

HOW BOTOX WORKS FOR THE TREATMENT OF CHRONIC PAIN:

Dr. G. Ko 08/09

Botox is a highly purified protein extracted from the *C. Botulinum* bacteria. It has to be stored in the freezer and used within 4 hours after mixing with preservative-free saline. When injected into muscle, it is taken up by the nerve endings. It then blocks the nerve from firing its neurotransmitter (acetylcholine) which normally makes the muscle contract. This block lasts around 3 months and allows the muscle to relax during that time period. Recent research also shows that Botox blocks the release of pain neurotransmitters (substance P, C-GRP, glutamate etc.). Botox has been used since the 1980's for treating severe muscle spasms (in children with cerebral palsy and adults with stroke, spinal cord injuries, MS etc.). Clinical observation led to its use for wrinkles. By the early 1990's, it was noted that migraines were reduced with the "wrinkle" injections. Since the 1980's, there have been an estimated 3 million injections in over a million people worldwide...without any severe allergic reactions. It works best for pain when combined with specialized FCAMT physiotherapy focused on post-injection exercise, postural retraining and core stability. For more info., check out website: www.NeuropathicPain.ca.

Supportive CLINICAL STUDIES include **randomized placebo-controlled trials:**

HEADACHES BTX-A = botulinum toxin type A.

Dodick D et.al. **Botulinum toxin type A for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind placebo controlled study.** HEADACHE 2005; 45: 315-24.

Freund BJ et.al. **Treatment of chronic cervical-associated headache with BTX-A: a pilot study.** HEADACHE 2000;40: 231-6.

Relja MA, Korsic M. **Treatment of tension-type headache by injections of botulinum toxin type A: double-blind placebo-controlled study.** NEUROLOGY 1999; 52 (6 Suppl 2): A203 P03.035.

Silberstein S, Mathew N, et.al. **Botulinum toxin type A as a migraine preventive treatment.** HEADACHE 2000; 40: 445-50.

Smuts JA, et.al. **Prophylactic treatment of chronic tension-type headache using botulinum toxin type A.** Eur J Neurol 6:S99-S102.

CHRONIC LOW BACK PAIN

Foster L et.al. **BTX-A and chronic low back pain: a randomized, double blind study.** NEUROLOGY 2001; 56: 1290-3.

Porta M. **A comparative trial of botulinum toxin A and methylprednisolone for the treatment of myofascial pain syndrome and pain from chronic muscle spasm.** PAIN 2000; 85: 101-5. [back pain: injections for iliopsoas / piriformis muscles]

Fishman LM et.al. **Botox and physical therapy in the treatment of piriformis syndrome.** Am J Phys Med Rehabil 2002;81:936-42.

Yoon SJ et.al. **Low-dose Botox, type A for the treatment of refractory piriformis syndrome.** Pharmacotherapy 2007;27:657-65.

MYOFASCIAL PAIN / FIBROMYALGIA

Asherson RA, Pascoe LP. **The use of botulinum toxin-A in the treatment of patients with fibromyalgia.** J Rheumatol 2001;28:1740.

Barwood S et.al **Analgesic effects of BTX-A: a randomized, placebo-controlled clinical trial.** Dev Med Child Neurol 2000;42:116-21

Lang AM. **A pilot study of botulinum toxin type A, administered using a novel injection technique, for the treatment of myofascial pain.** Am J Pain Manage 2000; 10: 108-12.

Gobel H et.al. **Efficacy and safety of a single Botulinum type A toxin complex treatment for the relief of upper back myofascial pain syndrome: results from a randomized double-blind placebo-controlled multicentre study.** PAIN 2006; 125: 82-88.

Ko GD, Whitmore S, Huang D, McDonald R. **Effective pain palliation in fibromyalgia patients with Botulinum Toxin type-A: case series of 25.** J Musculoskel Pain 2007;15(4):55-66.

NEUROPATHIC PAIN

Argoff CE. **A focused review on the use of Botulinum Toxins for neuropathic pain.** Clin J Pain 2002; 18: S177-181.

Borodic GE, Acquadro MA. **The use of Botulinum Toxin for the treatment of chronic facial pain.** J Pain 2002; 3:21-27

Ko GD, Finkelstein I, Hum A. **Botulinum Toxin-A alleviates Trigeminal and Post-Herpetic Neuralgia facial pain.** Clin Invest Med 2004; 27:204 and in Muscle Nerve 2004; 30:540.

Yuan RY, Sheu JJ et.al. **Botulinum toxin for diabetic neuropathic pain: a randomized double-blind crossover trial.** NEUROLOGY 2009; 72:1473-8.

OTHER:

Placzek R et.al. **Treatment of chronic radial epicondylitis with Botulinum Toxin A: a double-blind, placebo-controlled, randomized multicenter study.** JBJS 2007; 89-A:255-60 [TENNIS ELBOW]

Babcock MS et.al. **Treatment of pain attributed to plantar fasciitis with BTX-A.** Am J Phys Med Rehabil 2005;84:649-54.

