Terminology for Preparations of Botulinum Neurotoxins

What a Difference a Name Makes

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THE MARKET FOR BOTULINUM NEUROTOXINS IS BECOMing as crowded in the United States as in Europe. Last year, following approval of a second type A botulinum neurotoxins, the US Food and Drug Administration announced generic (or nonproprietary) name changes for all of the versions of injectable botulinum neurotoxins, and added a boxed warning on the labels of these potential biological weapons to describe the spread of the toxin and the attendant, possibly life-threatening effects.[1]

The botulinum neurotoxins marketed in the United States are now named onabotulinumtoxinA (brand name Botox), rimabotulinumtoxinB (Myobloc), abobotulinumtoxinA (Dysport), and incobotulinumtoxinA (Xeomin), which was recently approved in the US market (TABLE). With this recent entry, 3 type A and 1 type B brands of botulinum neurotoxins are available in the United States. The new generic names have not yet been adopted by other regulatory agencies. For example, the European Medicines Agency retains the official denomination of botulinum toxin for all products of botulinum neurotoxins.

These almost unpronounceable new names meet the World Health Organization's criteria for nonproprietary names in that they are "distinctive in sound and spelling and should not be liable to confusion with other names in common use."[2] The most important benefit of change in terminology is a gain in identity for different botulinum neurotoxins, which is expected to improve their usage in clinical practice. The 4 products have significant differences in terms of manufacturing (including purification and complexing), potency, and dosing (Table). A significant degree of medical expertise is required to switch patients from one formulation to another. The new naming acknowledges that botulinum neurotoxins are produced by different biological manufacturing processes, are obtained by different isolation and purification techniques, and are derived from different *Clostridium* batches. Differences in the products' molecular structures and formulations may affect their local migration from the injection site and potency characteristics, which in turn may influence their efficacy, safety profile, and antigenic potential.

All products of botulinum neurotoxins are approved for the treatment of cervical dystonia and most are approved for other indications, including strabismus, blepharospasm, hemifacial spasm, spasticity, axillary hyperhidrosis, and facial wrinkles. There are appreciable geographic differences in labeling across countries and notably within Europe. Given the wide number of indications for medical use, injections of botulinum neurotoxins are targeted to different body regions and tissues (eg, in the tiny oculomotor muscles, in large spastic limb muscles, in the sweat glands, or in the skin).

The American Academy of Neurology has published guidelines for usage of botulinum neurotoxins for autonomic disorders, pain, movement disorders, and spasticity.[3-5] These evidence-based reviews are based largely on trials comparing products of botulinum neurotoxins with placebo because there are no head-to-head comparisons on the efficacy and safety of different products of botulinum neurotoxins in patients with autonomic disorders, pain, or spasticity. For dystonia, there is only one trial comparing incobotulinumtoxinA with onabotulinumtoxinA in patients with cervical dystonia[6]; this information is insufficient due to limitations inherent to the noninferiority design of the trial and lack of comparisons in other dystonia types.

The implementation of these guidelines is limited by lack of consensus on standard methods for injecting botulinum neurotoxins and on training requirements for clinicians who administer this treatment. Factors such as dilution ratios, number of injections at each site, and targeting procedure (visual, electromyographic, or ultrasound-guided) vary considerably among centers and influence clinical outcome. Long-term safety and efficacy data suggest that all products of botulinum neurotoxins are safe and retain their efficacy with repeated treatments over several years, but also reveal differences among brands.[7]

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Table. Marketed Brands of Botulinum Toxins

	Generic Name			
	OnabotulinumtoxinA	RimabotulinumtoxinB	AbobotulinumtoxinA	IncobotulinumtoxinA
Brand name	Botox	Myobloc/Neurobloc[a]	Dysport	Xeomin
Manufacturer	Allergan Inc (United States)	Solstice Neurosciences (United States)	Ipsen (France)	Merz Pharmaceuticals GmbH (Germany)
Serotype	A	B	A	A
Specific activity, U/ng	20	75-125	40	167
Packaging, U/vial	100	2500, 5000, or 10 000	500	100
Constituents and excipients	Hemagglutinin, human albumin, saccharose, sodium chloride	Hemagglutinin, human albumin solution 0.05%, sodium chloride, sodium succinate	Hemagglutinin, human albumin 20% solution, lactose	Human albumin, saccharose
pH	7.4	5.6	7.4	7.4
Complex size, kDa	900	700	900	150
Preparation	Vacuum dried	Solution (5000 U/mL)	Lyophilized	Lyophilized
Storage of packaged product	–5°C or 2°C-8°C	2°C-8°C	Room temperature	Room temperature
Storage once reconstituted	2°C-8°C for 24 h	For a few hours	2°C-8°C for several hours	2°C-8°C for 24 h

[a]Myobloc is the brand name in Canada, the United States, and Korea. Neurobloc is the brand name in the European Union, Norway, and Iceland.

The availability of multiple products of botulinum neurotoxins type A may bring to the United States a number of practical problems already observed in Europe. Switching between one brand of botulinum neurotoxins with another occurs regularly in different European centers, mainly because of restricted availability and labeling differences. Due to overlapping indications, hospital managers may choose to purchase only one formulation of botulinum neurotoxins. If patients move from one center to another, in which physicians preferentially use a toxin brand different from the one the patient previously received, variations in outcome may be perceived. Each product of botulinum neurotoxins is measured with proprietary units that are considered to be noninterchangeable.[8] With the only possible exception of the asserted equivalence of incobotulinumtoxinA and onabotulinumtoxinA units for patients with cervical dystonia,[6] there is no unique dose ratio to allow switching from one toxin brand to another even for a single indication.[9]

Another practical problem is that patients may receive injections of multiple products of botulinum neurotoxins (for example, if they are independently treated by different specialists). For instance, some patients with cervical dystonia who receive treatment with one product of botulinum neurotoxins in a neurological practice may receive a separate treatment with a different product of botulinum neurotoxins for a cosmetic indication. Simultaneous treatment with different brands of botulinum neurotoxins, particularly if it occurs in close time intervals, may facilitate the onset of an immune reaction to botulinum neurotoxins, leading to loss of clinical efficacy.[10]

The new terminology introduced by the US Food and Drug Administration is a welcome innovation that is expected to reduce errors and misinterpretation and should be of benefit for patients who receive treatments with botulinum neurotoxins. This initial step should be followed by new consensus on clinical usage and comparative trials to provide the missing evidence necessary to develop new and comprehensive practice parameters.

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