin 32 (2014) 495–504
http://dx.doi.org/10.1016/j.det.2014.06.013
0733-8635/14/$ – see front matter

apoeccrine glands in the tissues of the axillary region investigated.[8,9] The existence of these glands remains controversial.[9,13,14]

BOTULINUM TOXIN

Intracutaneous injections of botulinum toxin (BoNT) have been used as a treatment for focal hyperhidrosis since 1996 with safety, efficacy, and high levels of patient satisfaction.[2,15] Two types of botulinum toxins, BoNT type A (BoNT-A) and BoNT type B (BoNT-B), were studied in axillary hyperhidrosis, and both demonstrated effectiveness in temporarily inhibiting sweating, although acting at different target sites. BoNT-A binds to and cleaves the 25-kDa synaptosomal-associated protein (SNAP-25), whereas BoNT-B acts on the vesicle-associated membrane protein (VAMP or Synaptobrevin),[16,17] both blocking the release of acetylcholine from cholinergic neurons that innervate sweat glands.[16,18]

The use of BoNT-A for the treatment of axillary hyperhidrosis was approved in 2004 by the US Food and Drug Administration (FDA),[19] since then a multitude of studies have confirmed its efficacy, beneficial effects, and paucity of side effects.[20–24]

There are many commercial available BoNT-A products available worldwide. The formulations are not identical and present individual potencies, making caution necessary to ensure proper use. In April 2009, the FDA established drug names to reinforce these differences,[25] summarized in **Table 1**.

There is no globally accepted exact ratio among the different formulations. Reviewing the related published literature, the most commonly accepted dose correlation among products are: 1 U onabotulinumtoxinA (OnaA) = 1 U incobotulinumtoxinA (IncoA) = 1 U BoNT-A (Lanzou) = 1 U BoNT-A (Medytox) = 2,5–3 U abobotulinumtoxinA (AboA).

The available BoNT-B (rimabotulinumtoxinB [RimaB]) products are Neurobloc in the European Union and Myobloc in the United States. Unlike BoNT-A, it is not commercially available worldwide, and probably for this reason a limited number of studies of axillary hyperhidrosis being treated with this toxin type have been published. The literature found describes side effects related to distant spread of the toxin, such as dry eyes and dry mouth, which are not commonly described after the use of BoNT-A.[26–28] The dose correlation between BoNT-A and BoNT-B varies from 20 to 100 U of RimaB to 1 U of OnaA.[26–29]

A recent evidence-based review[30] of hypersecretory disorders that searched for botulinum toxin as a treatment of axillary hyperhidrosis found 2 Class I (prospective, randomized, controlled, and with masked outcome assessment clinical trial with strict requirements) studies (1 with OnaA[21] and 1 with AboA[20]) and 5 Class II (similar to Class I trials but lacking 1 or more of the required criteria) studies. The investigators concluded that the evidence supports a level A recommendation for BoNT-A in general and a level B recommendation for OnaA and AboA individually, whereas RimaB and IncoA received a level U recommendation (insufficient data) for axillary hyperhidrosis.

Some studies have compared the use of different toxins for the treatment of axillary hyperhidrosis.

Studies Comparing BoNT-A Products

Kalner[15] performed a prospective same-patient comparison between OnaA in one axilla and AboA in the other, using a conversion factor of 1 U OnaA to 3 U AboA. She noted that OnaA resulted in a faster onset of action, within 1 week,

Table 1
Commercially available botulinum toxin A (BoNT-A)

Botulinum Toxin	Trade Name	Origin
OnabotulinumtoxinA (OnaA)	Botox	(Allergan, Irvine, CA, USA)
AbobotulinumtoxinA (AboA)	Dysport	(Ipsen Biopharm, UK) in USA, Europe, and Latin America
BoNT-A	Prosigne	(Lanzhou, China) in Asia and Latin America
BoNT-A	Neuronox	(Medytox, South Korea) in Asia, Botulift in Latin America
IncobotulinumtoxinA (IncoA)	Xeomin	(Merz Pharma, Germany) in Canada, Germany, USA, Latin America
BoNT-A	PureTox	(Mentor Corp, Santa Barbara, CA, USA) uncomplexed BoNT-A. Phase III studies

versus 2 weeks for AboA. She also observed a longer duration of benefit (9 months), whereas the axilla treated with AboA maintained the results for 6 months.[15] In another comparative study performed in 2007 on 10 patients, Talarico-Filho and colleagues[31] did not find statistically significant differences in the onset of sweating reduction or the duration of benefit using the same conversion factor.

In a double-blind comparative study of 46 patients, Dressler[32] injected 50 U OnaA in one axilla and 50 U IncoA in the contralateral axilla. Both 100-U/vial products were reconstituted in 10 mL of saline (10 U/mL). He found no difference in efficacy, onset of action, duration, or side effects between the 2 formulations.

