

# The Multispecialty Toxin: A Literature Review of Botulinum Toxin

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**Background:** Botulinum toxin (BoNT) is a potent biological exotoxin produced from *Clostridium botulinum*. Although it was first used therapeutically to treat strabismus, its clinical role has since expanded rapidly over the years to include treatment of a variety of head and neck, gastrointestinal, urogenital, musculoskeletal, neurological, dermatological, and cosmetic disorders. The main purpose of this review is to provide a brief updated overview of the history, mechanism of action, and clinical applications of BoNT therapy across multiple medical specialties, including the most common adverse effects and recommended Botox dosages.

**Methods:** A literature review was conducted in the PubMed database limited to English language articles. Specific search terms related to botulinum toxin in combination with various subspecialty fields were used, and relevant articles were identified and analyzed. The reference section for each article was also searched to find additional articles.

**Results:** BoNT is a powerful therapeutic tool and has a vast array of clinical uses in many specialties, including ophthalmology, neurology, plastic surgery, dermatology, orthopedic, gastrointestinal, gynecology, urology, and rheumatology. Due to its chemodenervation effects at the presynaptic nerve terminal, it is useful in treatments of disorders characterized by abnormal inappropriate muscle contractions.

**Conclusions:** BoNT has many clinical applications in several medical specialties. Future studies should focus on any additional indications of BoNT therapy as they arise and on any novel product developments. (*Plast Reconstr Surg Glob Open* 2022;10:e4228; doi: 10.1097/GOX.0000000000004228; Published online 6 April 2022.)

## INTRODUCTION

Botulinum toxin (BoNT) is a neurotoxin produced by the Gram-positive, rod-shaped, spore-forming anaerobic bacterium *Clostridium botulinum*. Although there are seven major serotypes of Botulinum Neurotoxin (BoNT/A-G), only type A and B are used clinically.<sup>1</sup> For the purpose of this article, we will refer to this agent as BoNT, and the distinction of Botox and Botox Cosmetic will be used when referring to Food and Drug Administration (FDA)-approved dosages. This literature review primarily serves to provide a historical review of the toxin, assess its mechanism of action, and highlight the many clinical applications of BoNT therapy in an organized, specialty-based

manner. Secondary goals aim to cover the most common side effects and toxicity, including their management options, and the recommended Botox dosage relative to their FDA-approved clinical application. Some of the conditions mentioned may be treated by multiple specialties.

## METHODS

A literature review was conducted in the PubMed database limited to English language articles published using the terms: “Botulinum Toxin,” “Botulinum Neurotoxin,” “Botulinum Toxin A,” “Botox” in various combinations with “Ophthalmology,” “Neurology,” “Plastic Surgery,” “Dermatology,” “Gastrointestinal,” “Urology,” “Gynecology,” “Rheumatology,” “Orthopedics,” “clinical applications,” “dose,” and “complications.” Articles describing the use of botulinum toxin were selected, reviewed, and summarized in this article. References from each article were also reviewed for additional relevant articles.

## Historical Review

Historically, the idea of using BoNT therapeutically originated from Justinus Kerner in the early 1800s. He referred to the toxin as “sausage poison” after noting its

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effects following ingestion of spoiled smoked blood sausages. In 1870, John Muller coined the term “botulism” (the Latin root *botulus* means “sausage”) and in 1895, van Ermengem isolated the bacterium for the first time.<sup>2,3</sup> The discovery of the bacterium and toxin led to the investigation of its use as a treatment for strabismus.<sup>3,4</sup> Finally, in 1989, it was FDA approved as a therapy for strabismus, blepharospasm, and hemifacial spasm.<sup>5,6</sup> In 2000, it was FDA approved for the treatment of cervical dystonia.<sup>7,8</sup> Since then, it has been widely accepted and utilized for both on- and off-label by multiple medical specialties for a variety of conditions (Fig. 1).

**Mechanism of Action**

BoNT is synthesized as an inactive 150-kDa single chain polypeptide, which undergoes cleavage, and thus activation, by trypsin or bacterial enzymes into a 100kDa heavy chain and 50kDa light chain.<sup>9</sup> BoNT selectively and reversibly binds in the presynaptic terminal of the neuromuscular junction to specific membrane protein complexes called SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) to prevent the release of acetylcholine.<sup>10,11</sup> BoNT type A and E cleave the SNARE component SNAP-25 (synaptosomal associated protein),<sup>12,13</sup> while type C cleaves both SNAP-25 and syntaxin.<sup>14</sup> Type B, D, and F cleave the SNARE component synaptobrevin (vesicle-associated membrane protein or VAMP).<sup>13,15</sup> Without the presynaptic release of acetylcholine, muscle contraction cannot occur, leading to its many beneficial uses in disorders with abnormal, excessive, or inappropriate muscle contractions.

