Chapter 3
Types of Toxins in Commercial Use, Their Similarities and Differences

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Abstract The clinical application of botulinum toxin currently spans across several medical specialties as new indications continue to be investigated and new products continue to be developed. This chapter discusses similarities and differences among the currently commercially available botulinum toxin products. The mechanism of action of both serotypes, BoNT-A and BoNT-B, is introduced. The clinical indications for each available botulinum toxin product including onabotulinumtoxinA, abobotulinumtoxinA, incobotulinumtoxinA, and rimabotulinumtoxinB are discussed along with potential adverse effects and the potential of developing immunogenicity. Finally, future products such as daxibotulinumtoxinA and praxibotulinumtoxinA with potential for further clinical indications are touched upon.

Keywords OnabotulinumtoxinA · AbobotulinumtoxinA · IncobotulinumtoxinA · RimabotulinumtoxinB · DaxibotulinumtoxinA · PraxibotulinumtoxinA

Introduction

Botulinum toxins (BoNTs) are currently widely used in clinical practice, and their clinical application is ever expanding. There are seven different serotypes of BoNTs; however, only types A and B are available for clinical applications [1, 2]. There is interest to use other serotypes or modifications of these serotypes in order to change the duration of action of the toxin. In this review, the general aspect of BoNTs will be discussed, and then each available toxin will be discussed in detail in regard to their clinical and therapeutic applications. This article will not delve into the cosmetic application of the toxins.

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BoNT Mechanism of Action and Their Diffusion

The BoNT-A and BoNT-B serotypes are neuromuscular blocking agents, and by blocking the release of acetylcholine at the neuromuscular junction (NMJ), they cause dampening or elimination of muscle overactivity [2–6]. The peak neuromuscular blocking clinical effect of the toxin occurs between 2 and 6 days after administration, and it can last for several months [7]. 7BoNT-A and BoNT-B inhibit the release of acetylcholine into the NMJ without interference with acetylcholine synthesis, uptake, or storage or the propagation of action potentials [6].

In nature, both BoNT-A and BoNT-B serotypes are synthesized as macromolecular protein complexes [6]. These protein complexes are referred to as progenitor toxins and consist of nontoxic accessory proteins (NAP) covalently bonded to the 150 kD neurotoxin [1, 3]. The BoNT-A progenitor toxins vary in molecular weight (300–900 kD) depending on the composition of NAPs and manufacturing process [1, 2, 6]. BoNT-B serotype only forms a 500 kD complex.4 The NAPs can be hemagglutinins (HA17, HA19, HA33, and HA52) or nontoxic–non-HA protein [1, 2, 6]. The NAPs are believed to be chaperones and serve to stabilize and protect the core 150 kD neurotoxin protein from degradation in harsh environments such as acidic PH of the stomach, but the therapeutic function of NAPs is unknown. However, it is clear that the 150 kD neurotoxin must dissociate from NAPs in order to exert pharmacologic effects [1, 2, 6]. The 150 kD core protein must be nicked to a dichain of heavy (100 kD) and light chains (50 kD) to be fully activated [1, 2, 6]. The light and heavy chains are connected through a disulfide bridge and noncovalent bonds.

BoNT formulations contain a variable percentage of “unnicked” toxin (which contributes to the overall protein load).

Upon blocking of the NMJ by BoNT, the binding sites for the toxin diminish, and a booster injection while the muscle is already denervated is not pharmacologically rational. This is due to significant reduction of the toxin uptake into the chemodenervated muscle.

The mechanism of action of BoNT can be described as a four-step process (Fig. 3.1): [1, 8] (1) toxin binding and capture, (2) endosome formation and internalization, (3) active transport of toxin from endosome into cytosol, and (4) cleavage of the acetylcholine neuroexocytosis apparatus (i.e., soluble N-ethylmaleimide-sensitive factor attachment protein receptors [SNAREs]).