Studies Comparing BoNT-A and BoNT-B Products

In 2011, Frasson and colleagues[29] treated 10 patients using 2500 U of RimaB in one axilla and 50 U of OnaA in the contralateral axilla (50 U B:1 U A). BoNT-B was more effective than BoNT-A in reducing sweating production in the affected area, with faster onset, longer duration of benefit, and higher treatment satisfaction scores. No systemic adverse effects were described. According to the investigators, their findings differed from those found in the literature because other studies used lower toxin ratios (40:1 or 20:1) and higher dilutions.

Further studies are needed to standardize the treatment while aiming at reducing side effects and improving the benefits. The toxin type will be selected at the physician's discretion and according to its safety and product availability.

TOXIN SOLUTION

A recent review about botulinum toxin handling found that "there is no standardized dilution for BoNT-A treatment of focal hyperhidrosis."[16] Reported dilutions found in the literature vary from 1 to 10 mL of saline for OnaA (with most physicians using between 2 and 5 mL), whereas for AboA the reconstitution volumes vary from 1.25 to 10 mL (with the use of 2.5–5 mL being the most frequent). In the only study of IncoA for hyperhidrosis, the dilution used was 10 U/mL.[16] **Table 2** summarizes the dilution volumes described in the literature.

The authors prefer to reconstitute the 100-U vial of OnaA (Botox) in 2 mL saline, achieving a dose of 50 U/mL.

The same article previously quoted also mentions that different substances can be added to the toxin solution with no harm to the toxin, such as hyaluronidase, lidocaine, and epinephrine.

Table 2
Reported dilutions for hyperhidrosis

Toxin	Dilution Range (mL saline)	Most Commonly Used Dilution (mL)
OnabotulinumtoxinA	1–10	2–5
AbobotulinumtoxinA	1.25–10	2.5–5
IncobotulinumtoxinA	1–10	10 (1 paper)

Among these substances, the most interesting for axillary treatment is lidocaine. A recent double-blind, randomized, comparative study treated 8 patients with 50 U OnaA diluted in 0.5 mL saline plus 1 mL of 2% lidocaine into one axilla, and 50 U OnaA diluted in 1.5 mL saline into the other axilla.[33] Vadoud-Seyedi and Simonart[34] also treated 29 patients in a similar manner in 2007, with a dilution of 5 mL. Both studies showed equal effectiveness of BoNT-A reconstituted in saline or lidocaine. However, the toxin diluted in lidocaine caused less pain, and may be preferable for treating axillary hyperhidrosis.[33,34]

When reconstituted with saline admixed with hyaluronidase, OnaA has its efficacy maintained after 2 weeks and shows enhanced diffusion, as observed by Goodman[35] in 2003.

EVALUATION METHODS

After the selection of the toxin, it is important to identify the area to be treated. The Minor iodine-starch test is a useful method to map the extension of the affected area[36] in addition to the posttreatment residual sweating, but it does not provide accurate information on the amount of sweat produced.

The test is usually applied before any topical or regional anesthesia, and is cheap and easy to perform.[37] The first step is to dry the affected area with an absorbent paper. Then a 3% to 5% iodine solution is applied to the underarm and neighboring region and is allowed to dry. In some patients, the continuous sweat must be wiped again just before the starch application to avoid false reactions (**Fig. 1**). In contact with starch plus iodine, the sweat acquires a dark purple color, being clearly visible. One must be aware that the commercial povidone-iodine topical solution with 10% iodopovidone contains only 1% free iodine. Therefore, when using this agent the Minor test results might not be satisfactory.[38]

Another important detail to observe is that the axillary hyperhidrotic area very often does not coincide with the hairy underarm region.

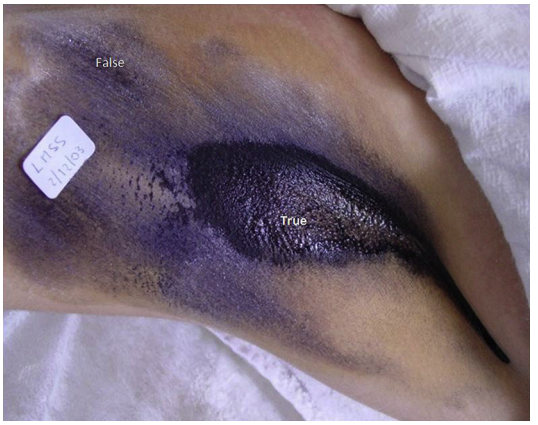

Fig. 1. In contact with starch plus iodine the sweat acquires a dark purple color (*center*), which is clearly visible. Normal areas need to be kept dry to avoid false reactions (*upper left quadrant*).

Therefore, the Minor test is mandatory to identify the actual affected area in a precise manner, so as to optimize the injection of the toxin and ensure effective treatment.

There are cases whereby sweating is excessive or is located outside the hairy area, as observed in **Fig. 2**. In such cases, if the BoNT treatment is confined to the terminal follicular area, the response will be unsatisfactory, as some regions will be left untreated. By contrast, when sweating is confined to small areas contained in the hairy region (**Figs. 3** and **4**), the treatment of the entire hair-bearing location implies in the use of an excessive and unnecessary amount of BoNT units. The distribution of the hyperhidrotic area frequently may assume different shapes, such as "M," "S," or "8," and the iodine-starch test will also highlight all of these situations (**Fig. 5**).