**Commercially Available Formulations of BoNT**

Several FDA-approved commercial formulations of BoNT (Botox, Dysport, Xeomin, Jeuveau, Myobloc/ Neurobloc) are available in the United States. Each product differs in pharmaceutical form, units per vial, molecular weight, expedients used for preparation, onset of action, dosing, storage, and FDA-approved indications. A comparison of these properties is provided in Table 1. Due to the distinct pharmacological properties of the formulations, these agents should not be used interchangeably.

**Takeaways**

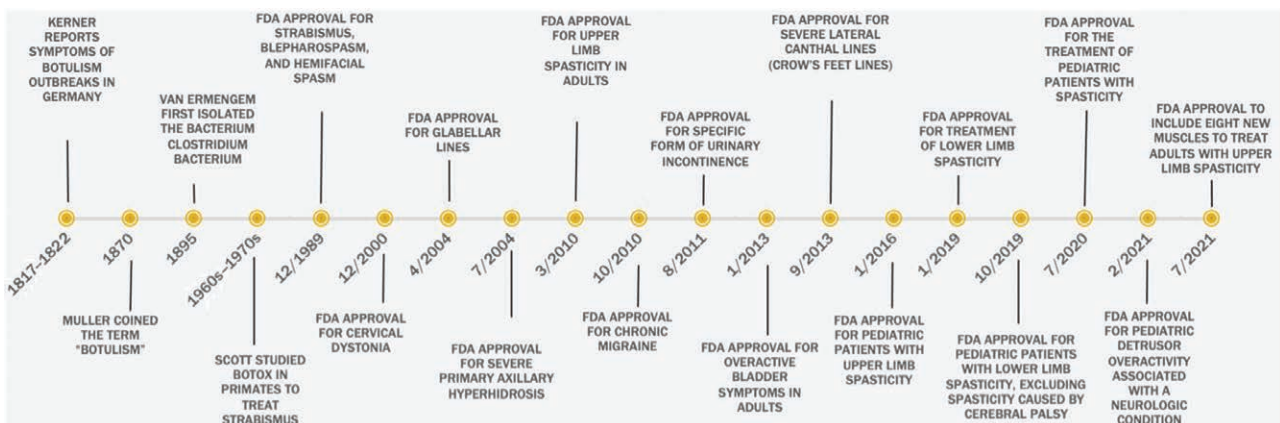
**Question:** What are the many clinical applications of botulinum toxin?

**Findings:** In this literature review, we provide an updated overview of the history, mechanism of action, and clinical applications of the toxin across multiple medical specialties, including the most common adverse effects and recommended Botox dosages.

**Meaning:** Botulinum toxin is a safe and effective therapeutic tool for many FDA-approved and off-label indications. It is frequently utilized by many different medical specialties and its use is continually evolving.

**General Complications**

The effects of BoNT are temporary, taking effect within 24–72 hours and lasting anywhere between 3 and 6 months depending on patient-specific factors, indications, and dosage. Dosing can be expressed in terms of international units, where 1 international unit corresponds to the median lethal dose (LD50) to kill 50% of a colony of mice by intraperitoneal injection. The LD50 for humans is approximately 0.8–0.9 µg by inhalation, 30 ng by ingestion, and 0.09–0.15 µg by intravenous route.<sup>16</sup> Notably, potency Units (U) are specific to each BoNT preparation and thus, are not interchangeable. Treatment is generally safe and well-tolerated by patients when used appropriately; however, a small subset of patients can experience side effects.<sup>17</sup> In most cases, the side effects are localized and self-limiting, such as erythema, edema, bruising, and pain. Systemic complications are rare and severe adverse effects, such as muscle weakness and allergic reactions, tend to be dose-dependent, with the frequency being 33 times higher for therapeutic cases than for cosmetic cases, and can be exacerbated if patients have a history of multiple treatments at the same site within a narrow time interval or concomitant neuromuscular junction disorders.<sup>18</sup> As with any procedures that breach the skin barrier, infections are also a possibility. Management of complications tends to focus on symptomatic treatment. Specific complications of BoNT and any antidotal treatment will



