Botulinum toxin: Pharmacology and injectable administration for the treatment of primary hyperhidrosis

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Hyperhidrosis is a dermatological condition defined by excessive sweating beyond thermoregulatory needs with significant effects on patients' quality of life. Hyperhidrosis is categorized as primary or secondary: primary hyperhidrosis is mostly focal and idiopathic, whereas secondary hyperhidrosis is commonly generalized and caused by an underlying medical condition or use of medications. Various surgical and nonsurgical therapies exist for primary hyperhidrosis. Although botulinum toxin is one of the deadliest toxins known, when used in small doses, it is one of the most effective therapies for primary hyperhidrosis. Botulinum toxin injections are widely used as a second-line primary hyperhidrosis treatment option once topical treatment strategies have failed. This article provides an overview of the commercially available botulinum toxin formulations and their applications in the treatment of primary hyperhidrosis. (J Am Acad Dermatol 2020;82:969-79.)

Key words: abobotulinumtoxinA; axillary hyperhidrosis; botulinum neurotoxin; botulinum toxin; *Clostridium* bacteria; craniofacial hyperhidrosis; excessive sweating; incobotulinumtoxinA; onabotulinumtoxinA; palmar hyperhidrosis; plantar hyperhidrosis; primary hyperhidrosis; prabotulinumtoxinA; rimabotulinumtoxinB.

Hyperhidrosis (HH) is defined as overactivity of eccrine sweat glands. There is a wide discrepancy in reported HH prevalence rates, ranging from less than 2%[1] in Israel to 12.3% to 38% in other countries (Canada, 12.3%[2]; Japan, 12.8%[3]; China, 14.5%[2]; Germany, 16.3%[4]; Poland, 16.7%[5]; Brazil, 20.6%[6]; India, 38%[7]). The most widely cited HH prevalence rate is 4.8% for the US population (based on a 2016 online survey).[8] HH is categorized as either primary or secondary. Primary HH (PHH) is idiopathic bilaterally symmetric excessive sweating; not derived from other known medical conditions or medication adverse effects; commonly affects the axillae, palms, soles, or craniofacial regions; and severely disturbs patients' quality of life.[9] Secondary HH may be focal or generalized and is caused by an underlying medical condition or medication adverse effect. PHH accounts for 93% of HH cases.[10] PHH is diagnosed when excessive sweating lasts for more than 6 months and includes 2 or more of the following characteristics: occurs more than once per week, presents in patients younger than 25 years of age, a family history exists, sweating is bilateral and symmetric, sweating ceases while asleep, and sweating severely affects the patient's daily activities.[11] Importantly, PHH is diagnosed after possible causes of secondary HH have been excluded.[12] In 90% of PHH cases, commonly affected areas include the axillae, palms, soles, or craniofacial regions.[13] Various nonsurgical (antiperspirants, iontophoresis, anticholinergics, laser or ultrasonography therapy, microwave thermolysis, fractional microneedle radiofrequency, etc) and surgical (excision of subcutaneous tissue, subcutaneous liposuction curettage, endoscopic sympathectomy, etc) therapies are available for the treatment of PHH.[9] This article focuses on the injectable botulinum toxin (BTX) therapy for the treatment of PHH.

BTX injections are widely used as a second-line PHH treatment once topical treatment strategies

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Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
Accepted for publication November 22, 2019.

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Published online December 4, 2019.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2019.11.042

have failed. Studies have shown sustainably higher satisfaction rates with injectable BTX (93%) than with placebo (30%).[14] Additionally, satisfaction with BTX treatment is often significantly higher than with other nonsurgical PHH treatment methods.[15,16] A survey of 1985 patients with PHH treated with BTX showed that 87.2% were most satisfied with BTX injections and least satisfied with antiperspirants.[17] In another study, approximately 96% of patients with PHH reported higher satisfaction with BTX-A injections than with other treatments.[18] In addition, iontophoresis with BTX-supplemented medium showed better anhidrotic results than iontophoresis with saline medium.[19,20]

CAPSULE SUMMARY

- Injectable botulinum toxin is a safe and effective treatment option for primary hyperhidrosis, an idiopathic excessive sweating condition that significantly affects patients' quality of life.
- Understanding the pharmacologic aspects and detailed injectable use of botulinum toxin will improve its application in the treatment of primary hyperhidrosis.