Toxin binding and capture involves an array of membrane receptors at the presynaptic motor neuron. Both BoNT-A and BoNT-B enter the neuron by a dual-capture mechanism involving gangliosides (complex glycolipids localized on the outer membrane) and membrane receptors [1, 8]. The BoNT-A binds to the membrane receptor synaptic vesicle protein 2, whereas BoNT-B binds to synaptotagmins I and II [1, 3–6]. The heavy and light chains of the nicked toxin are essential for the toxin activity and each have specific roles. The heavy chain is composed of two domains, HC and HN [1, 3–6]. The HC domain is essential for binding of toxin to the outer membrane receptors and capturing it inside a formed endosome. Once the toxin is inside an endosome, the disulfide bridge is broken, and the catalytic light

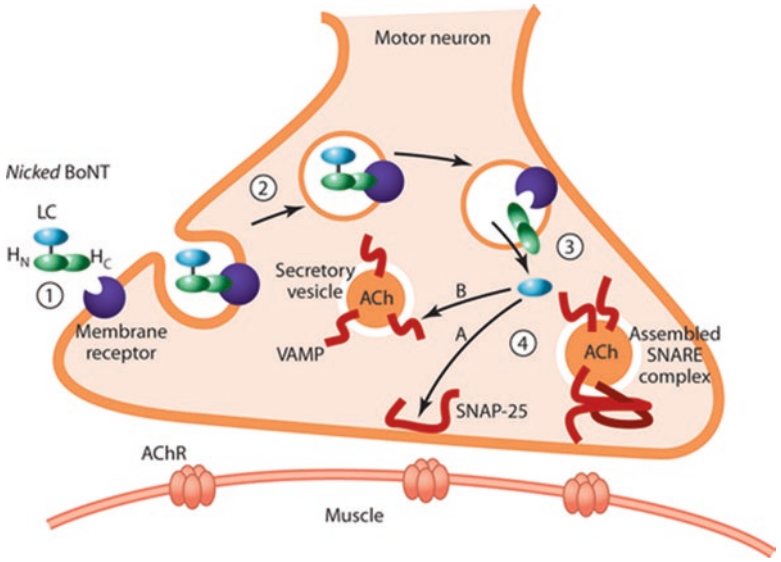

Fig. 3.1 Mechanism of action for botulinum toxins A and B.1–4, 6 Steps 1 and 2: The nicked (cleaved) botulinum neurotoxin (BoNT) is captured at neuronal membrane. Once captured, BoNT receptor binding is irreversible. The nicked BoNT is composed of a light chain (LC) and a heavy chain, which is further composed of two domains (HC and HN). The HC is essential for binding of toxin. On capture and endosome formation, the nicked BoNT disulfide bridge is broken, and the catalytic LC separates from the heavy chain. Step 3: The catalytic LC is released into the cytosol. Step 4: The LC begins to deactivate soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs). There are different components of the SNARE apparatus, such as synaptosomal-associated protein 25 kD (SNAP-25) and vesicle-associated membrane protein (VAMP, also known as synaptobrevin). One LC will cleave existing and newly synthesized SNAREs, one after another, until the supply is depleted. Botulinum toxin type A catalytically cleaves SNAP-25, which is anchored to the inner layer axonal membrane, and BoNT-B cleaves VAMP, which is embedded within the acetylcholine (ACh) vesicle membrane. Cleavage (deactivation) of SNAP-25 or VAMP results in inhibition of ACh exocytosis, release, and neuromuscular denervation. AChR ACh receptor. (From Chen and Dashtipour 2013 – with reproduced with permission from publisher Wiley and Sons)

chain separates from the heavy chain [1, 3–6]. The catalytic light chain is released from the endosome and enters the axonal cytosol. The heavy chain HN domain is involved in the active transport of light chains from inside the endosome into the axonal cytosolic milieu [1, 3–6].