**Fig. 1.** Historical timeline of BoNT and its FDA approvals.

**Table 1. Comparison of FDA-approved Botulinum Toxin (BoNT) Formulations in the United States**

Trade Name (Proprietary Name)	Manufacturer	Serotype	Form	Onset of Action	Length of Therapeutic Effect	Units per Vial	Molecular Weight	Excipients (Per Vial)	Cost Per Unit *	Year of FDA Approval	FDA Approved Indications
Botox (Onabotulinum-toxinA)	Allergan Inc., Irvine, Calif.	A	Powder	3–5 d (up to 2wk)	3–6 mo	50 or 100	900 kDa	HSA (0.5 mg) NaCl (0.9 mg)	Generally most expensive. Ranges from \$10–20 per unit in the United States.	1989	Blepharospasm hemifacial spasm strabismus Cervical dystonia, migraines Upper limb spasticity, lower limb spasticity, neurogenic detrusor overactivity Overactive bladder, forehead lines and wrinkles Cervical dystonia Frown lines and wrinkles Upper limb spasticity Lower limb spasticity
Dysport (Abobotulinum-toxinA)	Ipsen Limited, Berkshire (UK)	A	Powder	Within 24 h	3–6 mo	300 or 500	500–900 kDa	HSA (0.125 mg) Lactose (2.5 mg)	Generally least expensive. Ranges from \$4–8 per unit in the United States.	2009	Cervical dystonia Frown lines and wrinkles Upper limb spasticity Lower limb spasticity
Xeomin (Incobotulinum-toxinA)	Merz Pharmaceuticals GmbH, Frankfurt am Main (Germany)	A	Powder	5–7 d	3–6 mo	100	150 kDa	HSA (1.0 mg) Sucrose (5 mg)	Slightly less than Botox. Ranges from \$8–18 per unit in the United States.	2010	Cervical dystonia Blepharospasm Frown lines Upper limb spasticity Sialorrhea Glabella Lines
Jeuveau (Prabotulinum-toxinA)	Daewoong Pharmaceuticals (South Korea)	A	Powder	3–5 d	3–6 mo	50 or 100	900 kDa	HSA (0.5 mg) NaCl (0.9 mg)	Same or slightly less than Botox. Ranges from \$8–16 per unit in the United States.	2019	Cervical Dystonia Sialorrhea
Myobloc/ Neurobloc (Rimabotulinum-toxinB)	Solstice Neurosciences Inc., South San Francisco, CA, (USA)	B	Solution	3–5 d (up to 2wk)	3–6 mo	2500, 5000, or 10,000	700 kDa	HSA (0.5 mg) NaCl (5.844 mg) Sodium succinate (1.621 mg)	Variable.	2009	Cervical Dystonia Sialorrhea

Of note, Myobloc is the brand name in the United States, Canada, and Korea, whereas Neurobloc is the brand name in the European Union, Norway, and Iceland. Dysport has the fastest time to onset of action, and in general, all BoNT have approximately the same length of therapeutic effect. The average cost of BoNT injections vary depending on severity of the condition, amount of product used, expertise and qualifications of injector, and the geographic office location. Thus, trends on the costs of BoNT have been identified, with Botox typically being the most expensive per unit for treatment of common fine lines and wrinkles, whereas Dysport is the cheapest neuromodulator but more units are typically required to have the same effect. HSA, human serum albumin; NaCl, sodium chloride.

be further discussed in the sections below according to their use indications.

## RESULTS AND DISCUSSION

A detailed description of all the conditions for which BoNT has been shown to be effective in treating is beyond the extent of this article. Only conditions for which BoNT is commonly used will be discussed (Table 2). In addition to indication-specific dosages and administration recommendations of Botox for FDA-approved conditions, the most common adverse reactions will also be discussed (Table 3).

### Ophthalmology

As previously mentioned, the therapeutic potential of BoNT was first recognized in 1981 by Scott following their studies of injecting the toxin into ocular muscles to treat strabismus.<sup>4</sup> In 1989, the FDA approved this agent for the treatment of strabismus, blepharospasms, and hemifacial spasm in patients aged younger than 12 years. The current recommended Botox dose for strabismus is based on the prism diopter correction or prior treatment response.<sup>20</sup> For blepharospasm, 1.25–2.5 U is recommended for each of the approved three sites per affected eye.<sup>20</sup> The role of BoNT therapy in ophthalmology has since expanded to treat several other conditions, including eyelid retraction due to thyroid disease, apraxia of lid opening, entropion, exposure keratopathy, lacrimal hypersecretion, and chronic dry eyes.<sup>21,22</sup>

Complications with BoNT use in ophthalmology arise as a result of toxin diffusion or inadvertent placement into the adjacent muscles. Ptosis of the eyelid is the most common complication of BoNT treatment of strabismus and blepharospasms.<sup>23</sup> Although this effect is almost always temporary and self-resolving, apraclonidine 0.5% (Iopidine) or phenylephrine hydrochloride 2.5% (Neosynephrine) ophthalmic solution may be used. These eye drops are adrenergic agonists that help contract Müller's muscles located beneath the levator muscle and elevate the lash margin.<sup>24,25</sup> Other complications include diplopia, dry eye, blurred vision, and very rarely, acute angle closure glaucoma, and retinal detachments.<sup>26–28</sup> Acute angle closure glaucoma is an interesting adverse effect, as BoNT has been shown to be beneficial in alleviating pain from acute angle closure glaucoma.<sup>29</sup> The exact mechanism behind this is unclear, although BoNT has demonstrated antinociceptive effects through the inhibition of peripheral sensitization in prior studies.<sup>30</sup>

