**Botulinum Toxin**

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**Overview**

Botulinum toxin (abbreviated either as BTX or BoNT) is produced by *Clostridium botulinum,* a gram-positive anaerobic bacterium. The clinical syndrome of botulism can occur following ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from a wound infection.

BoNT is broken into 7 neurotoxins (labeled as types A, B, C [C1, C2], D, E, F, and G), which are antigenically and serologically distinct but structurally similar. Human botulism is caused mainly by types A, B, E, and (rarely) F. Types C and D cause toxicity only in animals.

The various botulinum toxins possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the FDA were intended to reinforce these differences and prevent medication errors. The products and their approved indications include the following:

* [OnabotulinumtoxinA](http://reference.medscape.com/drug/botox-cosmetic-onabotulinumtoxina-999222) (Botox, Botox Cosmetic)
	+ Botox - Cervical dystonia, severe primary axillary hyperhidrosis, strabismus, blepharospasm, neurogenic detrusor overactivity, chronic migraine, upper limb spasticity
	+ Botox Cosmetic - Moderate-to-severe glabellar lines
* [AbobotulinumtoxinA](http://reference.medscape.com/drug/dysport-abobotulinumtoxina-999220) (Dysport) - Cervical dystonia, moderate-to-severe glabellar lines
* [IncobotulinumtoxinA](http://reference.medscape.com/drug/xeomin-incobotulinumtoxina-999589) (Xeomin) - Cervical dystonia, blepharospasm
* [RimabotulinumtoxinB](http://reference.medscape.com/drug/myobloc-rimabotulinumtoxinb-999221) (Myobloc) - Cervical dystonia

The BoNT molecule is synthesized as a single chain (150 kD) and then cleaved to form the dichain molecule with a disulfide bridge (see image below).

Botulinum toxin structure (schematic diagram).

The light chain (~50 kD - amino acids 1-448) acts as a zinc (Zn2+) endopeptidase similar to tetanus toxin with proteolytic activity located at the N-terminal end (see image below). The heavy chain (~100 kD - amino acids 449-1280) provides cholinergic specificity and is responsible for binding the toxin to presynaptic receptors; it also promotes light-chain translocation across the endosomal membrane.

Proteolytic activity is located at the N-terminal end of the light chain of botulinum toxin type A.

For patient education resources, see the [Procedures Center](http://www.emedicinehealth.com/Collections/SU304.asp), as well as [BOTOX® Injections](http://www.emedicinehealth.com/articles/40377-1.asp).

**History**

The German physician and poet Justinus Kerner (1786-1862) first developed the idea of a possible therapeutic use of botulinum toxin, which he called "sausage poison."