BTX is the deadliest bacterial toxin known, with a median lethal dose of 0.1-1 ng/kg.[21,22] BTXs are produced by several spore-forming, rod-shaped, anaerobic, neurotoxigenic bacterial species from the *Clostridium* genus.[23,24] There are 7 BTX serotypes (BTX/A-G).[23] BTX/A, B, E, and F are toxic to humans, and BTX/C and D are toxic to animals.[23,25] BTX blocks cholinergic innervation at the neuromuscular junctions of smooth and striated muscles as well as autonomic innervation of the sweat, salivary, and tear exocrine glands.[25-28] BTX prevents the docking and exocytosis of acetylcholine from presynaptic vesicles at neurosecretory and neuromuscular junctions by cleaving the soluble *N*-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs).[29-32]

The damage caused by BTXs is reversible.[33] The duration of clinical efficacy associated with BTX treatment depends on the functional return of conduction at the neurosecretory and neuromuscular junctions. This is mediated by nerve sprouting and regeneration of synaptic junctions.[33-37] BTX treatment blocks vesicular acetylcholine release for 3 days. Thereafter, transitory sprouting nerves from the presynaptic nerve endings of the paralyzed endplate begin to appear, the number of acetylcholine receptors increases, and new synaptic junctions form.[37-41] After 7 days, 20% of previous neuronal activity is restored.[42] The development of nerve sprouts correlates with the synaptic activity level at the neural endplates. Eventually, fully functional synapses are restored within 3 to 6 months, and the temporary neuronal sprouts regress.[33,39] Although BTX can effectively inhibit skeletal muscular contractions for approximately 3 to 4 months,[43,44] inhibition of sweating (autonomic cholinergic nerve terminals) can last for 6 to 8 months.[18,45,46] It has been suggested that BTX reduces sweat gland responsiveness to acetylcholine in addition to inhibiting neurotransmitter release from cholinergic nerves.[47] Moreover, repeated BTX injections may increase the duration of symptomatic relief.[48,49] A retrospective study showed a median 3-month increase in the duration of efficacy of BTX/A in patients treated with an average of 4 sessions of axillary injections.[18,49] BTX injections for PHH treatment need to be repeated 2 to 3 times per year for a continuous therapeutic effect.

COMMERCIAL BTX PRODUCTS AVAILABLE IN THE UNITED STATES

Currently, 4 BTX/A and 1 BTX/B preparations are approved by the US Food and Drug Administration (FDA) for various therapeutic and cosmetic purposes[50,51]: onabotulinumtoxinA (Botox; Allergan, Irvine, CA),[52] abobotulinumtoxinA (Dysport; Galderma Laboratories, Fort Worth, TX),[53] incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Greensboro, NC),[54] prabotulinumtoxinA (Jeuveau; Evolus, Inc, Santa Barbara, CA),[55,56] and rimabotulinumtoxinB (Myobloc; Solstice Neurosciences, Louisville, KY).[57] OnabotulinumtoxinA is the only FDA-approved BTX formulation for the "treatment of severe axillary PHH that is inadequately managed by topical agents in adult patients (p 1. Ref 52)."[52,58]

Different BTX serotypes are obtained from specific bacterial strains: Hall strain is used for BTX/A, and Bean strain is used for BTX/B (Table I).[59] The 5 BTX preparations have different molecular weights due to varied neurotoxin-associated proteins used in drug production.[26,60,61]

All commercial BTX products contain additional components.[62] Excipients such as sucrose, sodium chloride, or lactose are added to maintain protein conformation,[63] and human serum albumin is added to minimize neurotoxin waste during lyophilization and to prevent protein aggregation on vial walls.[63,64]

After biosynthesis, the neurotoxins are precipitated and purified.[28,65,66] Thereafter, either freeze drying (for abobotulinumtoxinA and incobotulinumtoxinA) or vacuum drying (for onabotulinumtoxinA and prabotulinumtoxinA) is

Abbreviations used:

BTX: botulinum toxin
FDA: US Food and Drug Administration
HH: hyperhidrosis
PHH: primary hyperhidrosis

performed to produce a powdered BTX/A product.[63] BTX/B is supplied as a liquid with a pH of 5.6.