### Neurology

BoNT has many neurological applications in the management of movement disorders and painful conditions. In 2000, the FDA approved its use for the treatment of cervical dystonia in patients 16 and older. The recommended Botox dose for cervical dystonia is dependent on the patient's presentation, including the head and neck position, pain, and degree of muscle.<sup>20</sup> It is advised to use a lower dose initially if there has been no prior treatment and adjust the dose accordingly based on response. Other

movement disorders treated with BoNT besides dystonia include hemifacial spasm, tremor, tics, bruxism, myokymia, neuromyotonia, palatal myoclonus, and spasticity, in addition to synkinesis.<sup>31</sup> Synkinesis refers to abnormal involuntary muscle contraction that occur with voluntary contraction of other muscle groups and in rare cases, such as oculonasal synkinesis, Botox may provide a nonsurgical treatment option to address the paroxysmal contraction.<sup>32</sup> Botox is FDA approved for the treatment of spasticity in both adult and pediatric populations. The recommended dose for spasticity is divided among affected muscles and is as follows: adult upper limb (max 400 U), adult lower limb (300–400 U), pediatric upper limb (3–6 U/kg with a max of 200 U), and pediatric lower limb (4–8 U/kg with a max of 300 U).<sup>20</sup> BoNT therapy has also been proven effective in treating debilitating conditions such as tension headaches, migraines, myofascial pain, temporomandibular joint syndrome, and trigeminal neuralgia.<sup>31</sup> The FDA-approved BoNT in 2010 for the prevention of headaches in adults suffering from chronic migraines who have 15 or more headache days each month, with each episode lasting four hours or more a day.<sup>33</sup> The recommended total Botox dose for chronic migraines is 155 U, with 5 U (0.1 mL) injections per site divided across seven head or neck muscles.<sup>20</sup> The mechanism behind its therapeutic effects relates to the blockade of pain neurotransmission. BoNT has also shown beneficial in treating brachial plexus birth injuries (BPBIs). Administration of the toxin into muscles, such as the pectoralis major, latissimus dorsi, subscapularis, and teres major, help reduce muscle imbalances and excessive inappropriate contractures in brachial plexus birth injuries.<sup>34</sup>

The side effect profile of BoNT use in neurology is generally benign and well-tolerated. For the treatment of cervical dystonia, the most common reported effect is resistance to therapy, with an incidence as high as 6.5%.<sup>35</sup> Other reactions include dysphagia, upper respiratory infection, increased cough, and rhinitis. For the treatment of chronic migraine, adverse reactions of bruising, pain, ptosis, and diplopia have been reported.<sup>36</sup>

### Plastic Surgery and Dermatology

In 2002, BoNT was approved by the FDA for cosmetic use to improve the appearance of vertical eye furrows (glabellar lines) when injected into the corrugator or procerus muscles. Injections into the lateral orbicularis oculi can help eliminate lateral canthal wrinkles (crow's feet) and was granted approval in 2013. Injection into the frontalis muscle targets the horizontal forehead lines while injection into the platysma muscle can improve the appearance of age-related platysma muscle bands. Botox Cosmetic injections are FDA approved only for the glabellar lines, lateral canthal lines, and forehead lines. Wrinkles are caused by dermal atrophy that occurs with aging and repeated contractions of the underlying muscles. When BoNT is injected into these muscles, it causes relaxation of the muscle and improve appearance of overlying lines. The recommended dose for glabellar lines is 4 U (0.1 mL) into each of the five sites, 4 U (0.1 mL) into each of the three sites per side for lateral canthal lines, and 4