* In 1870, Muller (another German physician) coined the name botulism. The Latin form is *botulus*, which means sausage.
* In 1895, Professor Emile Van Ermengem, of Belgium, first isolated the bacterium *Clostridium botulinum*.
* In 1928, Dr. Herman Sommer, at the University of California, San Francisco, first isolated in purified form botulinum toxin type A (BoNT-A) as a stable acid precipitate.
* In 1946, Dr. Edward J Schantz succeeded in purifying BoNT-A in crystalline form–cultured *Clostridium botulinum* and isolated the toxin.
* In 1949, Dr. Burgen's ASV group discovered that botulinum toxin blocks neuromuscular transmission.
* In the 1950s, Dr. Vernon Brooks discovered that when BoNT-A is injected into a hyperactive muscle, it blocks the release of acetylcholine from motor nerve endings.
* In 1973, Dr. Alan B. Scott, of Smith-Kettlewell Eye Research Institute, used BoNT-A in monkey experiments; in 1980, he used BoNT-A for the first time in humans to treat strabismus.
* In December 1989, BoNT-A (BOTOX®) was approved by the US Food and Drug Administration (FDA) for the treatment of strabismus, blepharospasm, and hemifacial spasm in patients aged younger than 12 years.
* On December 21, 2000, BoNT-A received FDA approval for treatment of cervical dystonia.
* In 2001, the United Kingdom approved BOTOX®, synthesized by Allergan, for axillary hyperhidrosis (excessive sweating). Canada approved BOTOX® for axillary hyperhidrosis, focal muscle spasticity, and cosmetic treatment of wrinkles at the brow line.
* On April 15, 2002, the FDA announced the approval of BOTOX® Cosmetic to temporarily improve the appearance of moderate-to-severe frown lines between the eyebrows (glabellar lines). On July 21, 2011, the FDA approved incobotulinumtoxinA (Xeomin) for temporary improvement in the appearance of moderate-to-severe glabellar lines, or frown lines between the eyebrows, in adult patients.
* In July 2004, the FDA approved BOTOX® to treat severe underarm sweating, known as primary axillary hyperhidrosis, that cannot be managed by topical agents, such as prescription antiperspirants.
* Although it has not been approved by the FDA for any other indications, the acceptance of BoNT-A use for the treatment of spasticity and muscle pain disorders is growing, with approvals pending in many European countries.
* The clinical use of BoNT-B has been studied, and several products currently are available commercially (eg, MyoBloc, in the United States; NeuroBloc, in Europe). MyoBloc was approved by the FDA on December 8, 2000, for treatment of cervical dystonia, to reduce the severity of abnormal head position and neck pain.
* Use of BoNT-F also is under investigation in patients who have become immunologically resistant to serotypes A and B.
* On April 29, 2009, abobotulinumtoxinA (Dysport) was approved by the FDA for the 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.
* On March 9, 2010, the FDA approved onabotulinumtoxinA (BOTOX®) to treat spasticity in the flexor muscles of the elbow, wrist, and fingers in adults with stroke, traumatic brain injury, or the progression of multiple sclerosis.
* On August 2, 2010, the FDA announced the approval of incobotulinumtoxinA (Xeomin) for the 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 and for blepharospasm in adults previously treated with BOTOX®.
* On October 15, 2010, the FDA approved onabotulinumtoxinA (BOTOX®) injection to prevent headaches in adult patients with chronic migraine. Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.
* On August 24, 2011, the FDA approved onabotulinumtoxinA (BOTOX®) injection for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury, multiple sclerosis) in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

**Mechanism of Action**

Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. This mechanism laid the foundation for the development of the toxin as a therapeutic tool.

Recovery occurs through proximal axonal sprouting and muscle re-innervation by formation of a new neuromuscular junction. De Paiva and colleagues suggest that eventually the original neuromuscular junction regenerates.[1]

* BoNT-A and BoNT-E cleave synaptosome-associated protein (SNAP-25), a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles.
* BoNT-B, BoNT-D, and BoNT-F cleave a vesicle-associated membrane protein (VAMP), also known as synaptobrevin.
* BoNT-C acts by cleaving syntaxin, a target membrane protein.

Table 1. Botulinum Toxin Types, Target Sites, Discoverers, and Year Discovered (Open Table in a new window)

|  |  |  |  |
| --- | --- | --- | --- |
| **Type** | **Target** | **Discoverer** | **Year** |
| A | SNAP-25 | Landman | 1904 |
| B | VAMP | Ermengem | 1897 |
| C1 | Syntaxin | Bengston and Seldon | 1922 |
| D | VAMP | Robinson | 1929 |
| E | SNAP-25 | Gunnison | 1936 |
| F | VAMP | Moller and Scheibel | 1960 |
| G | VAMP | Gimenez and Ciccarelli | 1970 |

**Preparations**

The different preparations of BoNT-A, onabotulinumtoxinA (BOTOX®; Allergan; Irvine, Calif), abobotulinumtoxinA (Dysport; Ipsen; Paris, France), incobotulinumtoxinA (Xeomin; Merz Pharmaceuticals, Frankfurt, Germany) and CS-BOT (Chiba Serum Institute; Chiba, Japan), differ in potency.

* BoNT-A is prepared by laboratory fermentation of *C botulinum* cultures. Crude botulinum toxin is a protein with a molecular weight of about 190,000 Daltons. After purification, the toxin is diluted with human serum albumin, bottled in vials, lyophilized (freeze-dried), and sealed.
* Each freeze-dried vial containing 100 units (U) of BoNT-A is reconstituted with preservative-free normal saline (1-5 mL) just before use. The manufacturer recommends that the toxin be used within 4 hours of reconstitution.
* The potency of BoNT-A is measured in mouse units (MU). One MU of BoNT-A is equivalent to the amount of toxin that kills 50% of a group of 20 g Swiss-Webster mice within 3 days of intraperitoneal injection (LD50).
* According to one report, 1 nanogram of toxin contains approximately 20 U of BOTOX® (ie, 1 U of BOTOX® is equal to approximately 0.05 nanogram of the toxin).
* According to another report comparing the 3 different preparations of BoNT-A, 1 nanogram of Dysport contains approximately 40 MU, whereas 1 nanogram of the BOTOX® contains approximately 4 MU, and 1 nanogram of CS-BOT contains approximately 15.2 MU.
* LD50 of BoNT-A for a 70-kg adult male has been calculated to be 2500-3000 U (35-40 U/kg).
* Minimum lethal dose of BoNT-B in monkeys is 2400 U/kg.
* Clinically, 1 U of BoNT-A (BOTOX®) is approximately equivalent to 3 U of Dysport.[2]
* Standardization efforts are underway using measurements of the toxin's pharmacologically relevant actions (eg, median paralysis unit).
* BoNT-B is marketed in the United States as MyoBloc. This preparation is a ready-to-use solution that does not require reconstitution; it is available in 3 vial sizes (ie, 2500 U, 5000 U, and 10,000 U) and is stable for up to 21 months in refrigerator storage.

