Neurotoxin Therapy: A Closer Look at the Four Options

The field of neurotoxins has grown recently, but how do the agents compare? Here's a closer look at the therapies available on the US market.

By Stephen Gollomp, MD

Botulinum neurotoxin, available for clinical use in the US market as two serotypes, is a potent inhibitor of acetylcholine release from the presynaptic terminal. Since its development for therapeutic use more than 30 years ago, the agent has proven extremely versatile for a range of neurologic indications and even for cosmetic uses.

Currently, there are four preparations of botulinum toxin available in the US, three for botulinum toxin type A and one for botulinum toxin type B. The type A serotype is available as onabotulinumtoxinA (Botox, Allergan), abobotulinumtoxinA (Dysport, Ipsen and Medicis for cosmetic use), and incobotulinumtoxinA (Xeomin, Merz), while the type B serotype is available as rimabotulinumtoxinB (Myobloc, Solstice Medical). (Table 1) Although all three preparations of the type A serotype have similar mechanisms of action, the available forms of botulinum toxin type A are pharmacologically distinct and may differ in their chemical formulation, clinical potency, and migration and diffusion characteristics.[1,2] The clinical implications of the differences between the preparations has not been definitively established. The three types of A preparations also have distinct indications, based upon regulatory approval. There are differences in dosing between the agents, and there may be other practical differences between them, such as variation in cost or insurance coverage. Following is a review of the four "flavors" of botulinum toxin currently available.

Molecular Weight and Complexing Proteins

Each botulinum toxin preparation contains botulinum neurotoxin, comprised of a heavy amino acid chain (100kD) and a light chain (50kd). Preparations of ona- and abobotulinumtoxinA contain the toxin complexed with naturally occurring non-toxic proteins, producing a molecular weight of approximately 450kD. Two BNT (botulinum neurotoxin) molecules form a dimer with a molecular weight of approximately 900kD. For the incobotulinumtoxinA preparation, the complexing proteins are removed, yielding a molecular weight of 150kD.[2] Upon injection, complexing proteins, if present, rapidly disassociate from the toxin.

When one discusses characteristics of these proteins, issues surrounding potential immunoresistance arise. The development of clinically relevant immunoresistance to BNT is no longer a significant clinical concern, as analyses of data involving large pools of patients show that it currently rarely develops.[3,4] The formulation of onabotulinumtoxinA was changed in 1997 to reduce the amount of protein, which has been directly linked to a reduction in clinical resistance.[4]

Host formation of botulinum neurotoxin antibodies (called blocking or neutralizing antibodies) leads to resistance, while antibodies formed against non-toxic proteins (called non-neutralizing antibodies) do not.[2] It has been accepted for some time that high single doses of botulinum toxin at each injection cycle and brief inter-injection intervals increase the risk of developing resistance. Antigenicity is inversely proportional to biological activity, because highly biologically active formulations contain low levels of inactivated toxin, which can nonetheless act as antigen. The specific biological activity (SBA) of the formulation is expressed as MU (mouse units)/ng BNT, while the protein load is expressed as the inverse: ng BNT/MU. The SBA of the available toxin preparations is 60MU-EV/ng BNT for abobotulinumtoxinA, 100MU-EV/ng BNT for onabotulinumtoxinA, 167MU-EV/ng BNT for incobotulinumtoxinA, and 5MU-EV/ng BNT for rimabotulinumtoxinB.[2] While increasing levels of SBA are associated with reduced risk for resistance, there are no specific correlates of specific biological activity to resistance risk. Therefore clinical incidence of resistance is likely the best indicator of risk. Current clinical experience suggests a low risk with all currently available formulations. This observation dovetails with the laboratory observations that the development of clinical immunoresistance requires the induction of antibodies directed at several different molecular epitopes within

Table 1. Preparations At-a-Glance *See Table 2 for Indications*

Botox

Generic name: onabotulinumtoxinA

First approved: December 1989

Manufacturer and marketer: Allergan (Also Botox Cosmetic)

Strain: Hall strain of *C botulinum*

Formulation: A sterile lyophilized form of botulinum toxin type A. Toxin is purified by a series of acid precipitations to a crystalline complex containing the toxin and other proteins.

Molecular weight: Total molecular weight 900kD.

How supplied: 100 Units or 200 Units vacuum-dried powder for reconstitution only with sterile, non-preserved 0.9% Sodium Chloride Injection USP prior to injection.
Each vial contains either 100 U of Clostridium botulinum type A neurotoxin complex, 0.5mg of Albumin Human, and 0.9mg of sodium chloride; or 200 U of Clostridium botulinum type A neurotoxin complex, 1mg of Albumin Human, and 1.8mg of sodium chloride in sterile, vacuum-dried form without preservative.