**Table 2. Common Clinical Applications of Botulinum Toxin (BoNT) according to Specialty**

Specialty	FDA-approved Use ( <i>Indication-specific Recommended Dosage</i> )	Off-label Use
Ophthalmology	<ul style="list-style-type: none"> <li>• Strabismus* (<i>variable</i>)</li> <li>• Blepharospasm (1.25–2.5 U into each of the three sites per affected eye)</li> <li>• Hemifacial spasm*</li> </ul>	<ul style="list-style-type: none"> <li>• Eyelid retraction due to thyroid disease</li> <li>• Apraxia of lid opening</li> <li>• Entropion</li> <li>• Exposure keratopathy</li> <li>• Lacrimal hypersecretion</li> <li>• Chronic dry eyes</li> <li>• Pain relief following acute angle closure glaucoma</li> </ul>
Neurology	<ul style="list-style-type: none"> <li>• Cervical dystonia (<i>variable</i>)</li> <li>• Spasticity*                             <ul style="list-style-type: none"> <li>└ Adult upper limb spasticity (400 U total)</li> <li>└ Adult lower limb spasticity (300–400 U total)</li> <li>└ Pediatric upper limb spasticity (3–6 U/kg; 200 U total)</li> <li>└ Pediatric lower limb spasticity (4–8 U/kg; 300 U total)</li> </ul> </li> <li>• Chronic migraines (5 U (0.1 mL) injections per site divided across seven head or neck muscles; total 155 U)</li> </ul>	<p><i>Movement disorders:</i></p> <ul style="list-style-type: none"> <li>• Other types of dystonia (laryngeal, limb, oromandibular, orolingual, truncal)</li> <li>• Hemifacial spasm*</li> <li>• Tremor</li> <li>• Tics</li> <li>• Bruxism*</li> <li>• Myokymia and synkinesis (ie, oculonasal synkinesis)</li> <li>• Palatal myoclonus</li> </ul> <p><i>Painful disorders:</i></p> <ul style="list-style-type: none"> <li>• Tension headaches</li> <li>• Myofascial pain syndrome</li> <li>• Temporomandibular joint (TMJ) disorders* trigeminal Neuralgia</li> <li>• Brachial plexus injury*</li> </ul> <p><i>Cosmetic use:</i></p> <ul style="list-style-type: none"> <li>• Eyebrow depression</li> <li>• Horizontal nasal bridge lines</li> <li>• Horizontal forehead lines</li> <li>• Vertical lip lines</li> <li>• Ptosis of lateral commissure</li> <li>• Platysmal neck bands</li> <li>• Gummy smile</li> <li>• Peau d'orange chin</li> </ul> <p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Bruxism*</li> <li>• Masseter hypertrophy</li> <li>• TMJ dysfunction*</li> <li>• Hyperhidrosis in other regions, such as the palms and soles</li> <li>• Hidradenitis suppurativa</li> <li>• Frey's syndrome</li> <li>• Congenital talipes equinovarus</li> <li>• Idiopathic toe walking</li> <li>• Brachial plexus injury*</li> <li>• Sport injuries (ie, lateral epicondylitis/tennis elbow and tendon repair)</li> <li>• Posttraumatic elbow stiffness caused by heterotopic ossification</li> <li>• Club foot</li> <li>• Piriformis syndrome</li> </ul>
Plastic surgery and dermatology	<ul style="list-style-type: none"> <li>• Glabellar lines (4 U (0.1 mL) into each of the five sites; 20 U total)</li> <li>• Lateral canthal lines (4 U (0.1 mL) into each of the three sites per side; 24 U total)</li> <li>• Forehead lines (4 U (0.1 mL) into each of five forehead lines; 20 U total)</li> <li>• Axillary hyperhidrosis (50 U per axilla)</li> </ul>	<p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Hyperhidrosis in other regions, such as the palms and soles</li> <li>• Hidradenitis suppurativa</li> <li>• Frey's syndrome</li> <li>• Congenital talipes equinovarus</li> <li>• Idiopathic toe walking</li> <li>• Brachial plexus injury*</li> <li>• Sport injuries (ie, lateral epicondylitis/tennis elbow and tendon repair)</li> <li>• Posttraumatic elbow stiffness caused by heterotopic ossification</li> <li>• Club foot</li> <li>• Piriformis syndrome</li> </ul> <p><i>Esophageal:</i></p> <ul style="list-style-type: none"> <li>• Achalasia</li> <li>• Diffuse esophageal spasms</li> </ul> <p><i>Gastroduodenal:</i></p> <ul style="list-style-type: none"> <li>• Gastroparesis</li> </ul> <p><i>Anorectal:</i></p> <ul style="list-style-type: none"> <li>• Chronic anal fissures</li> <li>• Rectal fissures or spasms</li> <li>• Anismus</li> </ul> <p><i>Biliary:</i></p> <ul style="list-style-type: none"> <li>• Sphincter of oddi dysfunction</li> </ul> <p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Proctalgia fugax</li> <li>• Prostatic obstruction</li> <li>• Sterile prostatitis</li> <li>• Outflow obstruction Symptoms</li> <li>• Urinary retention</li> <li>• Vaginismus</li> <li>• Vulvodynia</li> <li>• Chronic pelvic pain</li> <li>• Painful bladder syndrome/interstitial cystitis</li> <li>• Raynaud's phenomenon</li> </ul>
Orthopedics	<ul style="list-style-type: none"> <li>• Spasticity*                             <ul style="list-style-type: none"> <li>└ Adult upper limb spasticity (400 U total)</li> <li>└ Adult lower limb spasticity (300–400 U total)</li> <li>└ Pediatric upper limb spasticity (3–6 U/kg; 200 U total)</li> <li>└ Pediatric lower limb spasticity (4–8 U/kg; 300 U total)</li> </ul> </li> </ul>	<p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Proctalgia fugax</li> <li>• Prostatic obstruction</li> <li>• Sterile prostatitis</li> <li>• Outflow obstruction Symptoms</li> <li>• Urinary retention</li> <li>• Vaginismus</li> <li>• Vulvodynia</li> <li>• Chronic pelvic pain</li> <li>• Painful bladder syndrome/interstitial cystitis</li> <li>• Raynaud's phenomenon</li> </ul>
Gastrointestinal	None	<p><i>Esophageal:</i></p> <ul style="list-style-type: none"> <li>• Achalasia</li> <li>• Diffuse esophageal spasms</li> </ul> <p><i>Gastroduodenal:</i></p> <ul style="list-style-type: none"> <li>• Gastroparesis</li> </ul> <p><i>Anorectal:</i></p> <ul style="list-style-type: none"> <li>• Chronic anal fissures</li> <li>• Rectal fissures or spasms</li> <li>• Anismus</li> </ul> <p><i>Biliary:</i></p> <ul style="list-style-type: none"> <li>• Sphincter of oddi dysfunction</li> </ul> <p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Proctalgia fugax</li> <li>• Prostatic obstruction</li> <li>• Sterile prostatitis</li> <li>• Outflow obstruction Symptoms</li> <li>• Urinary retention</li> <li>• Vaginismus</li> <li>• Vulvodynia</li> <li>• Chronic pelvic pain</li> <li>• Painful bladder syndrome/interstitial cystitis</li> <li>• Raynaud's phenomenon</li> </ul>
Urology and gynecology	<ul style="list-style-type: none"> <li>• Adult neurogenic detrusor overactivity (~6.7 U (0.1 mL) injections across 30 sites into detrusor; 200 U total)</li> <li>• Pediatric neurogenic detrusor Overactivity (0.5 mL injections across 20 sites into detrusor; total dose of 200 U if ≥34 kg and 6 U/kg if &lt;34 kg)</li> <li>• Nonneurogenic overactive bladder (5 U (0.5 mL) injections across 20 sites into detrusor; 100 U total)</li> </ul>	<p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Proctalgia fugax</li> <li>• Prostatic obstruction</li> <li>• Sterile prostatitis</li> <li>• Outflow obstruction Symptoms</li> <li>• Urinary retention</li> <li>• Vaginismus</li> <li>• Vulvodynia</li> <li>• Chronic pelvic pain</li> <li>• Painful bladder syndrome/interstitial cystitis</li> <li>• Raynaud's phenomenon</li> </ul>
Rheumatology	None	<p><i>Other indications:</i></p> <ul style="list-style-type: none"> <li>• Obesity</li> <li>• Proctalgia fugax</li> <li>• Prostatic obstruction</li> <li>• Sterile prostatitis</li> <li>• Outflow obstruction Symptoms</li> <li>• Urinary retention</li> <li>• Vaginismus</li> <li>• Vulvodynia</li> <li>• Chronic pelvic pain</li> <li>• Painful bladder syndrome/interstitial cystitis</li> <li>• Raynaud's phenomenon</li> </ul>