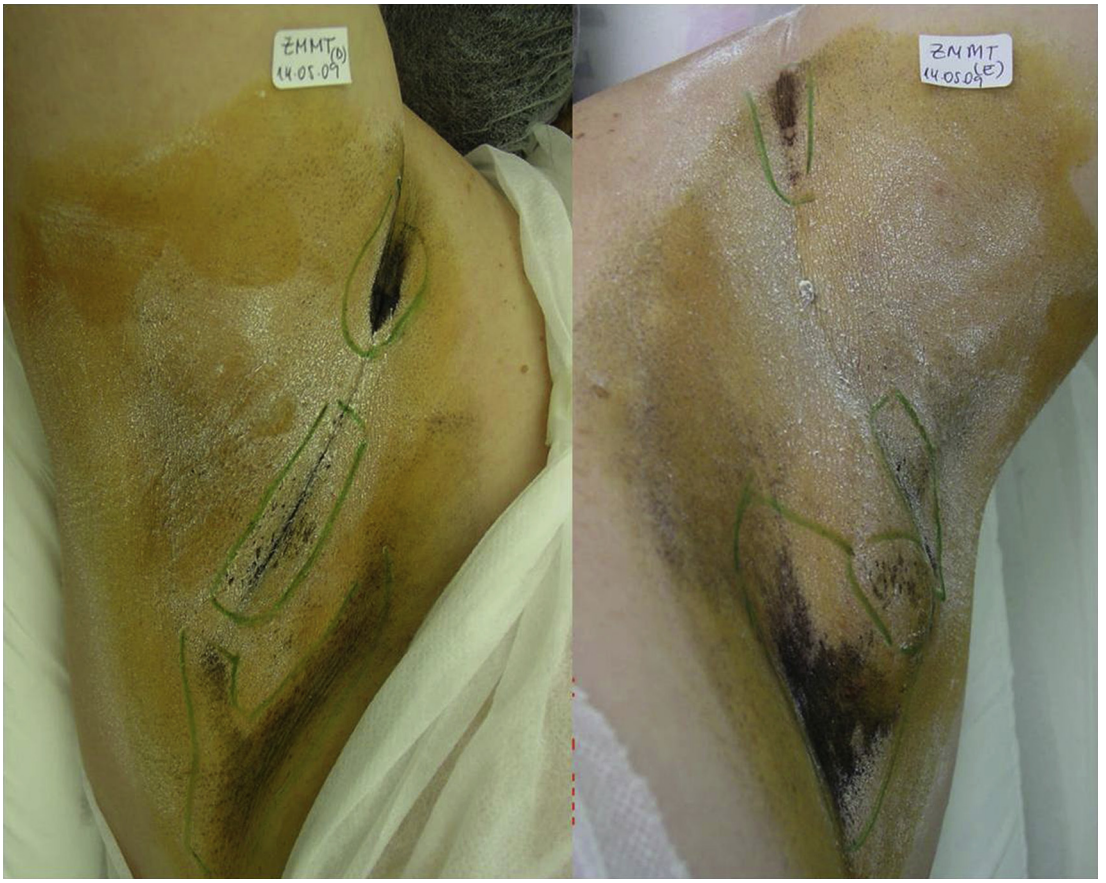

Fig. 2. In this female patient, the excessive sweating areas are not limited to the hair-bearing regions, and an effective botulinum toxin treatment cannot be achieved if precise localization is not delimited before the procedure.

Fig. 3. In this male individual, the iodine-starch test shows that the hyperhidrotic region is smaller than the hairy area.

For iodine-sensitive patients, Ponceau red tincture is an alternative. When mixed with starch and in contact with sweat, this tincture develops a pinkish color.[39] For both techniques, the distribution and maximal perspiration sites must be recorded photographically for future comparison.

Another useful method for research trials, but time-consuming in daily practice (and thus not often applied), is gravimetric testing. The volume of produced sweat is measured over a fixed period of time under controlled conditions. First, the affected area is dried using absorbent tissue; then a previous weighed filter paper is applied and left in place for a certain period of time. The volume of produced sweat during this time interval is quantified by measuring the weight of the paper before and after contact. The evaluation period varies among investigators. One group prefers contact with the affected area for 1 minute,[20] whereas other investigators prefer 5,[21,40] 10,[41] or 15 minutes.[42]

Use of the 2 aforementioned methods (gravimetry and Minor test) based on point counting using a transparent square-lattice grid was proposed by Bahmer and Sachse[41] as the Hyperhidrosis Area and Severity Index (HASI). One centimeter represents 1 point. After estimation of the sweating area, the volume of secretion weighed through gravimetry after 10 minutes is divided by the number of sites in the affected area. The HASI score is given in mg of sweat per cm^2 per minute. It is assumed hyperhidrosis is present if HASI values are greater than 1 mg/cm^2 per minute.