Storage and handling requirements: Unopened vials require refrigeration (2° to 8°C, up to 36 months for 100 Units vial; up to 24 months for 200 Units vial). Administer within 24 hours of reconstitution; store reconstituted Botox in a refrigerator.

Boxed Warnings: Re: Distant Spread of Toxin Effect

Contraindications:

• Known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation

• Infection at the proposed injection site

Dysport

Generic name: abobotulinumtoxinA

First approved: April 2009

Manufacturer and marketer: Ipsen (Also distributed for cosmetic indications by Medicis)

Strain: Hall strain of *C botulinum*

Formulation: Purified from culture supernatant by a series of precipitation, dialysis, and chromatography steps. The neurotoxin complex is composed of the neurotoxin, hemagglutinin proteins and non-toxin non-hemagglutinin protein.

Molecular weight: Ranges from 500kD to 900kD

How supplied: Single-use, sterile 3mL glass vial. Each vial contains 500 or 300 Units of lyophilized abobotulinumtoxinA, 125 micrograms human serum albumin and 2.5mg lactose.
*May contain trace amounts of cow's milk proteins.

Storage and handling requirements: Must be stored under refrigeration at (2–8°C or 36–46°F). Protect from light. Administer within 4 hours of reconstitution; during this period keep refrigerated. Do not freeze after reconstitution.

Boxed Warnings: Re: Distant Spread of Toxin Effect

Contraindications:

• Known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation

• Patients known to be allergic to cow's milk protein

• Infection at the proposed injection site

the toxin complex. In addition, patient-specific factors, such as immune system reagibility, immunocompetence, and female sex appear to play a role in resistance induction.[2] Of note, cross-reactivity of toxin type A and toxin type B does not occur.

From a clinical standpoint, a patient who develops resistance to A serotype preparation can be successfully transitioned to serotype B. Unfortunately, a significant number of these patients have eventually developed clinical immunoresistance to the B serotype within 18 months of the therapy transition.[5] There is little available evidence to suggest that transitioning to a different serotype A preparation will be effective for the serotype A resistant patient.

Onset of Action and Diffusion

There has also been speculation that a smaller molecular weight could contribute to more rapid onset of action and perhaps to different diffusion rates, though this is unlikely, due to the fact that the native toxin rapidly dissociates from the complexing proteins upon injection. The issue of diffusion has been discussed more widely in the aesthetic arena, perhaps because cosmetic surgeons are particularly averse to inducing any undesirable cosmetic outcomes due to toxin spread. However, the presence or absence of complexing proteins does not appear to influence diffusion.[6,7] Furthermore, studies do not suggest a notable difference in the diffusion of the three botulinum toxin type

Xeomin

Generic name: incobotulinumtoxinA

First approved: 2010

Manufacturer and marketer: Merz Pharmaceuticals

Strain: Hall strain of *C botulinum*

Formulation: Purified from the culture supernatant and then the active ingredient is separated from the proteins (hemaglutinins and non-hemaglutinins) through a series of steps yielding the active neurotoxin with molecular weight of 150 kDa, without accessory proteins.

Molecular weight: 150 kDa.

How supplied: A sterile white to off-white lyophilized powder to be reconstituted with 0.9% Saline for Injection. One vial of Xeomin contains 50 or 100 Units of incobotulinumtoxinA, 1 mg of human albumin, and 4.7 mg sucrose.

Storage and handling requirements: Unopened vials can be stored at room temperature 20 to 25°C (68 to 77° F), in a refrigerator at 2 to 8°C (36 to 46°F), or a freezer at -20 to -10°C (-4 to 14°F) for up to 36 months. Reconstituted Xeomin should be stored in a refrigerator and administered within 24 hours.

Boxed Warnings: Re: Distant Spread of Toxin Effect

Contraindications:

• Known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation

• Infection at the proposed injection site

Myobloc

Generic name: RimabotulinumtoxinB

First Approved: 2000

Manufacturer or Marketer: Solstice Neurosciences

Strain: *C botulinum* type B (Bean strain)

Formulation: The neurotoxin exists in noncovalent association with hemagglutinin and nonhemagglutinin proteins as a neurotoxin complex. The neurotoxin complex is recovered from the fermentation process and purified through a series of precipitation and chromatography steps.