The shelf life of abobotulinumtoxinA is 24 months, and those of onabotulinumtoxinA and rimabotulinumtoxinB are 36 months when stored at 4°C to 8°C. IncobotulinumtoxinA is stable for at least 48 months at room temperature.[26,67]

FDA approval guidelines recommend BTX/A reconstitution in nonpreserved saline.[52] However, it has been shown (in 60% of cases) that BTX-A preparations with nonpreserved saline are statistically ($P < .0001$) more painful than those with preserved saline.[68,69] Thus, benzyl alcohol–containing saline is often used for its anesthetic effects.[69-71] The use of lidocaine as the diluent agent has shown similar efficacy in pain reduction.[72,73] After reconstitution, a slightly acidic BTX/A solution is obtained,[26,62,74] which can be safely used for 4 weeks when frozen or refrigerated at -20°C or 4°C, respectively.[75-80] One BTX vial can be used for multiple patients.[75]

The enzyme units of the different BTX preparations are not interchangeable.[26,28,71,81-90] The reported dose conversion factors applied are specified in Table II. Additionally, every neurotoxin displays a nonparallel dose-response curve.[91]

BTX/B is equipotent to BTX/A formulations; the anhidrotic effects and satisfaction rates are similar.[87,88,92] RimabotulinumtoxinB has a quicker onset (3-5 days) but shorter efficacy period (9-16 weeks) compared to BTX/A.[93] Additionally, the low pH (5.6) of the solution causes pain at the injection site.[94,95] Treatment with rimabotulinumtoxinB has also been correlated with more adverse events (ie, dry mouth, headaches, corneal irritation, accommodation difficulties, and changes in sensory and motor functions of the hand) than treatment with onabotulinumtoxinA.[96-99] RimabotulinumtoxinB shows no cross reactivity with BTX/A formulations[100]; thus, it is useful in patients who do not respond to, or have developed antibodies against, BTX/A.[101]

CURRENT THERAPEUTIC APPROACH FOR BTX IN HH

BTX should be administered via intradermal injections at the dermal-subcutaneous junction to target the sweat glands. The injection depth depends on the injection site (the dermal-subcutaneous junction of the axilla can lie 2 mm deep, whereas at the sole it can reach 4.5 mm), and the amount and concentration of the toxin.[102] Injections administered too deeply may cause unwanted denervation.[58] A hypodermic needle, oriented at 30° to 45° to the skin surface with the needle's bevel facing up, is used to prevent liquid leakage (Fig 1).[103] It is often difficult to precisely detect the HH area.[104-106] For example, the axillary HH area does not always overlap with the hair-bearing region, or the plantar HH zone may extend to the sides and dorsal aspects of the foot.[104,105] The Minor (starch-iodine) test or Ponceau Red staining (for iodine-sensitive patients) can be used to precisely detect the HH area to accurately target the drug.[58] The number of injections depends on the treatment area size and the severity of PHH.[107] Injection volumes of 0.1 to 0.2 ml are commonly used.[107,108] Higher volumes may diffuse to unwanted areas or extrude from the injection site.[107] The optimal result is achieved when confluent overlapping anhidrotic halos are created.[109]

There are no confirmed dilution protocols for BTX preparations for PHH treatment. Lower concentrations are assumed to diffuse better in the treated area.[89] OnabotulinumtoxinA can be prepared using 1 to 10 ml of diluent, although most clinicians use 2 to 5 ml.[110] AbobotulinumtoxinA is commonly diluted with 2.5 to 5 ml of diluent, although the dilution volumes may vary between 1.25 and 10 ml.[110,111]