The quality of life of patients affected with focal idiopathic hyperhidrosis may be measured through several tests, the most frequently used being the Hyperhidrosis Disease Severity Scale.

INJECTION TECHNIQUE

After identifying and photographing the affected area, it has to be delimited with a marker pen or gentian violet. At this point it is possible to apply a local topical anesthetic, which will improve the patient's comfort during the procedure. If applied before, the anesthetic cream might impair the test.

The injection should be intradermal using a 30-gauge needle attached to the syringe (0.3- or 0.5-mL syringes, Ultrafine II 30-U or 50-U insulin syringes; Becton Dickinson, Franklin Lakes, NJ, USA), which eliminates the dead space between the needle and the syringe, and also the risk of expelling the needle during injection.

One study investigated whether the use of a 30-gauge rather than a 27-gauge needle influenced pain intensity in 38 patients treated with BoNT-A for axillary hyperhidrosis. The pain scores

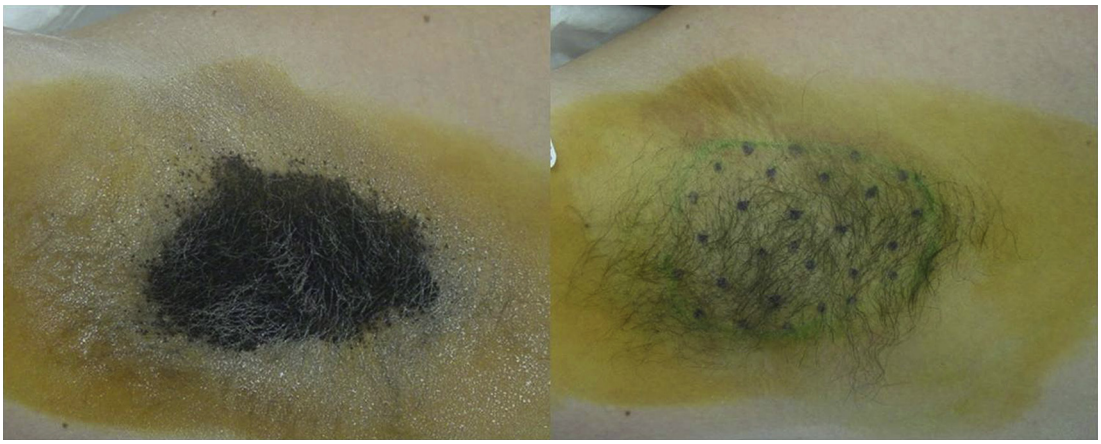

Fig. 4. In the same patient shown in Fig. 3, injection sites 1.5 cm apart are marked inside the delimited area.

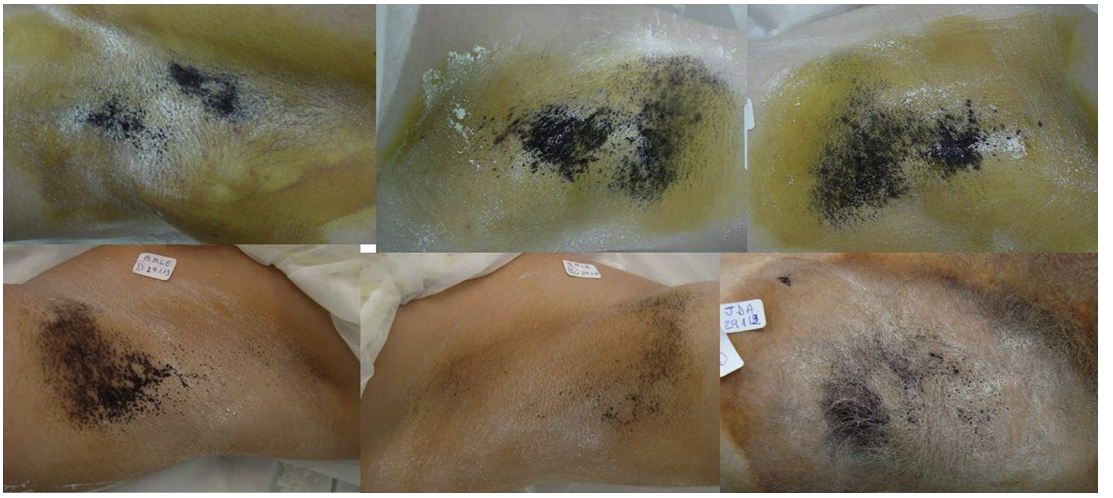

Fig. 5. Several underarms of different individuals where the locations of excessive sweating assume irregular, bizarre shapes.

recorded after the first 5 injections were significantly lower for the 30-gauge needle.[43]

The number of injections and the total dose depend on the involved surface area. Once injected, the toxin concentration will be higher at the central point, with a decreasing gradient along the peripheral areas.[37] The treatment goal is to create confluent overlapping anhidrotic halos to achieve an optimal outcome.[44] **Table 3** summarizes the usual BoNT doses for axillary hyperhidrosis as described in the literature.

