

Botulinum neurotoxin: A therapeutic powerhouse with broad clinical implications

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ABSTRACT

Clostridium botulinum is a Gram-positive bacterium that produces one of the most deadly chemodenervating toxins in the world. To date, six distinct neurotoxins are available for prescription use in the United States. Decades of data across aesthetic therapeutic areas and therapeutic disease states support the safety and efficacy of *C. botulinum*, providing good symptom management and improved quality of life in appropriately chosen patients. Unfortunately, many clinicians are slow to progress patients to toxin therapy from more conservative measures, and others wrongly interchange the products despite characteristics unique to each. Commensurate with an improved understanding of the complex pharmacology and clinical implications of botulinum neurotoxins is the importance for clinicians to appropriately identify, educate, refer, and/or treat candidate patients. This article provides an overview of the history, mechanism of action, differentiation, indications, and uses for botulinum neurotoxins.

Keywords: toxin, *Clostridium botulinum*, botulism, spasticity, migraine, overactive bladder

Botulinum neurotoxins belong to a class of chemodenervating agents that are considered among the most deadly in the world.¹ As the complex pharmacology and clinical implications of botulinum neurotoxins have become better understood, they have developed an evolving place in clinical practice.²⁻⁸ This article provides an overview of the history, mechanism of action, differentiation, indications, and uses for botulinum neurotoxins.

Clostridium botulinum is a Gram-positive, toxin-producing, rod-shaped bacterium that was discovered more than 200 years ago in humans and animals who developed botulism after eating infected meat.⁹⁻¹¹ Ingestion or infiltration of *C. botulinum* in mammals is followed by its proliferation and subsequent release of exotoxin into the

body, causing symptoms including generalized weakness, dyspnea, dysphagia, and death.^{10,11} Although clinicians today are mindful of botulism, cases in the United States still occur (231 confirmed cases in 2018).¹² Rather, most patients are exposed to botulinum neurotoxins through the syringe of a trusted clinician in focused locations at doses that are hundreds of times below the lethal level.^{3-8,12}

MECHANISM OF ACTION

Once in the body, botulinum neurotoxins target acetylcholinergic nerve terminals and are endocytosed into the presynaptic neuron.¹³ The toxin then separates into its component parts: a heavy chain and a proteolytic light chain.¹⁴ The light chain enters the axoplasm from the endosome and proceeds to lyse the soluble N-ethylmaleimide-sensitive factor-attachment protein-receptor (SNARE) proteins responsible for releasing neurotransmitters into the synapse.^{15,16} Which SNARE proteins are lysed is unique to each toxin, and lysing leads to reduced synaptic availability of acetylcholine. The subsequent attenuation in muscle contraction underlies the clinical effects commonly desired from neurotoxin therapy.¹³

CLINICAL USE

Six botulinum neurotoxins have been approved by the FDA for aesthetic and/or therapeutic use: BOTOX (onabotulinumtoxinA), Dysport (abobotulinumtoxinA), Xeomin (incobotulinumtoxinA), Jeuveau (prabotulinumtoxinA), Myobloc (rimabotulinumtoxinB), and Daxxify (daxibotulinumtoxinA).^{3-8,17} Although a full review of each is outside of the scope of this article, on- and off-label indications for these drugs are varied.^{3-8,17-20} **Table 1** summarizes their FDA-approved uses. With decades of data supporting their safety and efficacy, botulinum neurotoxins gained a foothold in treatment guidelines across neurology, urology, neuro-urology, and cosmetic therapeutic areas, and in appropriately selected patients, toxin therapy can provide good symptom management and improve patient quality of life.²¹⁻³³ Even so, the progression of patients to botulinum neurotoxins can be slow, in part due to a paucity of easily accessible clinician and patient education material on disease diagnosis and toxins as a treatment option.^{21,22,34-37} At a minimum, clinicians should be aware of the conditions for which

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TABLE 1. Indications for botulinum neurotoxins as of January 2023³⁻⁸

	Botox	Dysport	Xeomin	Jeuveau	Daxxify	Myobloc
Blepharospasm	X		X			
Strabismus	X					
Glabellar lines	X	X	X	X	X	
Lateral canthal lines	X					
Forehead lines	X					
Primary axillary hyperhidrosis	X					
Chronic migraine prophylaxis	X					
Adult spasticity	X	X	X (Upper limb only)			
Pediatric spasticity	X	X	X (Upper limb only)			
Cervical dystonia	X	X	X			X
Chronic sialorrhea (children)			X			
Chronic sialorrhea (adults)			X			X
Overactive bladder	X					
Neurogenic detrusor overactivity (children)	X					
Neurogenic detrusor overactivity (adults)	X					

botulinum neurotoxins are used, in order to appropriately identify, educate, refer, or treat patients who may be therapeutic candidates (Table 1).

TOXIN DIFFERENTIATION AND SAFETY

The existence of multiple botulinum neurotoxins may lead some clinicians to believe these drugs have interchangeable indications and easily converted dosing paradigms. However, because of the characteristics unique to each toxin, substitution is strongly discouraged, and is even warned against in all prescribing information.³⁻⁸ This recommendation comes in part because botulinum neurotoxins are dosed in units of biologic potency that are unique to each product and determined by assays specific to the toxin in question.^{3-8,38-40} Because of this fact, *in vivo* testing of identical unit doses of distinct toxins yields dissimilar potency findings when clinically appropriate diluents (such as 0.9% sodium chloride solution) are used in animal and human models.⁴¹⁻⁴⁵ These studies underscore the fact that potency equivalence between the toxins does not exist. Some clinicians inappropriately switch patients between toxins, particularly for nonmedical reasons, and doing so has been shown to cause adverse reactions and reduce patient treatment satisfaction.^{46,47}

Botulinum neurotoxin treatment is considered safe with mild adverse reactions that typically align with the indication of use.³⁻⁸ For example, headache is more common

with injections in the head, face, and neck; intradetrusor administration carries an increased risk of urinary tract infection.^{3,4,6-8} Review indication-specific adverse reactions with patients before use.³⁻⁸ A boxed warning that applies to all botulinum neurotoxins informs clinicians and patients about the remote, but possible, spread of toxin away from the intended target, occasionally manifesting as symptoms consistent with *C. botulinum* infection.³⁻⁸

CONCLUSION

The therapeutic potential and broad clinical utility of botulinum neurotoxins is apparent. Although the decision to treat a patient's condition with neurotoxins should be based on the patient's goals, clinician training, and the balance of risks versus benefits, clinicians must first understand the potential of these drugs. A thorough examination and conversation with patients before treatment is essential for appropriate

evaluation and expectation management.

Physician associates/assistants interested in practicing with botulinum neurotoxins should first ensure that this work is supported by their state governing board and attending physician. Injection training is available through each toxin company. **JAAPA**

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