# Botulinum Toxin Type A

(Onabotulinum toxin A/Abobotulinum toxin A)

## Therapeutics

### Brands
- Botox, Botox cosmetic, Dysport, Xeomin, Vistabel, Neuronox

### Generic?
No

### Class
- Neurotoxin

### Commonly Prescribed For
(FDA approved in bold)
- **Chronic migraine**
- **Headache**
- **Diabetic neuropathic pain**
- **Myofascial pain**
- **Cervical dystonia (CD)**
- **Axillary hyperhidrosis (onabotulinum toxin A only)**
- **Strabismus and blepharospasm associated with dystonia (onabotulinum toxin A only)**
- **Upper limb spasticity in adults**
- **Hemifacial spasm**
- **Spasmodic torticollis**
- **Spasmodic dysphonia (laryngeal dystonia)**
- **Writer’s cramp and other task-specific dystonias**
- **Spasticity associated with stroke**
- **Dynamic muscle contracture in cerebral palsy**
- **Acquired nystagmus**
- **Oscillopodia**
- **Sialorrhea (drooling)**
- **Temporomandibular joint dysfunction**
- **Detrusor sphincter dyssynergia**
- **Palmar hyperhidrosis**
- **Tics**
- **Cosmesis**
- **Incontinence due to overactive neurogenic bladder**
- **Achalasia (esophageal motility disorder)**

### How the Drug Works
- Blocks neuromuscular transmission by cleaving SNAP-25 protein, which inhibits the vesicular release of acetylcholine from nerve terminals
- In CD and other dystonias, produces partial denervation of muscle and localized reduction in muscle activity. In hyperhidrosis, produces chemical denervation of sweat gland
- Also appears to inhibit release of neurotransmitters involved in pain transmission (including glutamate, calcitonin gene-related peptide, and substance P) and may enter CNS via retrograde axonal transport

### How Long until It Works
- Usually 2–3 days, with peak effect beginning at 2–3 weeks. Effect is quicker in blepharospasm compared to CD

### If It Works
- Continue to use as long as effective, but monitor for clinical effects

### If It Doesn’t Work
- Increase dose or change injection technique. Some pain disorders may respond better to oral medications
- Patients can develop neutralizing antibodies from prior exposure. Response to a test dose of 15 units (u) in the frontalis muscle indicates a physiologic response. Antibody formulation has not been reported with newer type-A formulations

### Best Augmenting Combos for Partial Response or Treatment Resistance
- Increase dose, number of injections or change site of location

### Tests
- None

## Adverse Effects (AEs)

### How Drug Causes AEs
- Most AEs are related to muscle weakness adjacent to the site of injection. Serious systemic AEs are rare, but injectors should use the lowest dose and be familiar with injection technique to minimize AEs

### Notable AEs
- Injection site pain and hemorrhage, infection, fever, headache, pruritis, and myalgia. Most AEs depend on site of injection
- CD: dysphagia, neck weakness, upper respiratory infection
- Blepharospasm/strabismus: ptosis, diplopia, dry or watery eyes, keratitis (from reduced blinking)
- Spasmodic dysphonia: hypophonia ("breathy" voice)
- Writer's cramp: hand weakness

**Life-Threatening or Dangerous AEs**
- Rarely patients may experience severe dysphagia requiring a feeding tube or leading to aspiration pneumonia
- Use with caution in patients with motor neuropathies or neuromuscular junctional disorders. These patients may be at greater risk for systemic weakness or respirator problems

**Weight Gain**
- Unusual

**Sedation**
- Unusual

**What to Do about AEs**
- Most AEs will improve with time (weeks)

**Best Augmenting Agents for AEs**
- Most AEs cannot be improved with an augmenting agent

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**DOSING AND USE**

**Usual Dose Range**
- The following units are for Botox formulation. The appropriate conversion from Botox to Dysport is unknown, but studies of CD suggest a ratio of 1:3 or less (100 u Botox less than or equal to 300 u Dysport). Xeomin has a similar strength to Botox CD: Botox mean dose 236 u (usually 150–300). Per muscle: sternocleidomastoid 12.5–70 u, trapezius 25–100 u, levator scapulae 25–60 u, splenius 20–100 u, scalenus 15–50 u
- Dysport: typical 250–1000 u
- **Blepharospasm**: 1.25–5 u at each site (15–100 u total)
- **Oromandibular dystonia**: massee 10–75 u, temporalis 5–50 u, medial and lateral pterygoids 5–40 u each
- **Spasmodic**: 2.5–5 u

**Sialorrhea**: 7.5–40 u
- **Limb dystonia**: intrinsic hand muscles 2.5–12.5 u, arm 5–45 u, intrinsic hand muscles 35–85 u, leg muscles 50–200 u
- **Primary axillary hyperhidrosis**: 50 u per axilla
- **Headache**: 50–200 u
- **Upper limb spasticity**: 75–360 u