Approximately 10 to 20 intradermal injections in 0.1- to 0.2-mL aliquots (total dose: 50–100 U OnaA) are used for each axilla, spaced 1 to 2 cm apart. Injections may also be performed in the superficial fat without adverse events or significant reduction in efficacy.

Most patients have excellent treatment results. The effects begin 2 to 4 days after injection and last approximately 6 to 9 months, although in some cases they may last more than 1 year. In the authors' experience, the longest successful outcomes are obtained when the excessive sweating location can be precisely delimited. Only when the patient could not sweat during iodine starch test the hair-bearing area is injected, and in some of these cases, longer duration could not be achieved.

Table 3
Reported mean dose per axilla for each BoNT

Toxin	Mean Dose (U)
OnabotulinumtoxinA	50–100
AbobotulinumtoxinA	100–300
IncobotulinumtoxinA	50
RimabotulinumtoxinB	2500–5000

Figs. 6–8 show examples of short-term and long-term results after OnaA treatment of axillary hyperhidrosis.

Other techniques have been used as a variation of the traditional punctures. A device used for intralesional corticosteroid treatment of alopecia areata was described as an alternative method of BoNT application in axillary hyperhidrosis by means of a multi-injection round plate with 5 or 7 27-gauge needles. According to the investigators a rapid application in uniform and homogeneous manner was obtained, avoiding repeated punctures.[45]

A multiple-site marking grid has also been described, made of a flexible silicon sheet with holes punched out at a 1-cm distance (Exmoor Plastics Ltd, Taunton, UK). Once the excessive sweating area is defined, the grid is positioned on the affected area and the site is marked through the holes in the grid with a skin-marker pen. Jain[46] argues that this device saves time.

However, the use of these alternative techniques implies availability of the devices, whereas traditional injections only depend on easily available materials, in addition to well-trained professionals. **Box 1** provides a summary of practical information needed for successful BoNT treatment of excessive underarm sweating.

TRANSCUTANEOUS BOTULINUM TOXIN

There is a growing demand for the development of an effective, safe, and noninvasive treatment of axillary hyperhidrosis.[47] A means to deliver the toxin through the skin without needles or

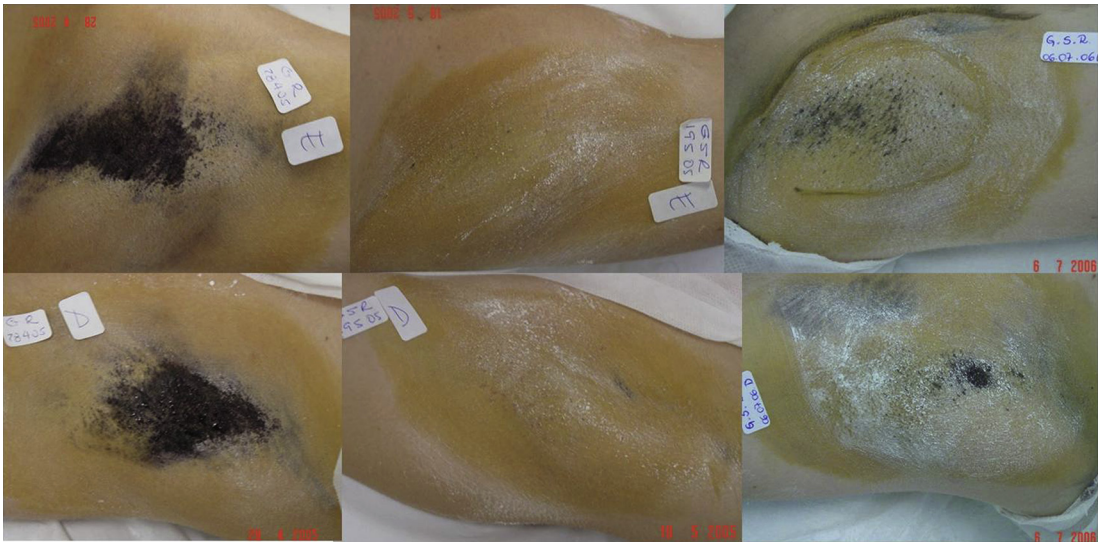

Fig. 6. A 28-year-old woman treated with 50 U of onabotulinumtoxinA (OnaA) per axilla. (*Upper and lower left*) Before treatment. (*Upper and lower central*) after 21 days. (*Upper and lower right*) After 15 months, when she returned for a new session.

