**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
apocrine glands in the tissues of the axillary region investigated. The existence of these glands remains controversial.

**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. 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), both blocking the release of acetylcholine from cholinergic neurons that innervate sweat glands.

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

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, 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.

A recent evidence-based review 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 and 1 with AboA) 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 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.
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. In another comparative study performed in 2007 on 10 patients, Talarico-Filho and colleagues 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 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 treated 10 patients using 2500 U of RimaB in one axilla and 50 U of OnaA in the contralateral axilla (50 U: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.” 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.

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.

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. Vadoud-Seyedi and Simonart 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.

When reconstituted with saline admixed with hyaluronidase, OnaA has its efficacy maintained after 2 weeks and shows enhanced diffusion, as observed by Goodman 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 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. 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% iodosopovidone contains only 1% free iodine. Therefore, when using this agent the Minor test results might not be satisfactory.

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

Table 2

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Dilution Range (mL saline)</th>
<th>Most Commonly Used Dilution (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>1–10</td>
<td>2–5</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>1.25–10</td>
<td>2.5–5</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>1–10</td>
<td>10 (1 paper)</td>
</tr>
</tbody>
</table>
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. 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).

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.
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.\(^3\) 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,\(^2\) whereas other investigators prefer 5,\(^1\),\(^0\),\(^4\),\(^1\) or 15 minutes.\(^5\)

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\(^4\) 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
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.

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 intralvesional 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. Jain46 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

---

**Table 3**

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Mean Dose (U)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OnabotulinumtoxinA</td>
<td>50–100</td>
</tr>
<tr>
<td>AbobotulinumtoxinA</td>
<td>100–300</td>
</tr>
<tr>
<td>IncobotulinumtoxinA</td>
<td>50</td>
</tr>
<tr>
<td>RimabotulinumtoxinB</td>
<td>2500–5000</td>
</tr>
</tbody>
</table>

---

**Fig. 5.** Several underarms of different individuals where the locations of excessive sweating assume irregular, bizarre shapes.
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.
punctures has been recently tried, with promising results. However, BoNT directly applied to the skin is not absorbed because of its large molecular size. A small, controlled clinical trial investigated a novel proprietary transport peptide to deliver BoNT-A through the skin. Chow and Wilder-Smith 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.

**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**


**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

**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.