**Dosage Forms**
- Powder for injection: 100 u, 50 u

**How to Dose**
- Administer every 3 months using the lowest effective dose
- The following units are for Botox formulation
- **CD**: start at a low dose and adjust as needed. Limiting the dose injected into the sternocleidomastoid muscles to 100 u or less may decrease incidence of dysphagia
- **Blepharospasm**: use 1.25–2.5 u per injection initially. Injecting more than 5 u per site does not produce added benefit. Inject the medial and lateral pretarsal orbicularis oculi of the upper lid and lateral pretarsal orbicularis oculi of the lower lid
- **Oromandibular dystonia**: for jaw-closing inject the massee at two to three sites, and for jaw-opening inject the submentalis complex
- **Spasmodic dysphonia**: for more common adductor type inject 1–2.5 u into each side of the thyroarytenoid muscles, for abductor type inject the posterior cricoarytenoid
- **Sialorrhea**: inject 5–20 u into each parotid gland initially. The mandibular or sublingual glands may also be injected
- **Limb dystonia**: inject using EMG guidance and dose based on muscle size and severity. Large shoulder and lower limb muscles may require hundreds of units for clinical benefit
- **Primary axillary hyperhidrosis**: perform 10–15 injections approximately 1–2 cm apart
- **Headache**: common sites include procerus (2.5–5 u), corrugators (2.5–5 u each side), frontalis (10–25 u, 2.5 u per site), temporalis (5–20 u), occipitalis (2.5–10 u each site), and splendius capitus (5–15 u each side)
- **Upper limb spasticity**: common sites include biceps brachii (100–200 u total), flexor carpi radialis/ulnaris (12.5–50 u), and flexor digitorum profundis (25–50 u)

**Dosing Tips**
- Physicians should be familiar with the anatomy of the injection site and the specific disorders
- Inject using a needle or hollow electrode
EMG recording helps to identify muscle involved in complex dystonias
Reconstitute with 0.9% sodium chloride. Rotate gently to mix with the saline. Administer within 4 hours
Dilute with 1, 2, 4, or 8 mL depending on the type of injections to be performed. Dilute more when injecting smaller muscles (such as ocular muscles) that require fewer units
When injecting blepharospasm, avoid the levator palpebrae superioris to reduce incidence of ptosis

Overdose
Signs and symptoms of overdose may be delayed for several weeks. If accidental overdose occurs, monitor for signs of systemic weakness or paralysis

Long-Term Use
Safe for long-term use

Habit Forming
No

How to Stop
No need to taper

Pharmacokinetics
Does not reach peripheral blood after injection with recommended doses. There may be changes in clinical EMG in muscles distant to the injection site. The cause of this spread (circulation, axonal transport) is unclear

Drug Interactions
Use with caution in patients taking medications, such as aminoglycosides or curare-like compounds, that can interfere with neuromuscular transmission

Other Warnings/Precautions
Contains albumin, a blood derivative that can theoretically carry risk of viral infection or Creutzfeldt–Jacob disease
Hypersensitivity reactions such as anaphylaxis, urticaria, and soft-tissue edema have been reported

Do Not Use
Patients with known hypersensitivity to the drug or any of its components; infection at the proposed injection site

Renal Impairment
No known effects

Hepatic Impairment
No known effects

Cardiac Impairment
There are rare reports of cardiac events including myocardial infarction following administration of botulinum toxin type A. The relationship of the events to the injections is unclear and some of these patients had risk factors for heart disease

Elderly
No known effects

Children and Adolescents
Studies in children age 12 and older for strabismus and blepharospasm, age 16 and older for CD, and age 18 and over for hyperhidrosis. Used for treatment of sialorrhea in cerebral palsy

Pregnancy
Category C: use only if benefit of medication outweighs risks

Breast-Feeding
Concentration in breast milk unknown. Use only if benefits outweigh risk

THE ART OF PAIN PHARMACOLOGY

Potential Advantages
Effective in multiple refractory conditions, including pain, with very few AEs or drug interactions

Potential Disadvantages
Cost and need for frequent injections to maintain effect. Dose requirement increases with muscle size

Primary Target Symptoms
Dystonia, spasticity, pain, drooling, or sweating (depending on indication)

Pearls
Botulinum toxin is most effective in focal dystonias. Generalized dystonias can be treated
with anticholinergic therapy, especially in younger, cognitively normal patients

- It often takes a series of injections to determine the optimal dose for a given patient
- Anterocollis (forward neck flexion) is often associated with neuroleptic exposure and Parkinsonism and is the most difficult cervical dystonia to treat. Injections of sternocleidomastoid and anterior scalene muscles are standard but fluoroscopic injections of deep cervical flexors may reduce clinical failures
- In oromandibular dystonia, botulinum toxin appears more effective in jaw-closing dystonias than jaw-opening or mixed dystonias
- Meige syndrome is a combination of dystonias, including blepharospasm plus oromandibular dystonia. Symptoms also include tongue protrusion, light sensitivity, muddled speech, contraction of the platysma muscle, and laryngeal dystonia. In addition to the usual sites for blepharospasm and oromandibular dystonia, consider injections of zygomaticus (usually 2.6–7.5 u) and risorius (2.5–10 u)
- Some studies report benefit in patients with chronic migraine at a dose of 50–250 u. Patients with allodynia, ocular headache, and “imploding” pain may be more likely to benefit. Patients with episodic migraine and chronic tension-type headache did not do better than with placebo injections
- Consider as an alternative for patients with focal “nummular” (coin-shaped) headache and trigeminal neuralgia
- A recent double-blind trial found that botulinum toxin type A was effective in some patients for reducing pain associated with diabetic neuropathy. This suggests the toxin has an effect on nerve rather than muscle alone
- Studies of CD suggest the appropriate conversion factor between Botox and Dysport units is less than 3 (100 u of Dysport). Compared to Botox, Dysport appears to disperse to a greater area. It is unknown if this might cause problems when doing injections for CD, strabismus, or blepharospasm
- The most effective agent for post-stroke spasticity due to its focal action and lack of systemic side effects. Use to improve specific functions such as dressing, eating, etc. Higher doses may be needed
- Recently botulinum toxin type A was renamed onabotulinum toxin A (for Botox and Botox cosmetic) and abobotulinum toxin A (Dysport)

Suggested Reading