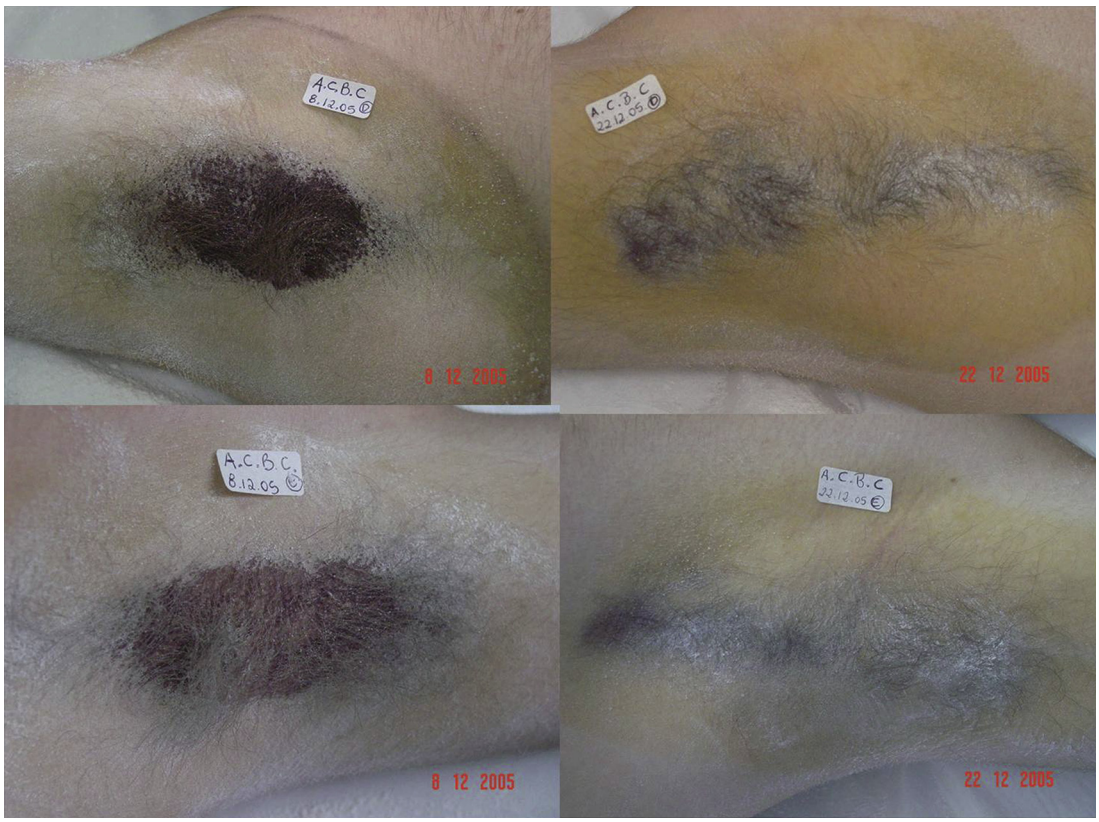

Fig. 7. A 29-year-old male patient, before (*left*) and after (*right*) his first treatment of 50 U OnaA per axilla.

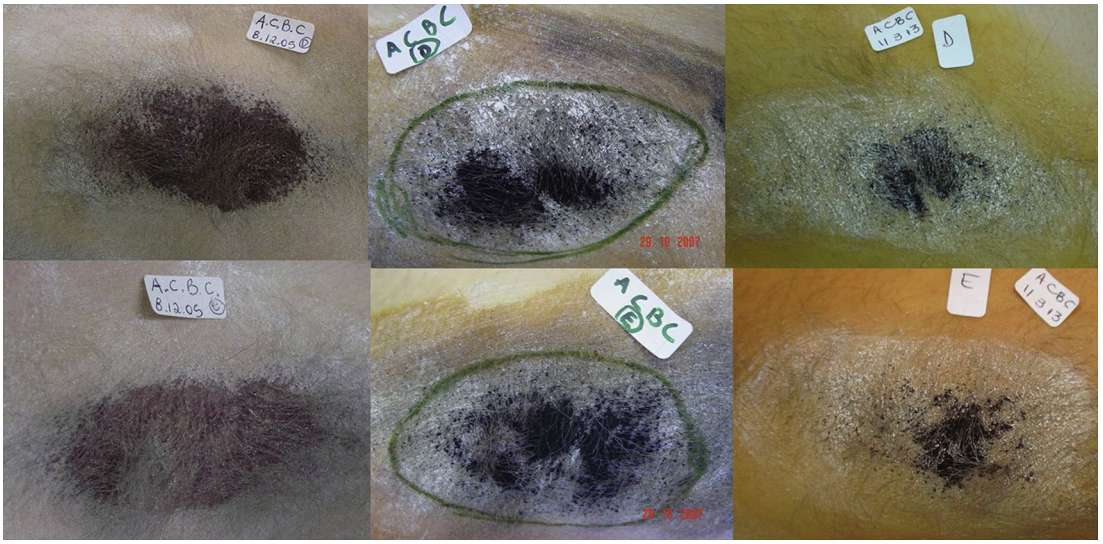

Fig. 8. The same patient shown in **Fig. 7**. He had been receiving regular biannual OnaA treatment for 8 years. (*Upper and lower left*) Before treatment. (*Upper and lower central*) Two years after his first treatment and just before the second. (*Upper and lower right*) After 4 biannual OnaA treatments. Note the long-term effect and possible reduction in the total extension of the affected area.

punctures has been recently tried, with promising results. However, BoNT directly applied to the skin is not absorbed because of its large molecular size.[48]

A small, controlled clinical trial investigated a novel proprietary transport peptide to deliver BoNT-A through the skin. Chow and Wilder-Smith[48] found a statistically significant reduction of sweat production in 12 cases of axillary hyperhidrosis using 200 U of OnaA reconstituted with saline admixed with the transport peptide. The duration of effect was not mentioned. This innovative method promises a revolution in the treatment of hyperhidrotic affected areas, and may also be useful in the future for other indications.