Upon release of light chains into the cytosol, they begin to deactivate SNARE proteins [1, 3–6]. Within an axon terminal, the light chain cleaves existing and newly synthesized SNAREs, one after another, until the supply is depleted. There are different components of the SNARE apparatus, such as synaptosomal-associated protein 25 kD (SNAP-25) and vesicle-associated membrane protein (VAMP, also known as synaptobrevin) [1, 3–6]. The BoNT-A serotype catalytically cleaves SNAP-25 and BoNT-B cleaves VAMP [1, 3–6]. The SNARE proteins are essential for acetylcholine vesicle docking, exocytosis, and neurotransmitter release [1, 3–6].

The light chain is structurally resistant to inactivation by intracellular protein degradation systems (e.g., ubiquitin-proteasome system), and the slow intracellular removal results in a persistence of pharmacodynamic effects at the NMJ [9]. It is important to note that although the NMJ loses functionality, the motor neuron, NMJ, and muscle fiber remain viable and regain function over time. The disabled axon terminal produces collateral sprouts, which induces the formation of new NMJs and motor endplates with the affected muscle fiber [1, 4]. As the original NMJ recovers, the collateral sprouts eventually retreat and are eliminated. On recovery of the NMJ acetylcholine activity, muscle (hyper) activity is resumed.

The mechanism of action of BoNT at myoepithelial cells (salivary and sweat glands) is not well known. Myoepithelial cells are specialized smooth muscle structures, and contraction is mediated by acetylcholine. Presumably, the mechanism is analogous to what occurs at the NMJ, but it seems that the duration of effect is more prolonged in intraglandular applications [1, 4]. In addition, BoNT-B appears to have a greater effect than BoNT-A in intraglandular applications [1, 4]. This may be due to differences in BoNT kinetics or binding affinity at the neuromyoepithelial effector junction.

BoNT is also known to possess antinociceptive effects, which may be mediated by inhibition of substance P and calcitonin gene-related peptide release [1, 4].

Despite having the same mechanism of action, each BoNT has distinct biologic properties with its own characteristic features. Each toxin has its own unique molecular structure, formulation, potency, and pharmacokinetics. Each toxin exerts its effect at the site of injection and spreads. The diffusion and migration of the BoNT is responsible for its local, distal, and systemic side effects [1, 2].

Multiple studies revealed that central effects can also occur as a consequence of botulinum toxin peripheral injections, possibly due to the retrograde axonal transport to antinociceptive nuclei within the central nervous system [10]. This presumption is based on observations of instances of clinical improvement despite minimal weakness following botulinum toxin injections as well as previous animal and human studies exploring central effects of botulinum toxin [10]. This central effect is believed to occur through retrograde axonal transport of toxin into the CNS or indirect modulation of cortical regions and/or cerebellum. One of the earlier animal studies looking at retrograde transport of botulinum toxin found that 48 hours after injection of radiolabeled botulinum toxin A into the gastrocnemius muscles of cats, there was increased radioactivity in the ventral roots and spinal cord ipsilateral to the side of injection [11]. In a more recent animal study, botulinum toxin A was injected into facial motor neurons of cats, and 3 days later the ipsilateral facial nucleus demonstrated significant amounts of botulinum toxin with Western blot analysis [12]. This evidence has been translated to human studies as well, and one study revealed the reduction of quadriceps H reflex in individuals treated with botulinum toxin to the soleus muscle [13]. This phenomenon resulted from presumed retrograde transport of botulinum toxin exerting effects on Renshaw cells [13]. In addition to the available evidence of retrograde transport resulting in central effects of botulinum toxin, there are several functional MRI studies demonstrating changes in cortical areas and cerebellum following peripheral Botox injection. The proposed

central effects of BoNTs raise the possibility of an additional therapeutic impact rather than being attributable to causing additional side effects. However, there is still much to be explored in regard to discovering new applications and therapeutic indications [10].

BoNT for Clinical Application

At the time of this article, only four distinct BoNTs were commercially available for clinical applications (Fig. 3.2). In 2009, the FDA released the updated version of the safety warning on BoNTs with emphasis on the lack of interchangeability among toxins due to difference in units. Another concern of this safety report was about the

Fig. 3.2 Currently available botulinum toxins in the USA and Europe. (From Chen and Dashtipour 2013, reproduced with permission from Publisher (Wiley and Sons))

spread of the toxin to other body parts and the possibility of unwanted effects as extreme as respiratory failure and death [1, 2].