Mahowald ML, Singh JA, Dykstra DD. **Long term effects of intra-articular BTX-A for refractory joint pain.** Neurotoxicity Research 2006; 9:179-88.. [SEVERE OSTEOARTHRITIS, RHEUMATOID, PSORIATIC ARTHRITIS]

Cullen DM et.al. **Botulinum toxin injection to facilitate rehabilitation of muscle imbalance syndromes in sports medicine.** Disability and Rehabilitation 2007; 29:1832-9. [SPORTS MEDICINE]

LABORATORY STUDIES on mechanisms of pain relief:

1. Botox decreases muscle hyperactivity and excessive muscle spindle activity (Aoki 1998, Jankovic 1990, Filippi 1993, Rosales 1996)
2. Retrograde neuronal uptake (Wiegand 1977) leads to decreased calcium-dependent substance P release in the dorsal horn of spinal cord (Purkiss 2000), brain (Van den Bergh 1996), trigeminal nerve endings (Ishikawa 2000).
3. Decreased nociceptive neuropeptides such as glutamate, C-GRP, VIP (Cui 2002, Morris 2001, Durham 2004)
4. Increased enkephalin release in the dorsal horn (Humm 2000).
5. Anti-inflammatory dose-dependent effect shown in the rat formalin model (Cui, Aoki 2000)
6. Reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin (Tugnoli V et.al. PAIN 2007; 130:76-83)

NEUROTOXIN THERAPY: PRE-TREATMENT PATIENT INFORMATION updated August 2009

Botulinum toxin type A (Botox) is approved by Health Protection Board (HPB) in Canada for treatment of **blepharospasm, hemifacial spasm, cervical dystonia, juvenile cerebral palsy, and focal muscle spasticity** (in stroke, brain/ spinal cord injury, MS). It is also approved for **hyperhidrosis** (excess sweating), **sialorrhea** (excess drooling) and **cosmetics** (wrinkles); Botox has NOT yet been approved in treating osteoarthritis, neuropathic pain or muscle pain (including migraine headaches, chronic low back pain). However, the American Academy of Neurology and the National Institute of Health have deemed Botox safe and effective in the treatment of such muscle disorders. Several randomized controlled clinical trials document its effectiveness for such chronic pain syndromes. This includes a double-blind crossover study (Yuan RY et.al. Neurology 2009) finding intradermal (skin) injections of Botox to be helpful for painful diabetic neuropathy. A multi-centre trial for Migraine called the PREEMPT study will be published later this year with positive results. See website www.DrKoPRP.com for media interviews, publications and more up to date information.

The procedure will consist of the following: you will receive the Botox by injection into the muscle and/or joint and/or skin. The skin will be cleaned with an alcohol pad/ betadine/ chlorhexidine. For muscle injections, the site to be injected may be determined by using a small electric recorder or a larger machine called an EMG machine. This allows the physician to correctly localize the proper area of the muscle to inject. Ultrasound guided injections may also be used for deeper joints or muscles. You may receive 1-3 needle insertions to each muscle for even distribution of Botox, and about 0.3 cc of fluid (less than a teaspoon) will be injected at each site.

EXPECTED BENEFITS:

Botox may relieve symptoms of muscle pain and spasm for 6 weeks to 4 months.

Botox may relieve symptoms of osteoarthritis for 3 to 6 months.

Botox may relieve symptoms of neuropathic pain (e.g. shingles) for 3 to 6 months.

ALTERNATIVES TO TREATMENT:

Oral medications (side-effects such as weight gain, dry mouth, constipation with amitriptyline; stomach ulcers, kidney, liver, heart problems with anti-inflammatories; drowsiness, unsteadiness with gabapentin; constipation, nausea, addiction risk with opioids etc.)

Physiotherapy including aquatic exercise, osteopathic manipulation. Chiropractic and massage therapy.

Psychological counselling and biofeedback.

Other types of injections including cortisone, viscosupplements for joint pain/ osteoarthritis; and nerve blocks (such as epidurals for back pain); Surgery including radiofrequency denervation of facet joints in the spine.

SIGNIFICANT RISKS:

For any type of needle or injection (including acupuncture):

Allergic reaction

Dizziness, feeling faint

Infection, needle break

Joint injury, avascular necrosis (hip joint)

Nerve injury, Puncture of internal organ (lung, abdomen)

Skin bruising, bleeding, discolouration

For Botox injections around the eyes / face:

Ptosis (eyelid drooping)

Diplopia (double vision)

Burning and pain

Eyelid swelling and bruising

Tearing

For Botox injections around the throat / cervical dystonia:

Dysphasia (swallowing and chewing difficulties)

Dysarthria (talking difficulty)

Hoarseness

Drooling

Singing difficulty

Neck weakness

For injections in the arms or leg / treatment of Focal dystonia (e.g. writer's cramp):

Arm / Hand weakness

Foot drop

Wrist drop

Rare side-effects have been reported but are not necessarily a result of Botox. These include:

Nausea

Muscle soreness

Headaches

Light-headedness

Fever

Chills

Hypertension

Weakness

Difficulty breathing

Diarrhea

Abdominal pain

Special warning of risk to females of childbearing potential

The effects of Botox on human babies are unknown, but could cause harm. For this reason it is necessary to:

1. Use adequate birth control to avoid getting pregnant while receiving treatment.
2. Inform us immediately if you get pregnant.