OnabotulinumtoxinA is the only FDA-approved BTX formulation for the management of adult patients with severe axillary PHH once topical agents have failed.[52,58] It has been determined to be a safe, effective, and long-lasting treatment option.[14,15,90,112-115] Studies have shown that the off-label use of onabotulinumtoxinA is also effective for other HH regions such as the palms,[116-118] soles,[105] trunk,[119] and craniofacial regions.[120] Furthermore, reports have indicated that PHH can successfully be treated with off-label administration of other BTX formulations, such as abobotulinumtoxinA,[116] rimabotulinumtoxinB,[94,95] and incobotulinumtoxinA (Table III).[121,122]

During axillary PHH treatment, each axilla is treated with 50 U (2.5 ng) of onabotulinumtoxinA. Injection volumes of 0.1 to 0.2 mL are uniformly distributed into 10 to 15 sites spaced 1 to 2 cm apart. When the PHH surface area is larger, up to 60 to 100 U per axilla can be administered.[58,106] No consensus exists regarding the dosing of other BTX/A preparations.[58] RimabotulinumtoxinB injections of 2500 to 5000 U per axilla also result in focal anhidrosis.[96]

Table I. Properties of commercially available BTX/A and BTX/B products

Properties	OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	PrabotulinumtoxinA	RimabotulinumtoxinB
Brand name, manufacturer	Botox, Allergan	Dysport, Galderma Laboratories	Xeomin, Merz Pharmaceuticals	Jeuveau, Evolus	Myobloc, Solstice Neurosciences
Botulinum toxin serotype	A	A	A	A	B
Clostridium botulinum bacterial strain	Hall	Hall	Hall	Hall	Bean
Complex molecular weight, kDa	900	500-700	150	900	700
Pharmaceutical form	Vacuum-dried powder	Freeze-dried, lyophilized powder	Freeze-dried, lyophilized powder	Vacuum-dried powder	Nonlyophilized solution
Manufactured dosage strength, units/vial	50, 100, and 200	300 and 500	50, 100, and 200	100	2500, 5000, and 10 000
Neurotoxin protein load	0.73 ng/100 U	0.65 ng/100 U	0.44 ng/100 U	—	5000 BTX/B units/1 ml
Excipients content	Per 100 U: • 0.5 mg HSA • 0.9 mg sodium chloride	Per vial: • 2.5 mg lactose • 0.125 mg HSA	Per vial: • 4.7 mg sucrose • 1 mg HSA	Per 100 U: • 0.5 mg HSA • 0.9 mg sodium chloride	Per vial: • 0.05% HSA • 0.1 mol/L NaCl • 0.01 mol/L sodium succinate
Specific biological potency, U/ng	137	154	227	Unknown	Unknown
Protein target	SNAP-25	SNAP-25	SNAP-25	SNAP-25	VAMP/synaptobrevin
Approximate pH	7	7	6	—	5.6
Shelf life, months	36	24	48	36	36

BTX, Botulinum toxin; *HSA,* human serum albumin; *SNAP-25*, synaptosomal-associated protein-25; *VAMP*, vesicle-associated membrane protein.

Table II. Botulinum toxin A formulation: Conversion factors

OnabotulinumtoxinA	AbobotulinumtoxinA	IncobotulinumtoxinA	RimabotulinumtoxinB
1	2[84]		
	2.5-3[71,82,85,89]		
	3-5[85,90]		
		0.5-0.75[84]	
		1[26,71,86]	
			20[87,88]
			40[28]