\*Denotes conditions that may be treated across multiple specialties. It is important to note that this is not an exhaustive list.

**Table 3. Summary of Common BoNT Complications and their Management**

	Complications	Management of Complications
<b>Local injection reactions</b>	Pain	Ice, EMLA cream, slow injection technique, pinching, use of smaller needles
	Swelling and bruising Erythema Headache Infection	Ice, arnica, avoidance of blood thinners and NSAIDs Ice Analgesics Aseptic injection technique, antibiotics (topical or oral)
Distant spread from injection site	Ptosis	Injection technique, apraclonidine 0.5% (Iopidine) or phenylephrine hydrochloride 2.5% (Neosynephrine) ophthalmic solution
	Dysphagia or dysarthria	Very rarely requires hospitalizations and tends to self-resolve in a few weeks. Avoid injection into sternocleidomastoid muscle. Symptomatic management and monitoring is key
	Unsatisfactory aesthetic results Ophthalmic emergencies (ie, acute angle closure glaucoma, retinal detachments)	Self-limiting. Reassure patient Emergency medical management
	Respiratory complications (upper respiratory infection, increased cough)	Symptomatic management but emergency medical management if severe
<b>Systemic involvement</b>	Urinary complications (urinary tract infections, urinary retention)	Screenings for infection before treatment. Prophylactic antibiotic use
	Hypersensitivity reaction	Antihistamine, steroids, epinephrine
	Antibodies against botulinum toxin	Patients typically build resistance to treatment. They may require more units for effect or fail to respond to treatment overall. This is non-life-threatening and does not need intervention. May be prevented by avoiding shorter dosing intervals and higher dosages per injection cycle
	Systemic botulism	Avoid any medications that may potentiate botulinum toxin effects (ie, aminoglycosides, quinidine, anticholinergics, muscle relaxants). Emergency medical management

Many of these adverse reactions are self-limiting and can be prevented with proper injection technique. However, it is important to be aware of more serious potential complications to timely manage them.