Molecular weight: Approximately 700kd

How supplied: A clear and colorless to light-yellow sterile injectable solution in single-use 3.5mL glass vials. Each single-use vial contains 5,000 Units of botulinum toxin type B per milliliter in 0.05% human serum albumin, 0.01 M sodium succinate, 0.1M sodium chloride at approximately pH 5.6. It is available as 2,500 U (0.5 mL vial); 5,000 U (1mL vial); and 10,000 U (2mL volume)

Storage and handling requirements: Refrigerate at 2°- 8°C (36-46°F). Do not freeze or shake. May be diluted with normal saline. Once diluted, the product must be used within 4 hours as the formulation does not contain a preservative.

Boxed Warnings: Re: Distant Spread of Toxin Effect

Contraindications:

• Known hypersensitivity to any ingredient in the formulation.

Table 2. FDA-Approved Indications

Botox:
- Prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer)
- Treatment of upper limb spasticity in adult patients
- Treatment of cervical dystonia in adult patients to reduce the severity of abnormal head position and neck pain
- Treatment of severe axillary hyperhidrosis that is inadequately managed by topical agents in adult patients
- Treatment of blepharospasm associated with dystonia in patients ≥12 years of age
- Treatment of strabismus in patients ?12 years of age

Dysport
- Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain in both toxin-naïve and previously treated patients

Xeomin:
- Treatment of adults with cervical dystonia to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients.
- Treatment of adults with blepharospasm previously treated with onabotulinumtoxinA (Botox).

Myobloc:
- Treatment of adults with cervical dystonia to reduce the severity of abnormal head position and neck pain associated with CD.

A preparations.[8] In fact, a recent study involving injections into mouse legs found no significant difference in diffusion rates between the three preparations.[9] Given that diffusion is expected to be equal for equal doses of toxin, it has been suggested that any clinically perceived difference in diffusion rates may relate to differences in dosing.[8] For example, a pilot study of diffusion of onabotulinumtoxinA versus abobotulinumtoxinA for forehead hyperhidrosis suggested greater and therapeutically beneficial diffusion with abobotulinumtoxinA.[10] However, abobotulinumtoxinA was provided at ratios from 2.5 up to 4 to 1 relative to onabotulinumtoxinA.

The possibility of diffusion is a clinical reality and an important clinical consideration, as indicated by the fact that FDA has added boxed warnings to all neurotoxins regarding this risk, as part of their REMS (Risk Evaluation and Mitigation Strategies) program.

Similarly, discussion of onset has been more prevalent in the cosmetic arena, where at least anecdotally some clinicians report more rapid onset of action with abobotulinumtoxinA.[11] In reality, the literature contains injector and patient reports of onset within 24 hours of injection for both abobotulinumtoxinA and onabotulinumtoxinA.[12,13] There are no head-to-head-to-head comparison trials to assess onset of efficacy in any indication. Again, differences in onset of action, if they exist, may be attributable to variability of dosing. Furthermore, the clinical significance of a 24- to 36-hour difference in onset may not be a primary consideration in treatment selection.

FDA-Approved Indications and Clinical Use

The FDA-approved indications for the available neurotoxin formulations vary. (Table 2) OnabotulinumtoxinA boasts the most indications. There is no reason to believe that the three prepartions of type A serotype cannot all be used for the same indications, and Medicare carriers, as referenced in their Local Carrier Determinations (LCD) in many parts of the country treat the agents as interchangeable. Botulinum toxin type B presents a notable exception. Given the low pH of the formulation, injection into sensitive areas is associated with significant burning and patient discomfort. Therefore, rimabotulinumtoxinB is not recommended for injection anywhere above the neck, discouraging its use for most cases of blepharospasm, migraine, and cosmetic indications.

Dosing

One clear, practical difference between neurotoxin preparations relates to dosing. One analysis showed the mean concentration[14] of BNT/A neurotoxin in onabotulinumtoxinA is 0.73ng per 100 unit vial; in abobotulinumtoxinA is 3.24ng per 500 unit vial; and in incobotulinumtoxinA is 0.44ng per 100 unit vial

While the marketed preparations of onabotulinumtoxinA and incobotulinumtoxinA are equipotent and dosed at a 1:1 ratio,[15] abobotulinumtoxinA is not. The potency of abobotulinumtoxinA relative to onabotulinumtoxinA has been estimated from 2:1 up to 6:1.[16] A 2009 study concluded that dose-conversion ratios be-

Table 3. Neurotoxins Have Unique Dosing

	Botox	Xeomin	Dysport	Myobloc
Dystonia, per PI**	~236 U (mean dose administered in studies); Range 198 U to 300 U	120 U	500 U	2,500 to 5,000 U

***These are dosing guidelines printed in the prescribing information and provided for illustrative pursposes. Clinical dosing and use vary.*

REMS and Patient Counseling

In addition to implementing the boxed warning on all botulinum toxin products regarding a risk of distant spread in April 2009, FDA also required the marketers/manufacturers of each preparation of botulinum toxin to implement a Risk Evaluation and Mitigation Strategy or REMS.

