

Botulinum Toxin

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Overview

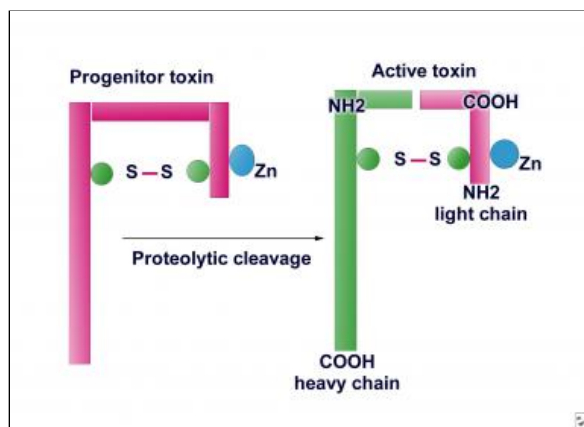
Botulinum toxin (abbreviated either as BTX or BoNT) is produced by *Clostridium botulinum*, a gram-positive anaerobic bacterium.^[1] The clinical syndrome of botulism can occur following ingestion of contaminated food, from colonization of the infant gastrointestinal tract, or from a wound infection.

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** (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, moderate to severe lateral canthal lines, known as crow's feet
- **AbobotulinumtoxinA** (Dysport®) - Cervical dystonia, moderate to severe glabellar lines.
- **IncobotulinumtoxinA** (Xeomin®) - Cervical dystonia, blepharospasm, moderate to severe glabellar lines.
- **RimabotulinumtoxinB** (Myobloc®) - Cervical dystonia

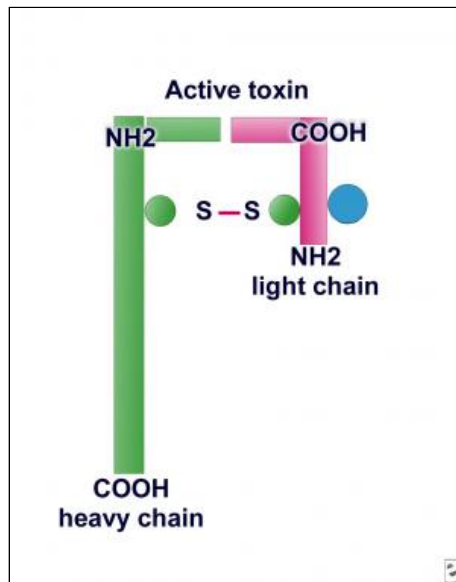
The BoNT molecule is synthesized as a single chain (150 kD) and then cleaved to form the dichain molecule with a disulfide bridge (see image below).



Botulinum toxin structure (schematic diagram).

The light chain (~50 kD - amino acids 1-448) acts as a zinc (Zn^{2+}) 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](#), as well as [BOTOX® Injections](#).

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."^[2]

- 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.
- The acceptance of BoNT-A use for the treatment of different chronic pain disorders is growing. However, it has not been approved by the FDA for any chronic pain conditions except for chronic migraine.
- 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.
- On September 11, 2013, the FDA approved onabotulinumtoxinA (BOTOX®) for the temporary improvement in the appearance of moderate to severe lateral canthal lines, known as crow's feet. This is the only FDA-approved drug treatment option for lateral canthal lines.

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.^[3]

- BoNT-A and BoNT-E cleave synaptosome-associated protein (SNAP-25), a presynaptic membrane protein required for fusion of neurotransmitter-containing vesicles.^[4]
- 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), CS-BOT (Chiba Serum Institute; Chiba, Japan), and Chinese BTX-A (*Prosigne*®; Lanzhou Biological Products Institute, China) differ in potency.^[5]

- 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.
- Median paralysis unit (MPU) is thought to be a more pharmacologically relevant unit of biologic activity. Comparison of the potency ratio based on the MPU values for Dysport and BOTOX® revealed a 2.44-fold difference in potency between these formulations.^[6]
- 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®.^[7]
- Studies of Xeomin® and Prosigne® use unit dosing comparable (1:1) with BOTOX®.^[8, 9]
- An animal study that found that Xeomin® contains the highest specific neurotoxin activity, followed by Dysport®, with BOTOX® having the lowest specific activity.^[10]
- Standardization efforts are underway using measurements of the toxin's pharmacologically relevant actions (eg, median paralysis unit).
- BOTOX® vials contain sodium chloride (0.9 mg) and human albumin (0.5 mg), and the protein load is 5 ng/100 units; Prosigne® vials contain porcine gelatin (5 mg), dextran (25 mg), and sucrose (25 mg), and the protein load is 4-5 ng/100 units of BoNT-A.^[11] BOTOX® is thought to be about 1.5 times more potent than Prosigne®.