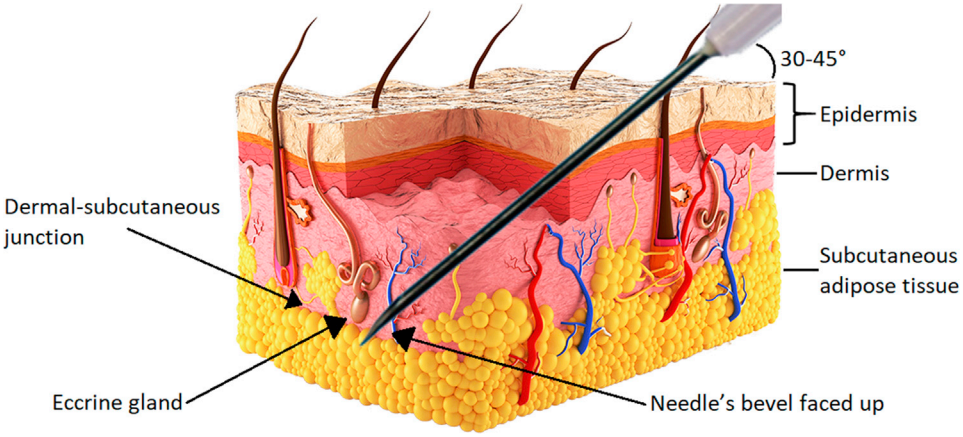

Fig 1. The proper technique for injecting botulinum toxin for the treatment of primary hyperhidrosis.

Adverse effects observed in patients treated with onabotulinumtoxinA and abobotulinumtoxinA include pain, hematomas, bruises, headaches, muscle soreness, mild local pruritus, and urticaria, as well as compensatory sweating in 5% of patients.[123-125]

After BTX/A treatment, the anhidrotic effect is commonly observed within 7 to 10 days and lasts for 6 to 10 months.[110,113] Patient satisfaction rates with axillary BTX injections range from 66% to 100%.[46]

Higher doses of BTX are required to treat palmar and plantar PHH than axillary PHH.[105] OnabotulinumtoxinA dosing of 75 to 100 U per hand is commonly used. Injection volumes of 0.05 to 0.1 mL (1.7-3.3 U) are uniformly distributed into 5 to 50 sites spaced 1 to 1.5 cm apart because the palms and soles are less susceptible to diffusion.[107,115,126] The digits usually require 2 or 3 injections each.[105,118] Pain is a major factor in palmar and plantar PHH treated with injectable BTX.[105] Methods used to control the pain during administration include cryoanalgesia,[127-129] iontophoretic administration of 2% lidocaine,[130] a needle-free pressure unit to administer local anesthesia,[131] microneedles,[132] repeated needle replacement,[126] vibration anesthesia,[58,133] topical anesthetics, intravenous regional anesthesia,[134,135] sedation, and nerve blocks (median, ulnar, and radial nerves for the palms[126,136-138]; sural and posterior tibial nerves for the soles).[126] Palmar PHH treatment may cause hand weakness, which typically lasts for 24 to 72 hours but may persist for up to 2 weeks.[118,139,140] Grip strength is commonly retained (although the thenar eminence can be affected), whereas pinch strength is usually weakened.[126,141] Other adverse effects include paresthesias, bruises, and hematomas at the injection sites.[126,139,141] BTX palmar injections reduce focal sweating by 80% to 90%,[110] and the anhidrotic effect lasts for 3 to 12 months.[142]

Plantar PHH typically requires 100 to 200 U of onabotulinumtoxinA per foot,[105] which is injected into 15 to 50 sites spaced 1 to 2 cm apart.[143] Plantar injections are painful, necessitating the use of pain relief measures, as previously described. Additional adverse effects may include hematomas and walking difficulties that last for several hours, particularly when a nerve block is performed before the procedure.[126,141] Subsequently, the anhidrotic effect is commonly observed within 7 to 10 days, and last for 3 to 6 months. Efficacy of plantar BTX treatment is usually lower than that of the palms or axillae[126]; 20%

Table III. Overview of botulinum toxin treatment for specific focal hyperhidrosis