Box 1
Practical information for BoNT treatment of axillary hyperhidrosis

Always perform Minor test before applying BoNT-A

The test must be performed before any topical anesthesia

Highlight the area to be treated

Take photographs for future comparison

Distance between injection sites: 1 to 2 cm

Onset of action: 2 to 4 days

Duration of effect: 6 to 9 months

SUMMARY

BoNT has proved to be a safe and effective treatment for axillary hyperhidrosis. Although its pathophysiology remains controversial, the beneficial effect of type-A neuromodulators in temporarily inhibiting localized sweating supports a level A recommendation from evidence-based review.

REFERENCES

1. Doft MA, Kasten JL, Ascherman JA. Treatment of axillary hyperhidrosis with botulinum toxin: a single surgeon's experience with 53 consecutive patients. Aesthetic Plast Surg 2011;35:1079–86.
2. Glaser DA, Hebert AA, Pariser DM, et al. Primary focal hyperhidrosis: scope of the problem. Cutis 2007;79(5):5–17.
3. Hornberger J, Grimes K, Naumann M, et al. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. J Am Acad Dermatol 2004;51:274–86.
4. Hamm H, Naumann MK, Kowalski JW, et al. Primary focal hyperhidrosis: disease characteristics and functional impairment. Dermatology 2006;212:343–53.
5. Sato K, Kang WH, Saga KT. Biology of sweat glands and their disorders I. Normal sweat gland function. J Am Acad Dermatol 1989;20:537–63.
6. Kreyden O, Scheidegger E. Anatomy of the sweat glands, pharmacology of botulinum toxin, and distinctive syndromes associated with hyperhidrosis. Clin Dermatol 2004;22:40–4.