**Therapeutic Uses**

**Therapeutic uses of botulinum toxin injection**

* Focal dystonias - Involuntary, sustained, or spasmodic patterned muscle activity
	+ Cervical dystonia (spasmodic torticollis)[3, 4]
	+ Blepharospasm (eyelid closure)
	+ Laryngeal dystonia (spasmodic dysphonia)
	+ Limb dystonia (writer's cramp)
	+ Oromandibular dystonia
	+ Orolingual dystonia
	+ Truncal dystonia
* Spasticity - Velocity-dependent increase in muscle tone
	+ [Stroke](http://www.medscape.com/resource/stroke)[5, 6]
	+ Traumatic brain injury
	+ Cerebral palsy
	+ [Multiple sclerosis](http://www.medscape.com/resource/ms)
	+ [Spinal cord injury](http://www.medscape.com/resource/spine)
* Nondystonic disorders of involuntary muscle activity
	+ Hemifacial spasm
	+ [Tremor](http://www.medscape.com/viewarticle/572015)
	+ Tics
	+ Myokymia and synkinesis
	+ Myoclonus (tensor veli palatini muscle [middle ear], causing tinnitus)
	+ Hereditary muscle cramps
	+ Nocturnal bruxism[7]
	+ Trismus[8]
	+ Anismus[9]
* Strabismus (disorder of conjugate eye movement) and nystagmus
* Chronic pain and disorders of localized muscle spasms
	+ Chronic low [back pain](http://www.medscape.com/resource/back-pain)[10]
	+ Myofascial pain syndrome[11]
	+ Tension [headache](http://www.medscape.com/resource/headache)[12, 13]
	+ Chronic [migraine headache](http://www.medscape.com/viewarticle/555844)[14, 15, 16, 17]
	+ Medication overuse headache[18]
	+ Lateral epicondylitis[19]
	+ Knee pain[20, 21]
	+ Shoulder pain[22, 23]
	+ Neuropathic pain[24, 25]
* Smooth muscle hyperactive disorders
	+ Neurogenic bladder – Detrusor hyperreflexia[26, 27, 28, 29]
	+ Detrusor-sphincter dyssynergia[30, 31]
	+ Benign prostatic hypertrophy[32]
	+ Achalasia cardia[33]
	+ [Hirschsprung disease](http://emedicine.medscape.com/article/178493-overview)[34]
	+ Sphincter of Oddi dysfunctions[35]
	+ Hemorhoids[36]
	+ Chronic anal fissures[37]
* Cosmetic use
	+ Hyperkinetic facial lines (glabellar frown lines, crow's feet)
	+ Hypertrophic platysma muscle bands
* Sweating, salivary, and allergy disorders
	+ Axillary and palmar hyperhidrosis
	+ Frey syndrome, also known as auriculotemporal syndrome (gustatory sweating of the cheek after parotid surgery)
	+ Drooling in cerebral palsy and other neurological disorders[38, 39, 40, 41]
	+ Nasal allergy[42]

**Botulinum Toxin Use in Dystonia**

Use of BoNT-A in different types of focal dystonias has been well studied and has proven to be very effective. Botulinum toxin injection is the treatment of choice for cervical dystonia (spasmodic torticollis).[3, 4, 43] This injection benefits the highest percentage of patients in the shortest time and has been proven effective in many double-blind, placebo-controlled trials. Botulinum toxin injection has fewer side effects than do other pharmacologic treatments.