In recent years, the clinical application of BoNTs has largely expanded beyond neurology and dermatology to numerous subspecialties such as ophthalmology, physical medicine and rehabilitation, dentistry, gynecology, gastroenterology, and urology [1, 2].

The current four formulations of BoNTs do not have the same FDA-approved clinical profile; however, their clinical utility expands beyond their FDA indications. Tables 3.1 and 3.2 summarize the clinical applications of BoNTs and recommended dosing.

Clinicians performing injections should refer to manufacturer suggested dosages for each indication. Factors such as size of muscle being injected, patients' previous response to injections, and type of tissue being targeted need to be taken into consideration as well when deciding on dosage. Studies have been conducted in an effort to establish the dose equivalency among toxin brands. The ratio of onabotulinumtoxinA to incobotulinumtoxinA is reported to be 1:1 [4, 14]. Two studies exploring dose equivalency between onabotulinumtoxinA and abobotulinumtoxinA in the treatment of cervical dystonia (CD) found that ratios of 1:1.7 and 1:2.5 were similar in terms of efficacy and adverse events. However, at a ratio of 1:3, onabotulinumtoxinA was determined to be less efficacious [15, 16].Overall, the conversion ratio between onabotulinumtoxinA and abobotulinumtoxinA of 1:2.5–1:3 is most commonly reported [17]. Conversion ratio for onabotulinumtoxinA/rimabotulinumtoxinB ranges from 1:30 to 1:50. RimabotulinumtoxinB has been reported to have more frequent dry mouth as a side effect and likely has more glandular activity which is also a consideration when deciding on dosing [4]. It is worth noting once again that these conversion ratios are not standardized or globally accepted and deciding on dosage should be based on patients, condition, site of injection, and the past exposure and response to the BoNT.

The conditions for optimal storage are different for incoBoNT-A and other botulinum toxins. OnaBoNT-A, aboBoNT-A, and rimaBoNT-B need to be stored at 2 °C to 8 °C. IncobotulinumtoxinA unopened vials can be stored frozen at −20 °C to −10 °C, refrigerated at 2 °C to 8 °C, or kept at room temperature at 20 °C to 25 °C. RimabotulinumtoxinB is in liquid form and ready to use for injection; however, all other BoNTs need to be reconstituted prior to administration. Only preservative-free normal saline is recommended for reconstitution [1, 2].

Table 3.3 outlines similarities and differences in excipients, packaging, and storage of the four botulinum toxin brands according to manufacturer labeling.

Botulinum toxins have the potential to develop immunogenicity. The concern regarding immunogenicity is important, especially with long-term use and multiple clinical applications of BoNTs.

Multiple factors play a role in inducing immunogenicity, such as the manufacturing process, the antigenic protein load, the presence of accessory proteins, the overall toxin dose, frequency of injections, and prior exposure to BoNTs [1, 2]. Immunogenicity can be primary when there is a lack of response to BoNTs in a toxin-naïve patient, or it can occur as a secondary nonresponsiveness in patients

Table 3.1 Recommended doses of botulinum toxin products for the FDA-approved therapeutic indications

