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Review

# Botulinum toxins: Mechanisms of action, antinociception and clinical applications

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ABSTRACT

Botulinum toxin (BoNT) is a potent neurotoxin that is produced by the gram-positive, spore-forming, anaerobic bacterium, Clostridum botulinum. There are 7 known immunologically distinct serotypes of BoNT: types A, B, C1, D, E, F, and G. Clostridum neurotoxins are produced as a single inactive polypeptide chain of 150 kDa, which is cleaved by tissue proteinases into an active di-chain molecule: a heavy chain (H) of ~100 kDa and a light chain (L) of ~50 kDa held together by a single disulfide bond. Each serotype demonstrates its own varied mechanisms of action and duration of effect. The heavy chain of each BoNT serotype binds to its specific neuronal ecto-acceptor, whereby, membrane translocation and endocytosis by intracellular synaptic vesicles occurs. The light chain acts to cleave SNAP-25, which inhibits synaptic exocytosis, and therefore, disables neural transmission. The action of BoNT to block the release of acetylcholine botulinum toxin at the neuromuscular junction is best understood, however, most experts acknowledge that this effect alone appears inadequate to explain the entirety of the neurotoxin's apparent analgesic activity. Consequently, scientific and clinical evidence has emerged that suggests multiple antinociceptive mechanisms for botulinum toxins in a variety of painful disorders, including: chronic musculoskeletal, neurological, pelvic, perineal, osteoarticular, and some headache conditions.



**Contents**



*Abbreviations:* BoNT, botulinum neurotoxin; BoNT/A, botulinum neurotoxin type A; USFDA, United States Food and Drug Administration; NSF, Soluble N-ethylmaleimide-sensitive factor; NSF, Soluble N-ethylmaleimide-sensitive factor; SNARE complex, adaptor protein receptor complex; Sbr, Synaptobrevin; EHD1, EH (Eps15 homology; SM, (Sec1/Munc18-like) protein; BSA, bovine serum albumin; DAS, digit abduction score; MNA, mouse neutralization assay; MPA, mouse protection assay; MPS, myofascial pain syndrome; ODQ, the Oswestry Disability Questionnaire; TTH, tension-type headache; CDH, chronic daily headache; EM, episodic migraine; PBO, placebo.

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## 1. Introduction

Since its introduction in the late 1970s for strabismus, blepharospasm, and the focal dystonias, botulinum toxin type A (NoBTX-A) has been used increasingly in the treatment of numerous other disorders largely characterized by excessive or inappropriate muscle contraction (Table 1) (Brin, 1997, 1998; Jankovic and Hallett, 1994; Jankovic and Brin, 1997). These disorders include each form of focal dystonia; spasticity; inappropriate contraction in most of the body's sphincters, such as those associated with achalasia, anal spasm, and vaginismus; eye movement disorders including nystagmus; other hyperkinetic disorders including tics and tremors; (Brin, 2000; Jankovic and Brin, 1997) autonomic disorders such as hyperhidrosis; (Heckmann et al., 2001; Naumann and Lowe, 2001; Naumann et al., 2002) and cosmetically troublesome hyperfunctional facial lines (glabellar lines, crow's feet, forehead lines) (Brin, 2000; Blitzer et al., 1993; Binder et al., 1998a; Carruthers and Carruthers, 2001a,b). In addition, BoNT/A has been reported to be useful in the treatment of more commonly occuring pain syndromes, including myofascial pain syndrome, migraine and tension headaches (Brin et al., 2002).

**Table 1**
Therapeutic uses for botulinum toxin.

| |
|---|
| Focal dystonias-sustained muscular activity producing abnormal and functional disability. |
| • Blepharospasm[a] |
| • Cervical (torticollis, anterocollis, laterocollis)[a] |
| • Laryngeal (spasmodic dysphonia) |
| • Oromandibular (opening or closing of the mouth/jaw) |
| • Orolingual (mouth and tongue involved) |
| • Limb (occupational or task-driven, parkinsonism) |
| • Tremor (due to dystonia) |
| Nondystonic disorders of involuntary muscle contraction and movement |
| • Hemifacial spasm[a] |
| • Tremor (essential, parkinsonism) |
| • Myokymia and synkinesis |
| • Tics |
| • Myoclonus |
| • Benign fasiculations |
| • Bruxism |
| Disorders of conjugate eye movement (strabismus[a], nystagmus, oscillopsia) |
| Spasticity (due to stroke, cerebral palsy, multiple sclerosis, brain or spinal cord injury)[a] |
| Cosmetic disorders (hyperhidrosis[a], undesirable wrinkles caused by hyperkinetic muscles[a], e.g., face, anterior neck) |
| Disorders of localized muscle spasm |
| • Sphincter "spasms" |
| o |
| Bladder (detrusor-sphincter dyssynergia) |
| o |
| Gastrointestinal (achalasia, anismus, cricopharyngeal, lower esophagus, rectal) |
| • Skeletal muscle (myofascial pain, lumbar paraspinal muscle spasm, post-operative spasms after prostatectomy or hemorrhoidectomy) |
| Pain Disorders |
| • Headaches (1°-chronic migraine[a] & tension-type; 2°-TMJD, dystonia) |
| • Shoulder pain following stoke (caused by spasticity[a]) |
| • Osteoarthritis of large joints |
| • Pelvic pain (vestibulodynia, pelvic floor muscle spasm, interstitial cystitis) |
| • Neck pain after dissection surgery/radiotherapy for cancer |
| • Neuropathic pain (post-herpetic neuralgia, spinal radiculopathy) |

Conditions for which botulinum toxin has been shown to have proven or promising experimental results (modified from Wheeler, 1997).
[a] FDA approved indications.

In addition, BoNT/A has been reported to be useful in the treatment of more commonly occuring pain syndromes, including myofascial pain syndrome, migraine and tension headaches (Brin et al., 2002).

BoNT/A injections have several advantages over primary drug and surgical therapies in the management of intractable disease. Systemic pharmacologic effects are rare for botulinum toxin type A; permanent destruction of tissue does not occur. Graded degrees of therapeutic effect can be achieved by varying the dose injected and most adverse effects are transient. If the patient has a strong response to therapy and too much muscle weakness occurs, strength gradually returns. The patient's acceptance is high, and in most cases, botulinum toxin therapy is preferred to alternative pharmacotherapy, although drug therapy can be added as needed.

In the discussion that follows, we will refer to the botulinum toxins by serotype (NoBT/A, NoBT/B, etc.) and, when relevant, trade names. NoBT/A is available in 3 different biological formulations. Under the trade name BOTOX® (approved in 1989, U.S.; prior to 1992 marketed as Oculinum®), NoBT/A is manufactured in the United States by Allergan, Inc. It is licensed worldwide, and the product and its precursors have been successfully utilized in clinical trials since the 1970s. In the United States, BOTOX® is approved for treatment of strabismus, blepharospasm, hyperkinetic facial lines, cervical dystonia and chronic migraine. The United States Food and Drug Administration (USFDA) dictates standards of production, buffering, stability, potency and vial size. The European preparation of botulinum toxin type A has the trade name Dysport® (first approved, 1991 U.K.), and is manufactured in the U.K. and distributed by Beaufour-Ipsen Pharmaceuticals in France. This preparation has been used clinically with success, and is licensed for distribution by the Ministry of Health in England. BTX-B is available in the U.S. as MYOBLOC® (Elan Corporation, Ireland) and the same formulation is available in Europe under the name NeuroBloc®. MYOBLOC® was licensed in the U.S. in December, 2000 for treatment of cervical dystonia.Pharmacology of the botulinum toxins