In a double-blind, placebo-controlled trial by Greene and colleagues, 55 patients who previously had failed to find relief in 2 trials of medication received either BoNT or placebo in a double-blinded fashion and were tracked for 12 weeks.[44] Four weeks of open phase then followed when all patients received BoNT. By 6 weeks, 61% of patients showed improvement in head posture, and 39.5% reported reduction of pain. Both measures significantly improved (*P* < .05) compared to controls. During the open phase, patients who previously received placebo exhibited a similar response. Overall, 74% of patients improved by the end of the study.

A study by Brans and colleagues showed that in 64 patients with cervical dystonia, 84% reported long-term benefits in terms of impairment, disability, handicap, and quality of life (QOL).[45]

**Procedure**

Treatment dosages of BoNT-A in the United States have been reported to range from 100-300 U per patient. In a double-blind, placebo-controlled study, Poewe and colleagues demonstrated that magnitude and duration of improvement were greatest after injections of 1000 U of Dysport, but the injections caused significantly more adverse effects.[46] The researchers recommended a lower starting dose of 500 U of Dysport (1 U of BoNT-A = 3 U of Dysport). One hundred U of toxin per mL of preservative-free normal saline are commonly used.

Injections are performed with a Teflon-coated, 24-gauge needle connected to an electromyographic (EMG) machine. Those muscles with highest clinical and EMG activity are injected. Usually, 2-4 separate muscles are injected in 1 session and, in larger muscles, 2-4 sites per muscle are injected.

No general consensus exists among users of BoNT regarding the need for EMG guidance while injecting the compound for cervical dystonia. EMG guidance, however, is helpful, particularly in obese patients whose neck muscles cannot adequately be palpated.

Identifying the specific muscles involved in cervical dystonia prior to the injection is important. Those most commonly injected are the sternocleidomastoid, trapezius, splenius capitis, and levator scapulae muscles. An EMG study of 100 patients found that 2 or 3 muscles commonly are abnormal. Eighty-nine percent of patients with rotating torticollis had involvement of the ipsilateral splenius capitis and contralateral sternocleidomastoid with or without the additional involvement of the contralateral splenius capitis. Patients with laterocollis had ipsilateral sternocleidomastoid, splenius capitis, and trapezius involvement, while retrocollis was produced by bilateral splenius capitis activity.

Beneficial effect from toxin injection usually is apparent in 7-10 days. Maximum response from the toxin is reached in approximately 4-6 weeks and lasts for an average of 12 weeks. Injections usually are repeated every 3-4 months.

**Complications**

Neck weakness, dysphagia, and local pain at the injection site are the most commonly reported side effects. Other adverse effects (eg, local hematoma, generalized fatigue, lethargy, dizziness, dry mouth, dysphonia, flulike syndrome, pain in neighboring muscles) also have been reported.

Most studies have reported side effects in 20-30% of patients per treatment cycle. The incidence of adverse effects varies based on the dosage used (ie, the higher the dose, the more frequent the adverse effects); however, Jankovic and Schwartz reported that incidence of complications was not related to the total dose of BoNT used.[47] Women and patients who received injections into the sternocleidomastoid muscles had significantly higher rates of complications.

Dysphagia has been the most prevalent significant complication and most probably is related to diffusion of the toxin into nearby pharyngeal muscles. In the study by Comella and colleagues, 33% of patients receiving their first dose of botulinum toxin experienced dysphagia.[48] This complication most commonly occurs with injections of the sternocleidomastoid and can be reduced significantly when the dose of toxin administered is 100 U or less.

**Botulinum Toxin Use in Spasticity**

Spasticity is defined as a velocity-dependent increase in muscle tone. Intramuscular injections of BoNT have been studied and found to be useful in the treatment of spasticity in multiple sclerosis (MS), cerebral palsy (CP), stroke, traumatic brain injury (TBI), and spinal cord injury (SCI). Different studies have shown the effectiveness of BoNT-A injection in the management of spasticity.[5]