	Axillary	Palmar	Plantar	Craniofacial
Dosing	• 50 U onabotulinumtoxinA per axilla; a larger surface area may require 60-100 U per axilla • 2500-5000 U rimabotulinumtoxinB	• 75-100 U onabotulinumtoxinA per palm	• 100-200 U onabotulinumtoxinA per foot	• OnabotulinumtoxinA: 50-100 U for the forehead and frontal hairline, 200 U for the forehead and scalp boundaries, 300 U for the forehead and the entire scalp • Reconstitution of onabotulinumtoxinA to a high concentration (50 U/ml) to limit diffusion
Distribution of injections	• 0.1- to 0.2-ml aliquots are injected into 10 to 15 sites, spaced 1 to 2 cm apart	• 0.05- to 0.1-ml aliquots are injected into 5 to 50 sites, spaced 1 to 1.5 cm apart • Each digit requires 2 or 3 injections	• Aliquots are injected into 15 to 50 sites, spaced 1 to 2 cm apart	• 2- to 3-U aliquots are injected into 5 to 30 sites, spaced 1 to 2 cm apart
Adverse effects	• Pain, hematomas, ecchymosis, headaches, muscle soreness, pruritis, urticaria, compensatory sweating	• Pain may be severe, necessitating methods of pain reduction in most cases • Hand weakness, paresthesias, ecchymosis, hematomas	• Pain may be severe, necessitating methods of pain reduction in most cases • Hematomas, walking difficulties	• Frontalis muscle weakness, brow asymmetry
Anhidrotic effect	• Focal anhidrosis begins within 7 to 10 days and lasts for 6 to 10 months	• Focal anhidrotic effect lasts for 3 to 12 months	• Focal anhidrosis begins within 7 to 10 days and lasts for 6 to 10 months	• Focal anhidrotic effect lasts for an average of 4.5 months

of patients report lack of any beneficial effects after treatment.[143]

Craniofacial PHH commonly involves the forehead; the scalp may or may not be affected.[105,144] The following amounts of onabotulinumtoxinA are used depending on the treatment area: 50 to 100 U for the forehead and frontal hairline, 200 U for the forehead and scalp boundaries, and 300 U for the forehead and entire scalp.[145] OnabotulinumtoxinA is reconstituted to a high concentration (50 U/mL) to limit diffusion. 2 to 3 U are injected into 5 to 30 sites, 1 to 2 cm apart, with avoidance of the inferior forehead to minimize the risk of brow ptosis.[144] Adverse effects include functional (ie, frontalis muscle weakness) and cosmetic (ie, brow asymmetry) defects. Brow asymmetry is observed in 17% of patients and may persist for 1 to 12 months.[144,146] After BTX/A treatment, the anhidrotic effect lasts for an average of 4.5 months.[146]

BTX therapeutic preparations are safe, well tolerated, and display minimal adverse effects.[112] Some patients may develop neutralizing antibodies to the BTX 150-kDa core, which can block its pharmacologic activity.[101] The prevalence of patients developing neutralizing antibodies against BTX varies between 0.3% and 6%.[147,148] Naumann et al[149] showed that only 0.5% of patients (4 of 871) who received BTX for axillary PHH developed neutralizing antibodies, while still maintaining clinical responsiveness to BTX injections during treatment. Studies suggest that the immune response is dose dependent and correlates with frequency of injections.[100,150-152] BTX/B medications are more immunogenic than BTX/A formulations.[151]

BTX should not be used in pregnant or breastfeeding women, patients with hypersensitivity to any of the formulation components, or when the injection site is infected.[153] Furthermore, BTX injections should not be administered to patients with secondary HH, patients who have already undergone surgical removal of sweat glands, or those with significant blood-clotting disorders. Before BTX administration, patients are advised to avoid aspirin, nonsteroidal anti-inflammatory medications, and vitamin E to minimize the risk of bruising or bleeding. Additionally, patients with pre-existing amyotrophic lateral sclerosis, peripheral neuropathy, neuromuscular junctional disorders (ie, myasthenia gravis or Lambert-Eaton myasthenic syndrome), contraindications to anticholinergic drugs, or coadministration of drugs that can modify the metabolism of BTX (ie, aminoglycosides, calcium channel antagonists, cholinesterase inhibitors, or other neuromuscular blocking agents), should be monitored carefully after BTX administration.[126,141]

We thank the International Hyperhidrosis Society (SweatHelp.org) for granting us permission to use their instructional videos (https://www.sweathelp.org/education-and-resources/online-learning.html), which provide medical professionals practical instruction in the area of botulinum toxin injections for the treatment of hyperhidrosis.

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