Agent	Indication	Dose
OnabotulinumtoxinA	Axillary hyperhidrosis	50 U per axilla
	Blepharospasm	Blepharospasm: 1.25–2.5 U into the muscles of the upper and lower eyelid (three injection sites) per affected eye
	Strabismus	1.25–5 U into each of three sites per affected eye; dose based on severity of deviation. Total dose should not exceed 25 U per single treatment
	Cervical dystonia	15–150 U per affected muscle based on patient's head/neck/shoulder position, pain localization, muscle hypertrophy; lower dose is recommended for toxin-naïve patients; repeat treatment no more frequently than every 12 weeks Mean dose 236 units, range of 198 units to 300 units
	Chronic migraine prophylaxis	Total dose 155 U divided among seven muscles (total of 31 sites) in head/neck muscles; repeat treatment every 12 weeks
	Upper limb spasticity in adults Upper limb spasticity in pediatrics aged 2–17 years	75 units to 400 units divided among the selected muscles 3–6 units/kg divided among affected muscles
	Lower limb spasticity in adults Lower limb spasticity in pediatrics aged 2–17 years excluding spasticity caused by cerebral palsy	The recommended dose for lower limb spasticity is 300–400 U 4–8 units/kg divided among affected muscles
	Neurogenic detrusor	Total dose of 200 U divided across 30 injection sites in the detrusor muscle (~6.7 U/site); repeat treatment every 42–48 weeks
	Overactive bladder	The recommend dose is 100 U for overactive bladder and is the maximum recommended dose
AbobotulinumtoxinA	Cervical dystonia	Total dose of 500 U divided among affected muscles; repeat treatment every 12–16 weeks; titrate dose in 250 U increments to desired clinical response up to 1000 units
	Upper limb spasticity in adults Upper limb spasticity in pediatrics aged 2 and older excluding spasticity caused by cerebral palsy	500 and 1000 units were divided among selected muscles in the pivotal clinical trial 8–16 units/kg divided among affected muscles

(continued)

Table 3.1 (continued)

Agent	Indication	Dose
	Lower limb spasticity in adults Lower limb spasticity in pediatrics	1000–1500 units divided among affected muscles 10–15 units/kg for unilateral lower limb or 20–30 units/kg for bilateral lower limb injections Maximum of 1000 units
IncobotulinumtoxinA	Blepharospasm	1.25–2.5 U per injection site. For patients previously treated with ONA, INCO dose is the same as previous dose of ONA
	Cervical dystonia	120–240 U divided among affected muscles; repeat treatment no more frequently than every 12 weeks
	Upper limb spasticity	Up to 400 units; repeat no more frequently than every 12 weeks
	Sialorrhea	Recommended total dose is 100 units per treatment consisting of 30 units per parotid gland and 20 units per submandibular gland, no sooner than every 16 weeks
RimabotulinumtoxinB	Cervical dystonia Sialorrhea	Initial recommended dose 2500–5000 U; may be titrated up to 10,000 U based on patient's response; repeat treatment every 12–16 weeks 500 units to 1500 units per parotid gland and 250 units per submandibular gland. No more frequent than every 12 weeks

who have previously responded, but the development of neutralizing antibodies has caused BoNT to be less effective or ineffective. It seems that antigenic protein load is correlated to the protein content of the core toxin (150 kD).

The most recent clinical studies showed almost the same rate of immunogenicity for both toxins: 1.2% for onaBoNT-A and 1.1% for incoBoNT-A [1, 2]. Major differences in immunogenicity among the type A toxin brands is yet to be determined given differences in study populations, assay sensitivity in looking for the presence of neutralizing antibodies, and dose equivalency [18–20]. Serotype B toxin (rimabotulinumtoxinB) appears to be more immunogenic than serotype A with frequency of development of neutralizing antibodies as high as 10–44% [18]. However, the importance of this high percentage of developing antibody with serotype B is not known, and the same rate (10–44%) of clinical unresponsiveness has not been reported. Currently, the standard of care of injecting patients with a frequency of not less than every 3 months and avoiding high doses of toxin in each single injection controls immunogenicity at significantly low levels when compared with older reports. However, in patients with urologic disorders, secondary unresponsiveness may occur due to the fact that the uroepithelium is more sensitive to antigens (e.g., bacterial antigens). Nontoxic accessory proteins (NAPs) do not play a role in the mechanism of action of BoNTs, but the NAPs (e.g., hemagglutinating and non-hemagglutinating proteins) act as adjuvants for the development of neutralizing