- BoNT-B is marketed in the United States as RimaBotulinumB (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 ^[12]

- Focal dystonias - Involuntary, sustained, or spasmodic patterned muscle activity
 - Cervical dystonia (spasmodic torticollis)^[13, 14, 15, 16, 17]
 - Blepharospasm (eyelid closure)^[18]
 - Laryngeal dystonia (spasmodic dysphonia)^[19]
 - Limb dystonia (writer's cramp)
 - Oromandibular dystonia^[18]
 - Orolingual dystonia
 - Truncal dystonia
- Spasticity - Velocity-dependent increase in muscle tone
 - Stroke^[20, 21]
 - Traumatic brain injury^[22]
 - Cerebral palsy
 - Multiple sclerosis
 - Spinal cord injury
- Nondystonic disorders of involuntary muscle activity
 - Hemifacial spasm^[23]
 - Tremor^[24]
 - Tics^[25]
 - Myokymia and synkinesis
 - Tinnitus (due to myoclonus of stapedius muscle^[26] & tensor veli palatini muscle^[27])
 - Hereditary muscle cramps
 - Nocturnal bruxism^[28]
 - Trismus^[29]
 - Anismus^[30]
- Strabismus (disorder of conjugate eye movement) ^[31, 32] and nystagmus
- Chronic pain and disorders of localized muscle spasms
 - Chronic low back pain^[33]
 - Myofascial pain syndrome^[34, 35]
 - Tension headache^[36, 37, 38]
 - Chronic migraine headache^[39, 40, 41, 42]
 - Medication overuse headache^[43]
 - Lateral epicondylitis^[44]
 - Knee pain^[45, 46]
 - Shoulder pain^[47, 48]
 - Neuropathic pain^[49, 50]
- Smooth muscle hyperactive disorders
 - Neurogenic bladder – Detrusor hyperreflexia^[51, 52, 53, 54]
 - Detrusor-sphincter dyssynergia^[55, 56, 57, 58]
 - Benign prostatic hypertrophy^[59, 60, 61]
 - Achalasia cardia^[62, 63]
 - Hirschsprung disease^[64]
 - Sphincter of Oddi dysfunctions^[65, 66]
 - Hemorrhoids^[67, 68]
 - Chronic anal fissures^[69, 70]
 - Raynaud's Phenomenon^[71]
- Cosmetic use
 - Hyperkinetic facial lines (glabellar frown lines, crow's feet)^[72]
 - Hypertrophic platysma muscle bands^[73, 74]

- Sweating, salivary, and allergy disorders
 - Axillary and palmar hyperhidrosis^[75]
 - Frey syndrome, also known as auriculotemporal syndrome (gustatory sweating of the cheek after parotid surgery)^[76]
 - Drooling in cerebral palsy and other neurological disorders^[77, 78, 79, 80, 81]
 - Nasal allergy and allergic rhinitis^[82, 83]

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).^[13, 14, 84] A Cochrane review concluded that a single injection of BoNT-B was effective and safe for treating cervical dystonia.^[85] This injection benefits the highest percentage of patients in the shortest time and has been proven effective in many double-blind, placebo-controlled trials.

BoNT has fewer side effects than do other pharmacologic treatments. The efficacy and safety of BoNT injections for the treatment of certain movement disorders, including blepharospasm, hemifacial spasm, oromandibular dystonia, cervical dystonia, focal limb dystonias, laryngeal dystonia, tics, and essential tremor is ongoing.^[86]

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.^[87] 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).^[88] Mezaki et al described their experience with a Japanese type A toxin for the treatment of cervical and axial dystonias.^[89] Injections were given repeatedly at intervals of 28-30 days to carefully chosen muscles with increased activities, with a maximum dose per session of 300 units. The maximum improvements in subjective and objective ratings were obtained only after repeated injections.

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.^[90] 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.^[91] 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.^[92] 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.^[20]

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	Benecke	Open-label
	Borg-Stein et al ^[93]	Open-label
	Snow et al ^[94]	Double-blind, placebo-controlled, randomized, crossover

	Hyman et al ^[95]	Double-blind, placebo-controlled, randomized, dose-ranging
Spinal Cord Injury	Bohlega et al	Open-label
	Takenaga et al	Open-label
Cerebral Palsy		Open-label
	Koman et al ^[96] Koman et al ^[97]	Double-blind, placebo-controlled
		Open-label
	Cosgrove et al ^[98]	Open-label
	Chutorian and Root	Double-blind, placebo-controlled, randomized
	Chutorian, Root, and the BTA study group	Double-blind, placebo-controlled
	Corry et al ^[99]	Single-blind, randomized, controlled
	Fehlings et al ^[100]	Double-blind, randomized, placebo-controlled
	Wissel et al ^[101]	Double-blind, randomized, placebo-controlled
	Baker et al ^[102]	Double-blind, randomized, placebo-controlled
	Double-blind, randomized, placebo-controlled	
	Open-label	Open-label
	Das and Park Memin et al	Open-label