7. Mota Juang J, Sotto MN. Anatomy and histology of sweat glands. In: Almeida AR, Hexsel DM, editors. Hyperhidrosis and botulinum toxin. São Paulo (Brazil): Edition of authors; 2004. p. 3–6.
8. Bovell DL, Clunes MT, Elder HY, et al. Ultrastructure of the hyperhidrotic eccrine sweat gland. Br J Dermatol 2001;145:298–301.
9. Bovell DL, MacDonald A, Meyer BA, et al. The secretory clear cell of the eccrine sweat gland as the probable source of excess sweat production in hyperhidrosis. Exp Dermatol 2011;20(12):1017–20.
10. Lindsay SL, Holmes S, Corbett AD, et al. Innervation and receptor profiles of the human apocrine (epitrichial) sweat gland: routes for intervention in bromhidrosis. Br J Dermatol 2008;159:653–60.
11. Atkins JL, Butler PE. Hyperhidrosis: a review of current management. Plast Reconstr Surg 2002;110: 222–8.
12. Sato K, Kang WT, Saga KT. Biology of sweat glands and their disorders II. Disorders of sweat gland function. J Am Acad Dermatol 1989;20:713–26.
13. Bovell D, Corbett A, Holmes S, et al. The absence of apoeccrine glands in the human axilla has disease pathogenetic implications, including axillary hyperhidrosis. Br J Dermatol 2007;156:1278–86.
14. Bechara F. Do we have apoeccrine sweat glands? Int J Cosmet Sci 2008;30:67–8.
15. Kalner IJ. Same-patient prospective comparison of Botox versus Dysport for treatment of primary axillary hyperhidrosis and review of literature. J Drugs Dermatol 2011;10(9):1013–5.
16. Trindade De Almeida AR, Secco LC, Carruthers A. Handling botulinum toxins: an updated literature review. Dermatol Surg 2011;37(11):1553–65.
17. Rosell K, Hymnelius K, Swartling C. Botulinum toxin type A and B improve quality of life in patients with axillary and palmar hyperhidrosis. Acta Derm Venereol 2013;93:335–9.
18. Lowe NJ, Glaser DA, Eadie N, et al. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. J Am Acad Dermatol 2007;56(4):604–11.
19. Grunfeld A, Murray CA, Solish N. Botulinum toxin for hyperhidrosis: a review. Am J Clin Dermatol 2009; 10(2):87–102.
20. Heckmann M, Ceballos-Baumann AO, Plewig G. Botulinum toxin A for axillary hyperhidrosis (excessive sweating). N Engl J Med 2001;344(7):488–93.
21. Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomised, parallel group, double blind, placebo controlled trial. BMJ 2001;323(7):596–9.
22. Scamoni S, Valdatta L, Frigo C, et al. Treatment of primary axillary hyperhidrosis with botulinum toxin type A: our experience in 50 patients from 2007 to 2010. ISRN Dermatol 2012;2012:702714.
23. Lecouflet M, Leux C, Fenot M, et al. Duration of efficacy increases with the repetition of botulinum toxin A injections in primary axillary hyperhidrosis: a study in 83 patients. J Am Acad Dermatol 2013; 69(6):960–4.
24. Lakraj AA, Moghimi N, Jabbari B. Hyperhidrosis: anatomy, pathophysiology and treatment with emphasis on the role of botulinum toxins. Toxins (Basel) 2013;5:821–40.
25. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm174949.htm. Accessed October 1, 2010.
26. Baumann L, Slezinger A, Halem M, et al. Pilot study of the safety and efficacy of MyoblocTM (botulinum toxin type B) for treatment of axillary hyperhidrosis. Int J Dermatol 2005;44:418–24.
27. Nelson L, Bachoo P, Holmes J. Botulinum toxin type B: a new therapy for axillary hyperhidrosis. Br J Plast Surg 2005;58:228–32.
28. Dressler D, Adib Saberi F, Benecke R. Botulinum toxin type B for treatment of axillar hyperhidrosis. J Neurol 2002;249(12):1729–32.
29. Frasson E, Brigo F, Acler M, et al. Botulinum toxin type A vs type B for axillary hyperhidrosis in a case series of patients observed for 6 months. Arch Dermatol 2011;147(1):122–3.
30. Naumann M, Dressler D, Hallett M, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of secretory disorders. Toxicon 2013;67:141–52.
31. Talarico-Filho S, Mendonça DO, Nascimento M, et al. A double-blind, randomized, comparative study of two type A botulinum toxins in the treatment of primary axillary hyperhidrosis. Dermatol Surg 2007;33(1):44–50.
32. Dressler D. Comparing botox and xeomin for axillar hyperhidrosis. J Neural Transm 2010;117:317–9.
33. Gülec AT. Dilution of botulinum toxin A in lidocaine vs. in normal saline for the treatment of primary axillary hyperhidrosis: a double-blind, randomized, comparative preliminary study. J Eur Acad Dermatol Venereol 2012;26:314–8.
34. Vadoud-Seyedi J, Simonart T. Treatment of axillary hyperhidrosis with botulinum toxin type A reconstituted in lidocaine or in normal saline: a randomized, side-by-side, double-blind study. Br J Dermatol 2007;156:986–9.
35. Goodman G. Diffusion and Short-term efficacy of Botulinum toxin A after addition of hyaluronidase and its possible application for the treatment of axillary hyperhidrosis. Dermatol Surg 2003;29:533–8.
36. Cohen JL, Cohen G, Solish N, et al. Diagnosis, impact, and management of focal hyperhidrosis: treatment review including botulinum toxin therapy. Facial Plast Surg Clin North Am 2007;15: 17–30, v–vi.

37. Glogau R. Hyperhidrosis and botulinum toxin A: patient selection and techniques. Clin Dermatol 2004; 22:45–52.
38. Burks RI. Povidone-iodine solution in wound treatment. Phys Ther 1998;78(2):212–8.
39. Bushara KO, Park DM. Botulinum toxin and sweating [letter]. J Neurol Neurosurg Psychiatry 1994;54(11): 1437.
40. Hund M, Kinkelin I, Naumann M, et al. Definition of axillary hyperhidrosis by gravimetric assessment. Arch Dermatol 2002;138:539–41.
41. Bahmer F, Sachse M. Hyperhidrosis area and severity index [letter]. Dermatol Surg 2008;34: 1744–5.
42. Odderson IR. Long-term quantitative benefits of botulinum toxin A in the treatment of axillary hyperhidrosis. Dermatol Surg 2002;28:480–3.
43. Skiveren J, Larsen HN, Kjaerby E, et al. The influence of needle size on pain perception in patients treated with botulinum toxin A injections for axillary hyperhidrosis. Acta Derm Venereol 2011;91:72–4.
44. Klein AW. Complication, adverse reaction, and insights with the use of botulinum toxin. Dermatol Surg 2003;29:549–56.
45. Grimalt R, Moreno-Arias GA, Ferrando J. Multi-injection plate for botulinum toxin application in the treatment of axillary hyperhidrosis. Dermatol Surg 2001;27:543–4.
46. Jain S. A new multiple site marking grid for botulinum toxin application in the treatment of axillary hyperhidrosis. Br J Dermatol 2006;154:375–91.
47. Glogau RG. Topically applied botulinum toxin type A for the treatment of primary axillary hyperhidrosis: results of a randomized, blinded, vehicle-controlled study. Dermatol Surg 2007;33(1):S76–80.
48. Chow A, Wilder-Smith EP. Effect of transdermal botulinum toxin on sweat secretion in subjects with idiopathic palmar hyperhidrosis. Br J Dermatol 2009; 160(3):721–3.