Table 3.2 Clinical application of the botulinum toxins

Achalasia	Anal fissure	Benign prostatic hyperplasia	Blepharospasm[a]	Chronic anal fissures	Cervical dystonia[a]	Esophageal dysmotility	Facial esthetics[a]
Hemifacial spasms	Hyperhidrosis[a]	Limb dystonia	Lingual dystonia	Lumbosacral pain and spasms	Migraine[a]	Myofascial pain	Nystagmus
Oromandibular dystonia	Overactive bladder[a]	Palatal myoclonus	Pain syndromes	Pelvic floor spasm	Sialorrhea[a]	Spasticity of upper and lower limb[a]	Spasmodic dysphonia
Strabismus[a]	Stuttering	Temporomandibular joint disorders	Tendinopathies	Tics	Tremors	Vaginismus	Writer's cramp

[a]A current FDA-approved indication

Table 3.3 Summary of botulinum toxin formulations

Toxin name	Toxin serotype	Packaging (units/vial)	Preparation	Excipients	Storage	Storage after reconstitution
OnabotulinumtoxinA (Botox)	Serotype A	100, 200	Vacuum dried powder	HSA, NaCl	Refrigerate 2–8 degrees Celsius	Refrigerate 2–8 degrees Celsius. Use within 24 hours
IncobotulinumtoxinA (Xeomin)	Serotype A	50,100, 200	Lyophilized powder	HSA, sucrose	Frozen, refrigerated, or stored at room temperature	Refrigerate 2–8 degrees Celsius. Use within 24 hours
AbobotulinumtoxinA (Dysport)	Serotype A	300, 500	Lyophilized powder	HSA, lactose	Refrigerate 2–8 degrees Celsius	Refrigerate 2–8 degrees Celsius. Use within 4 hours
RimabotulinumtoxinB (Myobloc)	Serotype B	2500, 5000, 10000	Sterile solution	HSA, NaCl, sodium succinate	Refrigerate 2–8 degrees Celsius	No reconstitution necessary. If solution is further diluted, use within 4 hours

antibodies. In theory, reducing the NAP load may minimize immunoresistance, but this remains an unresolved issue among product comparisons.

A well-known adverse effect involved with therapeutic applications of botulinum toxin involves contiguous spread of toxin to adjacent tissues. This has potential to cause undesirable effects by impacting tissues that were not originally being targeted, for example, eyelid ptosis resulting from the treatment of blepharospasm or dysphagia due to pharyngeal muscle weakness when treating CD. Differences in contiguous spread among the toxin brands have been studied; however, results of these studies have not found significant differences. Variance in contiguous spread among toxin brands is difficult to determine because spread is likely dependent on a variety of factors including injection technique, dosage used, type of target site, level of muscle hyperactivity, postinjection massage, and location of injection within a muscle. Injection techniques that may affect spread of toxin include volume of solution used, injection pressure, and needle size [21, 22].

BoNT Type A

There are currently three commercially available BoNT-As in the United States, onabotulinumtoxinA (onaBoNT-A), abobotulinumtoxinA (aboBoNT-A), and incobotulinumtoxinA (incoBoNT-A). All BoNT-As work by deactivating SNARE proteins by catalytically cleaving synaptosomal-associated membrane protein 25 kD (SNAP-25). This deactivation prevents acetylcholine release. Differences among the three types of BoNT-A include potency, presence or absence of nontoxic accessory proteins, dosing, storage, and FDA-approved indications [1, 2].

OnabotulinumtoxinA

Botox® (Allergan plc, Dublin, Ireland) is the trade name for onaBoNT-A. Originally approved by the FDA in 1989 for clinical use, onaBoNT-A has now been approved by the FDA for all of the following therapeutic conditions: strabismus [23] and blepharospasm [24], CD [25], hyperhidrosis, upper and lower limb spasticity [26], migraine headache [27], overactive bladder, and pediatric spasticity [28]. OnaBoNT-A has been available for clinical use the longest compared to the other type A toxin formulations discussed in this chapter. For this reason, OnaBoNT-A tends to be the toxin of choice among many providers in the United States [2]. OnaBoNT-A requires refrigeration at 2 °C to 8 °C and must be reconstituted in preservative-free normal saline prior to administration. Patients need repeating the injection every 3 months except for overactive bladder when patients receive injection every 6 months [28].