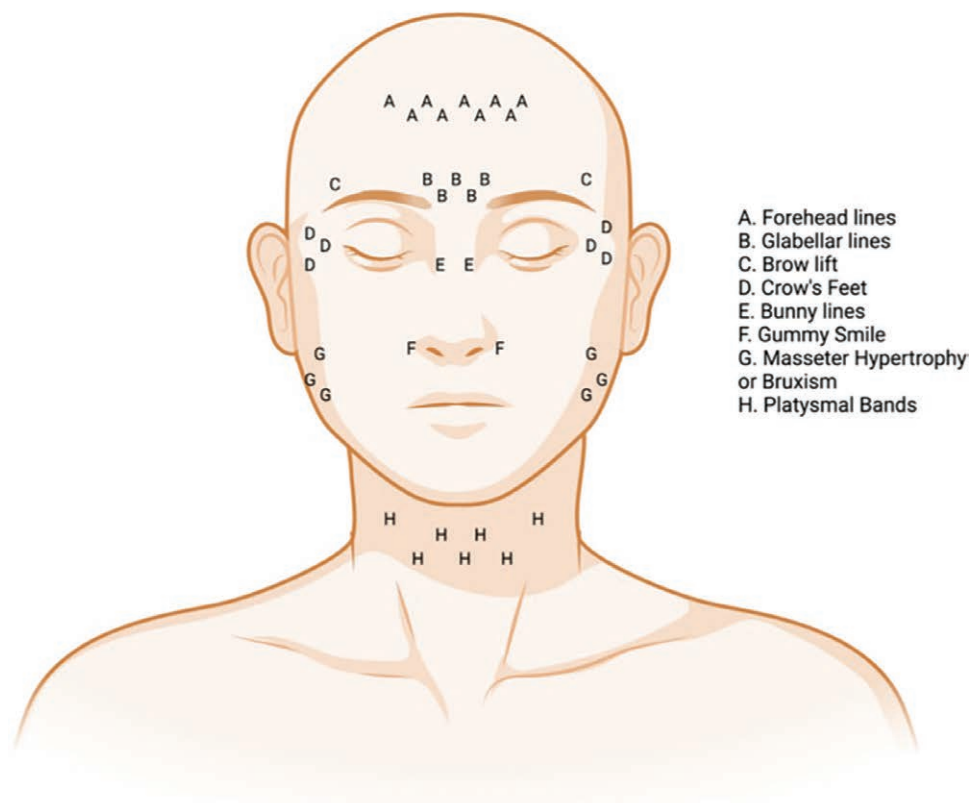
U (0.1 mL) into each of the five sites for forehead lines, adding up to a final total of 40 U.<sup>37</sup> Fig. 2 provides a brief overview of the frequently injected sites on the face. Other off-label applications in facial rejuvenation include but are not limited to eyebrow depression, nasal bridge lines, perioral rhytids (“smokers lines”), and mesolabial folds (“marionette lines”). Conditions such as migraines, vascular spasms of the hand, and facial paralysis secondary to interventions such as a facelift may also be treated by plastic surgeons. In addition to cosmesis, BoNT has proven therapeutic benefit for the treatment of hyperhidrosis, a condition characterized by excessive sweating in areas such as the axillae, palms, and soles. As of 2004, BoNT is FDA approved for the treatment of severe primary axillary hyperhidrosis refractory to other topical therapeutics. The recommended Botox dose for axillary hyperhidrosis is 50 U per axilla.<sup>20</sup> In a similar manner, BoNT also exerts a therapeutic effect in patients with gustatory sweating of the cheek, also known as Frey’s syndrome.<sup>38</sup> Masseter hypertrophy, although seldom presents a significant issue, may cause pain in some individuals, especially those with TMJ dysfunction or bruxism. BoNT injection into the masseter muscle has reportedly improved pain, and also reduced the size and volume of the muscle.<sup>39</sup> BoNT use for this clinical phenomenon is not FDA-approved yet, and further studies are needed to assess its efficacy and safety.<sup>39</sup>

Complications of cosmetic use of BoNT are typically self-limited and localized to the site of injection. These include the aforementioned pain, erythema, and bruising effects. Diffusion of the toxin during treatment of

glabellar lines or periorbital wrinkles may result in eyelid ptosis, with the most severe cases interfering with vision and requiring treatment with mydriatic agents such as apraclonidine 0.5% (Iopidine) or phenylephrine hydrochloride 2.5% (Neosynephrine) ophthalmic drops.<sup>25</sup> Other adverse reactions associated with Botox treatment of axillary hyperhidrosis include injection site pain and ecchymosis, nonaxillary sweating, pharyngitis, and flu syndrome.

**Orthopedic Surgery**

A broad range of clinical disorders in orthopedics may be addressed with BoNT therapy. However, many have underlying pathophysiology similar to that of muscle over-activity and/or spasticity and thus, may also be considered as neurological in nature. The first report of BoNT use in orthopedics was published in 1993 and it described the use of Botox injection to treat spasticity in children with cerebral palsy.<sup>40</sup> Spasticity related to other etiologies, such as multiple sclerosis, head injury, or spinal injury, may also be treated with BoNT injection. FDA approval and dosage recommendations for spasticity have already been discussed in the neurology section above. BoNT has also been reported to be useful in the treatment of piri-formis syndrome, brachial plexus palsy, congenital talipes equinovarus, idiopathic toe walking, and sports-related or other posttraumatic injuries.<sup>41,42</sup> It is important to be cognizant of toxin diffusion into surrounding tissues leading to weakness or paralysis of unwanted musculature. Major serious adverse events are of low incidence, but several accounts of incontinence and respiratory complications



**Fig. 2.** Frequently treated areas on the face and neck with BoNT. Figure created with BioRender.com.

have been reported in children with cerebral palsy treated with BoNT.<sup>43,44</sup> The other mentioned BoNT applications are novel and limited in data availability. Subsequent studies are needed to evaluate the long-term complications, if any, of BoNT use in orthopedics.