Stroke	Grazko et al	Double-blind, placebo-controlled, crossover
	Dengler et al	Open-label
	Jabbari et al	Double-blind, placebo-controlled, crossover
	Simpson et al	Double-blind, placebo-controlled
	Bhaktha et al ^[103]	Double-blind, placebo-controlled, randomized
	Smith et al ^[104]	Double-blind, placebo-controlled, randomized
	Childers et al ^[105]	Double-blind, placebo-controlled, randomized
	Pittock et al ^[106]	Double-blind, placebo-controlled, randomized
	Brashear et al ^[107]	Double-blind, placebo-controlled, randomized
Traumatic Brain Injury	Bakheit et al ^[108]	Double-blind, placebo-controlled, randomized
	Yablon et al ^[109]	Open-label
	Pavesi et al ^[110]	Open-label

Pain Management

Use of BoNT-A in the management of different pain disorders is being studied.^[111] 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.^[112] Hence, BoNT may, by blocking the release of substance P, produce an analgesic effect through peripheral inhibition of C and A delta fibers. Based on the research with animal models, BoNT-A in peripheral nociceptive neurons plays a direct role in its peripheral analgesic effect and an indirect role in its

central analgesic effect because of retrograde transport.^[113]

In a double-blind, randomized, placebo-controlled study, Foster and colleagues showed the efficacy of 200 U of BoNT-A injection, using 40 U per site at 5 lumbar paravertebral levels on the side of maximum discomfort, in chronic low back pain patients.^[114]

A Cochrane review regarding the use of BoNT-A injection for chronic low back pain has concluded evidence that BoNT injections improved pain, function, or both better than saline injections was limited, as was evidence this was better than acupuncture or steroid injections.^[115] They recommend further high quality randomized controlled studies.

BoNT-A injection has also been studied for chronic neck pain, cervicogenic headache, and whiplash-associated neck pain; however, a Cochrane review and systematic review and meta-analysis by Langevin et al concluded that current evidence fails to confirm either a clinically important or a statistically significant benefit of BoNT-A injection for whiplash-associated neck pain and chronic neck pain associated with or without cervicogenic headache.^[116, 117]

BoNT-A has been studied to treat different neuropathic pain disorders such as postherpetic neuralgia,^[118] trigeminal neuralgia,^[119, 120] and diabetic peripheral neuropathic pain,^[121] and has shown to be effective in managing pain in these conditions.

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) ^[122]	Tension headache	Open-label	6	Unilateral temporal injection not effective
Sherman et al (1995) ^[123]	Chronic pancreatitis	Open-label	7	Not effective
Paulson et al (1996) ^[124]	Fibromyalgia	Randomized, controlled	5	Not effective
Wheeler et al (1998) ^[125]	Myofascial pain ^[126]	Randomized, double-blind, controlled	33	No significant difference, second injection effective?
Wheeler (1998) ^[127]	Tension headache	Open-label	4	Effective in 4 patients
Schulte-Mattler et al (1999) ^[128]	Tension headache	Open-label	9	Effective in 8 of 9 patients
Freund et al (1999) ^[129]	Temporomandibular disorders	Open-label	15	Effective
Freund et al (2000) ^[130]	Temporomandibular disorders	Open-label	46	Effective
Silberstein et al (2000) ^[131]	Migraine headache	Double-blind, vehicle-controlled	123	Effective prophylaxis
Rollnik et al (2000) ^[132]	Tension headache	Double-blind, placebo-controlled	21	Not effective
Freund et		Randomized,		

al (2000) [133]	Cervicogenic Headache	double-blind, placebo-controlled	26	Effective
Freund et al (2000) [134]	Whiplash associated with neck pain	Randomized, double-blind, placebo-controlled	26	Effective
Barwood et al (2000) ^[135]	Severe postoperative pain and spasm in cerebral palsy	Randomized, double-blind, placebo-controlled	16	Effective prophylaxis
Porta (2000) ^[136]	Chronic myofascial pain syndrome	Randomized, controlled, comparative	40	BOTOX® better than methylprednisolone

For more information, see Medscape Reference article [Botulinum Toxin in Pain Management](#).

Adverse Events

Adverse events due to therapeutic and cosmetic injection of BoNT reported to the FDA include respiratory problems, dysphagia, seizure, flulike syndrome, facial and other muscle weakness, ptosis, and skin and injection site reactions.^[137] Of the 406 reports related to therapeutic use, 217 met the FDA's definition of serious, with 28 deaths and 17 seizures reported. Clinical characteristics submitted to the FDA for therapeutic cases differed from those of cosmetic BoNT cases, which were usually less serious. Most of the adverse effects linked to local tissue diffusion of BoNT. Careful attention to drug dose, dilution, handling, storage, and site of injection are required for optimal treatment outcome and to minimize adverse effects.

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