The boxed warning notes that neurotoxin may spread from the area of injection to other areas of the body, causing symptoms similar to those of botulism, including unexpected loss of strength or muscle weakness, hoarseness or trouble talking, trouble saying words clearly, loss of bladder control, trouble breathing, trouble swallowing, double vision, blurred vision and drooping eyelids. Of note, symptoms have mostly been reported in children with CP being treated with the products for muscle spasticity, an unapproved use. Symptoms have also been reported in adults.

The agency also at that time indicated that it recognized serious risks associated with the lack of interchangeability among the three licensed botulinum toxin products, leading to the four distinct formulation names now in place.

Each manufacturer/marketer has a unique REMS program, but they share the same main components:

• *Medication Guide:* FDA-approved handouts given to patients, or their families and caregivers, when a medicine is dispensed. The Medication Guides contain information about the risks associated with botulinum toxin products.

• *Communication Plan:* Injectors are to provide the medication guide to patients prior to injection, permit them to read it, and discuss any questions or concerns prior to initiating therapy. This should be done **each time** the patient receives neurotoxin therapy.

• Collection of safety data in children and adults with muscle spasticity to assess the signal of risk regarding distant spread of toxin effects.

Those who inject botulinum toxins should, according to FDA:

• Understand that dosage strength (potency) expressed in "Units" is different among the botulinum toxin products; clinical doses are not interchangeable from one product to another.

• Be alert to and educate patients and caregivers about the potential for effects following administration of botulinum toxins.

• Understand that these effects have been reported as early as several hours and as late as several weeks after treatment.

• Advise patients to seek immediate medical attention if they develop any of these symptoms.

tween abobotulinumtoxinA and onabotulinumtoxinA of 4:1 and greater are not supported by the literature. The authors identified four key areas of evidence: nonclinical and preclinical studies; studies exploring the diffusion characteristics and effects of complexing proteins; comparative experimental data from human studies; and clinical studies. Randomized, controlled clinical studies indicate that 3:1 is more appropriate than 4:1, but the two products still are not equivalent at this ratio.[7] In clinical practice, I have found a conversion ratio of 2.75:1 to work reasonably well.

It should be noted that the product literature for each preparation cautions against dosing conversion from one preparation to another. Rather, injectors should be familiar with the recommended dosing for each agent for specific indications. However, it is difficult for clinicians familiar with one agent not to think in terms of dosing for that agent. Nonetheless, recommended dosing for common indications for each preparation are provided in Table 3.

Each preparation comes with specific instructions for product reconstitution; individual preference often leads clinicians to develop preferred dilutions. For example, many clinicians typically use about a concentration 100U/cc with onabotulinumtoxinA or incobotulinumtoxinA, but I generally prefer to use 50U/cc. It is worth noting that due to the design of the vial, only 2cc of saline can be reliably used to dilute abobotulinumtoxin B, leading to a dilution of 250U/cc.

Cost and Insurance Coverage

Another practical consideration, and the one most

Table 4. Medicare LCDs

Local coverage determinations show that some Medicare carriers do not distinguish between toxins, despite the wide variability in their FDA indications. Following is a sample of coverage provisions from three different regions.