### Gastrointestinal

BoNT has proven to be effective in the management of several gastrointestinal conditions, in particular, those characterized by spasticity of the smooth muscle. Injection into the lower esophageal sphincter has demonstrated impressive results in patients with achalasia and provided a useful alternative treatment in patients who are not candidates for invasive procedures.<sup>45</sup> The use of BoNT in treating anal fissures has also been extensively studied and injection into the anal sphincter has been shown to improve the resolution of chronic anal fissures.<sup>46</sup> Other conditions treated may include diffuse esophageal spasm, gastroparesis, Sphincter of Oddi dysfunction, anismus, anal fissures, and rectal spasms or Proctalgia fugax.<sup>47,48</sup> Many trials have attempted to use BoNT injection into the antrum or body of the stomach to slow down gastric emptying for weight loss in patients with morbid obesity; however, the results have not been statistically significant.<sup>49,50</sup> Although gastroenterologists routinely use BoNT, the FDA has not yet approved its use for any gastrointestinal indications.

Injections of BoNT into the esophagus for relief of symptoms in achalasia and other spastic esophageal motility disorders have been associated with mild side effects

related to the injection itself or from decreased lower esophageal pressure. However, a few rare complications of acute mediastinitis and acute urinary retention have been reported.<sup>51</sup> There has been one reported case of systemic botulism toxicity secondary to BoNT treatment for gastroparesis.<sup>52</sup> However, it should be noted that the patient had a type of muscular dystrophy known as Emery-Dreifuss and in general, BoNT injection is contraindicated in those with existing neuromuscular disorders due to a baseline reduction in acetylcholine responsiveness. Short term incontinence of gas or stool is a self-resolving side effect in the treatment of chronic anal fissure.<sup>47</sup> Overall, the adverse effects are transient and reversible with use of BoNT in the treatment of esophageal, gastroduodenal, anorectal, and biliary disorders.

### Urology and Gynecology

BoNT therapy is currently FDA approved for the treatment of neurogenic detrusor overactivity, which results in presentations such as urinary incontinence, overactive bladder syndrome, and non-neurogenic overactive bladder syndrome.<sup>53</sup> For adult detrusor overactivity with an underlying neurologic condition, the recommended Botox dose is approximately 6.7 U (1 mL) injections across 30 sites in the detrusor muscle for a total of 200 U, and 0.5 mL injections across 20 sites in the detrusor muscle (total dose 200 U if  $\geq 34$  kg and 6 U/kg if  $< 34$  kg) for pediatric detrusor overactivity with an underlying neurologic condition.<sup>20</sup> In contrast, the

recommended Botox dose for overactive bladder alone without an underlying neurologic condition is 5 U (0.5 mL) injections across 20 sites in the detrusor muscle for a total dose of 100 U.<sup>20</sup> Off-label use of the toxin is also commonly done for a variety of other genito-urological conditions, including detrusor sphincter dyssynergia, prostatic obstruction, painful bladder syndrome, and other pelvic floor disorders like vaginismus and chronic pelvic pain.<sup>54–56</sup>

For treatment of overactive bladder syndrome and detrusor overactivity, the most common adverse effects are urinary tract infection and urinary retention.<sup>57</sup> These complications could possibly be avoided with screenings for acute urinary tract infections before treatment and prophylactic antibiotic use. The reported complications of BoNT injections for gynecologic indications vary from urinary retention to constipation.<sup>58</sup> In general, use of BoNT in the treatment of multiple urological and gynecological disorders appears to be safe and effective.

### Rheumatology

In recent years, BoNT has garnered increasing interest for its use in Raynaud's phenomenon, a condition characterized by an exaggerated vasoconstrictive physiological response of the extremities provoked by cold exposure or emotional stress. The first application for this purpose occurred in 2004, which demonstrated improved blood flow. Subsequently, further studies have proved BoNT's ability to increase blood flow, relieve painful symptoms of vasospasms, and prevent ischemic ulcerations in these patients. The proposed mechanism of action of BoNT efficacy in Raynaud's revolves around the agent's ability to inhibit arteriolar vasoconstriction in a dose-dependent manner via cleavage of SNAP-25 in sympathetic neurons, thus blocking the release of norepinephrine.<sup>59</sup> The most common complication reported is a transient intrinsic weakness of the hand.<sup>60</sup>

### CONCLUSIONS

The clinical applications of BoNT are extensive as it is used across different medical specialties. The prevention of acetylcholine release at cholinergic junctions makes BoNT effective in the treatment and management of numerous conditions characterized by hyperactivity of muscles and glands. It is important to note that this is not an exhaustive review and that many of the conditions described are not mutually exclusive to any one particular specialty. The main purpose of this review is to provide a brief updated overview of the history, mechanism of action, and most common clinical applications of BoNT therapy across multiple medical specialties, including their complications and recommended Botox dosages.

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