AbobotulinumtoxinA

Dysport® (Ipsen) is the trade name for aboBoNT-A. The FDA has approved the therapeutic application of aboBoNT-A for the following conditions: CD [9, 29], upper and lower limb spasticity in adults, and lower limb spasticity in pediatric patients 2 years of age or older [30]. AboBoNT-A was available in Europe years prior to its approval in the states by FDA. Similar to onaBoNT-A, aboBoNT-A requires refrigeration at 2 °C to 8 °C and must be reconstituted in preservative-free normal saline prior to administration. The typical dosing interval for aboBoNT-A is also about every 3 months [1, 2, 31].

IncobotulinumtoxinA

Xeomin® (Merz) is the trade name for incoBoNT-A. IncoBoNT-A is the most recent BoNT-A to come to the market in the United States. The FDA has approved the application of incoBoNT-A for the following therapeutic conditions: upper limb spasticity [32], CD [33], chronic sialorrhea, and blepharospasm [34]. IncoBoNT-A was manufactured free of potentially immunogenic proteins from clostridia in an attempt to reduce immunogenicity. Unlike the other BoNT-A, incoBoNT-A may be stored at room temperature prior to reconstitution with preservative-free normal saline. Patients tend to require dosing for therapeutic indications once every 3 months [1, 2, 35].

BoNT Type B

There is only one commercial available BoNT-B in the United States, rimabotulinumtoxinB (rimaBoNT-B). Both BoNT-A and BoNT-B work to deactivate SNARE proteins. The one difference between the two toxins is how the deactivation occurs. BoNT-A catalytically cleaves synaptosomal-associated membrane protein 25 kD (SNAP-25). BoNT-B deactivates SNARE by cleaving vesicle-associated membrane protein (VAMP) [1, 2].

RimabotulinumtoxinB

Myobloc® (Solstice Neuroscience) is the trade name for rimaBoNT-B. The FDA has approved rimaBoNT-B for CD [36] and sialorrhea [37]. Unlike the other toxins presented in this article, rimaBoNT-B is the only toxin in a liquid formulation. It seems to be more effective at neuroglandular junctions, lending itself well to use for

sialorrhea. The liquid formulation has an acidic pH and causes a stinging pain at the site of injection [1, 2, 22].

Future Products

DaxibotulinumtoxinA (daxiBoNT-A) is a novel BoNT-A product under development by Revance Therapeutics and has the potential to be the first long-acting neuromodulator [23, 36, 38]. DaxiBoNT-A is a purified 150 kDa BoNT-A (RTT150) that is devoid of accessory proteins and formulated with a proprietary stabilizing excipient peptide (RTP004) in a lyophilized powder. The peptide has a backbone of lysines that carry a positive charge which results in the peptide binding electrostatically to the negatively charged core neurotoxin. DaxiBoNT-A is without human serum albumin and is stable at room temperature prior to reconstitution. Preliminary data suggests that injectable daxiBoNT-A at doses of up to 450 U is well tolerated and may offer prolonged efficacy [39]. The median duration of response was 25.3 weeks (95% CI, 20.14–26.14 weeks). There were no serious adverse events, and the most common detected side effects were dysphagia (14%) and injection site erythema (8%). Further studies involving larger numbers of patients are now warranted and underway for cervical dystonia and spasticity.

PraxibotulinumtoxinA (Jeuveau ®) is another BoNT-A product originally developed in South Korea that recently received FDA approval for the cosmetic treatment of glabellar lines based on two randomized multicenter double blinded trials. The product comes as a vacuum dried powder in single-use 100 unit vials [40]. Currently, it has not received FDA approval for any other clinical applications within the United States; however, there is currently an ongoing phase II clinical trial for the treatment of CD.

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