	Region 3 (VA/WV)	Region 4 (FL)	Region 5 (IN)
Spasticity	ICD-9 codes must support medical necessity	**Botox:** Cervical dystonia; Upper limb spasticity; Lower limb spasticity with covered ICD-9 codes; Laryngeal spasm and torticollis; dystonia or lower limb spasticity resulting in functional impairment and/or pain in patients with various hereditary, acquired, degerative, or demyelinating diseases of the CNS **Dysport:** Adult cervical dystonia; Upper limbs following stroke **Xeomin:** Adult cervical dystonia **Myobloc:** Cervical dystonia	ICD-9 codes must support medical necessity
Blepharospasm	Accepted as first-line treatment	**Botox:** strabismus and blepharospasm associated with dystoni and benign essential belpharospasm; facial nerve disorders individuals 12yrs+ **Dysport:** Benign essential blepharospasm; Hemifacial spasm **Xeomin:** Belpharospasm in adults previously treated with Botox	Accepted as first-line treatment
Achalasia	Not responded to conventional therapy or has other risk factors	Not responded to dilation or are poor surgical candidates	Not responded to conventional therapy or has other risk factors
Anal fissure	Not responded to conventional therapy	Botox	Not responded to conventional therapy
Hyperhidrosis	Inadequately controlled with topical therapy	**Botox, Dysport:** Inadequately managed with topical agents	Inadequately controlled with topical therapy
Sialorrhea	Failed reasonable trial of traditional therapies, contraindication/intolerance of anticholinergic therapy		Failed reasonable trial of traditional therapies, contraindication/intolerance of anticholinergic therapy
Urinary incontinence	Not covered	Botox	Not covered
Hadache/migraine	CDH >15 days/mo for 3 mos; significant disability due to HA; refractory to standard conventional therapy; Continuing therapy rqures a significant decrease in number and frequency of HAs	**Botox:** CDH >15 days/mo, 4hrs+	CDH >15 days/mo for 3 mos; significant disability due to HA; refractory to standard conventional therapy; Continuing therapy rqures a significant decrease in number and frequency of HAs
Limitations	• Allows for one injection per site regardless of number of injections per site • Failure of 2 definitive, consecutive sessions involving a muscle or group could preclude further coverage of the serotype used for one year For regions 3,5: • Treatment of wrinkles is cosmetic and not covered • Payment will not be made for spastic conditions not listed under ICD-9 codes for medical necessity • Cost of syringes not separately payable For regions 3: • When HCPCS code J0585, J0586, J0587, J3590, C9399 is denied, related injection codes will also be subject to denial		

Patient Preference and Counseling

Patients are more educated than ever. They read reputable and unreputable sources. Be prepared for questions and specific requests. Talk about clinical realities and your experience. Discuss coverage, costs, and patient experience. Aside from cost difference, there is probably no significant clinical advantage to switching from one toxin A to another in a patient who has had good results.

likely to play a role in clinical decision-making, is the cost of therapy. Insurance coverage for neurotoxin therapy varies from plan to plan and region to region, but private insurers frequently follow the example of Medicare, making it worthwhile to assess how Medicare approaches treatment.

Medicare coverage decisions vary by region per the regional LCD (Table 4). Generally, carriers seem to cover onabotulinumtoxinA therapy for all of its FDA-approved therapeutic indications (not cosmetic use). However, in my experience, one national carrier, Aetna, has aggressively and excessively restricted coverage of botulinum toxin therapy, even in circumstances when it is universally recognized as being appropriate therapy. The newest indication, chronic headache, is also covered by many carriers, but with conditions placed on coverage, such as failure of conventional therapies. Some carriers view the serotype A preparations as virtually interchangeable and will cover abobotlinumtoxinA or incobotulinumtoxinA therapy for all the same indications for which onabotulinumtoxinA is covered. Others cover each agent only for its approved indications.

AbobotulinumtoxinA has instituted competitive pricing per unit relative to onabotulinumtoxinA or incobotulinumtoxinA. Even accounting for the need for more units of abobotulinumtoxinA, treatment is probably about 20 percent less with this agent. incobotulinumtoxinA and onabotulinumtoxinA have similar standard pricing. Recently, incobotulinumtoxinA launched a patient co-payment program that reduces an individual's out-of-pocket costs for treatment, thus potentially reducing the cost of treatment relative to onabotulinumtoxinA on a sustained basis. They alos launched a patient assistance program to provide no-cost therapy to the un- or under-insured. OnabotulinumtoxinA has a patient assistance program for those patients who are uninsured or underinsured and who have incomes at three times the federal poverty level. AbobotulinumtoxinA provides samples to clinicians, which can be used to off-set therapy costs for a patient or provide therapy to a patient without the means to pay for the drug.

Making Comparisons

Botulinum neurotoxin A is exceptionally effective in the therapy of a vast array of conditions. Now that there are three preparations of this serotype on the market, physicians must be familiar with the perceived, actual, and potential differences between these pharmacologically distinct agents. In reality, the clinical consequences of differences in molecular weight, protein content, and diffusion are probably negligible. Dosing and cost are likely the main differences between the preparations. Costs and insurance restrictions may drive selection of a preparation for a given patient, suggesting that clinicians may need to be comfortable with more than one preparation.

Botulinum neurotoxin type B largely remains a second-line option for the rare patient who demonstrates clinical resistance to serotype A therapy. ■

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