Table 2. Studies of Botulinum Toxin in the Treatment of Spasticity in Different Disorders (Open Table in a new window)

|  |  |  |
| --- | --- | --- |
| **Clinical Diagnosis** | **Author** | **Study Design** |
| **Multiple Sclerosis** | BeneckeBorg-Stein et al[49] Snow et al[50] Hyman et al[51]  | Open-labelOpen-labelDouble-blind, placebo-controlled, randomized, crossoverDouble-blind, placebo-controlled, randomized, dose-ranging |
| **Spinal Cord Injury** | Bohlega et alTakenaga et al | Open-labelOpen-label |
| **Cerebral Palsy** | Koman et al[52] Koman et al[53] Cosgrove et al[54] Chutorian and RootChutorian, Root, and the BTA study groupCorry et al[55] Fehlings et al[56] Wissel et al[57] Baker et al[58]  | Open-labelDouble-blind, placebo-controlledOpen-labelOpen-labelDouble-blind, placebo-controlled, randomizedDouble-blind, placebo-controlledSingle-blind, randomized, controlledDouble-blind, randomized, placebo-controlledDouble-blind, randomized, placebo-controlledDouble-blind, randomized, placebo-controlled |
| **Stroke** | Das and Park Memin et alGrazko et alDengler et alJabbari et alSimpson et alBhaktha et alSmith et al[59] Childers et al[60] Pittock et al[61] Brashear et al[62] Bakheit et al[63]  | Open-labelOpen-labelDouble-blind, placebo-controlled, crossoverOpen-labelDouble-blind, placebo-controlled, crossoverDouble-blind, placebo-controlledDouble-blind, placebo-controlled, randomizedDouble-blind, placebo-controlled, randomizedDouble-blind, placebo-controlled, randomizedDouble-blind, placebo-controlled, randomizedDouble-blind, placebo-controlled, randomized |
| **Traumatic Brain Injury** | Yablon et al[64] Pavesi et al[65]  | Open-labelOpen-label |

**Pain Management**

Use of BoNT-A in the management of different pain disorders is being studied. At this time, indications for the use of BoNT in managing muscle pain disorders still are controversial. The exact mechanism of action behind BoNT's analgesic effect is not known; however, a study by Purkiss and colleagues showed that BoNT inhibits calcium-dependent release of substance P in embryonic dorsal root ganglia.[66] Hence, BoNT may, by blocking the release of substance P, produce an analgesic effect through peripheral inhibition of C and A delta fibers. In a double-blind, randomized, placebo-controlled study, Foster and colleagues showed the efficacy of 200 U of BoNT-A injection, employing 40 U per site at 5 lumbar paravertebral levels on the side of maximum discomfort in chronic low back pain patients.[67] Different studies on the use of BoNT in the management of different pain disorders are listed in Table 3.

Table 3. Studies on the Use of Botulinum Toxin in Pain Management (Open Table in a new window)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Author(s) (Year)** | **Clinical Condition** | **Study Type** | **N** | **Results** |
| Zwart et al (1994)[68]  | Tension headache | Open-label | 6 | Unilateral temporal injection not effective |
| Sherman et al (1995)[69]  | Chronic pancreatitis | Open-label | 7 | Not effective |
| Paulson et al (1996)[70]  | Fibromyalgia | Randomized, controlled | 5 | Not effective |
| Wheeler et al (1998)[71]  | Myofascial pain[72]  | Randomized, double-blind, controlled | 33 | No significant difference, second injection effective? |
| Wheeler (1998)[73]  | Tension headache | Open-label | 4 | Effective in 4 patients |
| Schulte-Mattler et al (1999)[74]  | Tension headache | Open-label | 9 | Effective in 8 of 9 patients |
| Freund et al (1999)[75]  | Temporomandibular disorders | Open-label | 15 | Effective |
| Freund et al (2000)[76]  | Temporomandibular disorders | Open-label | 46 | Effective |
| Silberstein et al (2000)[77]  | Migraine headache | Double-blind, vehicle-controlled | 123 | Effective prophylaxis |
| Rollnik et al (2000)[78]  | Tension headache | Double-blind, placebo-controlled | 21 | Not effective |
| Freund et al (2000)[79]  | Cervicogenic Headache | Randomized, double-blind, placebo-controlled | 26 | Effective |
| Freund et al (2000)[80]  | Whiplash associated with neck pain | Randomized, double-blind, placebo-controlled | 26 | Effective |
| Barwood et al (2000)[81]  | Severe postoperative pain and spasm in cerebral palsy | Randomized, double-blind, placebo-controlled | 16 | Effective prophylaxis |
| Porta (2000)[82]  | Chronic myofascial pain syndrome | Randomized, controlled, comparative | 40 | BOTOX® better than methylprednisolone |

For more information, see Medscape Reference article [Botulinum Toxin in Pain Management](http://emedicine.medscape.com/article/325574-overview).

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