This treatment may cause an allergic reaction. Potentially, this reaction could be severe and life threatening.

As is true of all medications in medical treatment, there is always the possibility of a new or unexpected risk.

Please note that Botox has been used in North America since the 1980's and has an excellent safety record. A meta-analysis of 186 published studies (Naumann M. Curr Med Res Opin 2004; 20: 981-90) found that there were no severe adverse effects reported. Temporary weakness of the injected muscles was the only significant side-effect noted (and not unexpected). Unlike the repeated use of cortisone injections, Botox has NO adverse effects on bone density, blood pressure, blood sugar levels, liver, renal or cardiac function. A recent review by the FDA (USA) noted isolated case reports of systemic side-effects. This warrants the use of lower doses in the frail, young and elderly. The approach used at our Centre is to be conservative and start with low doses "Start Low and Go Slow". A 3 month pain diary should be completed after the first treatment which will help to determine future dosing.

Another Botulinum toxin type A from Germany called Xeomin is also available. It is equipotent to Botox but does not have to be refrigerated and has no complexing proteins (theoretically reduced risk for developing antibodies that would prevent it from working). It is approved by the HPB in Canada for upper extremity spasticity, cervical dystonia and blepharospasm.

HOW DOES BOTOX PROVIDE PAIN RELIEF?

(for more information, see full article on website www.DrKoPRP.com)

LABORATORY STUDIES identifying mechanisms for pain relief include:

1. DECREASES MUSCLE HYPERACTIVITY:

Aoki R. **The development of BOTOX: its history and pharmacology.** Pain Digest 1998; 8: 337-44.
Jankovic J, Schwartz K. **Botulinum toxin injections for cervical dystonia.** Neurology 1990; 40: 277-280.

2. DECREASES EXCESSIVE MUSCLE SPINDLE ACTIVITY

Filippi GM, Errico P, Santarelli R. et.al. **Botulinum A toxin effects on rat jaw muscle spindles.** Acta Otolaryngol 1993; 113: 400-404.
Rosales RL, Arimura K, Takenaga S, Osame M. **Extrafusal and intrafusal muscle effects in experimental botulinum toxin-A injection.** Muscle Nerve 1996; 19: 488-496.

3. RETROGRADE NEURONAL UPTAKE INTO THE CNS.

Wiegand H, Wellhoner HH. **The action of botulinum A neurotoxin on the inhibition by antidromic stimulation of the lumbar monosynaptic reflex.** Naunyn Schmiedebergs Arch Pharmacol 1977; 298: 235-238.

4. DECREASED CALCIUM-DEPENDENT SUBSTANCE P RELEASE IN THE DORSAL HORN OF THE SPINAL CORD.

Purkiss JR, Welch MJ, Doward S, Foster KA. **Capsaicin-stimulated release of substance P from cultured dorsal root ganglion neurons: involvement of two distinct mechanisms.** Biochem Pharmacol 2000; 59: 1403-6.

AND IN THE BRAIN:

Van den Bergh P, De Beukelaer M, Deconinck N. **Effect of muscle denervation on the expression of substance P in the ventral raphe-spinal pathway of the rat.** Brain Res 1996; 707: 206-12.

AND FROM TRIGEMINAL NERVE ENDINGS:

Ishikawa H, Mitsui Y, Yoshitomi T et.al. **Presynaptic effects of botulinum toxin type A on the neuronally evoked response of albino and pigmented rabbit iris sphincter and dilator muscles.** Jpn J Ophthalmol 2000; 44: 106-109.

5. DECREASED NOCICEPTIVE NEUROPEPTIDES (glutamate, CGRP, VIP)

Cui M, Li Z, You S, Khanijou S, Aoki R. **Mechanisms of the antinociceptive effect of subcutaneous Botox: inhibition of peripheral and central nociceptive processing.** Arch Pharmacol 2002; 365: R17.
Morris JL, Jobling P, Gibbins IL. **Differential inhibition by botulinum neuro-toxin A of cotransmitters released from autonomic vasodilator neurons.** Am J Physiol Heart Circ Physiol 2001; 281: 2124-32.
Durham PL, Cady R, Cady R. **Regulation of Calcitonin Gene-Related Peptide secretion from Trigeminal nerve cells by Botulinum Toxin type A: Implications for Migraine therapy.** Headache 2004; 44: 35-43.
Tugnoli V et.al. **Reduces capsaicin-evoked pain and neurogenic vasodilatation in human skin PAIN** 2007; 130:76-83)

6. INCREASED ENKEPHALIN RELEASE IN THE DORSAL HORN:

Humm AM, Pabst C, Lauterburg T, Burgunder JM. **Enkephalin and aFGF are differentially regulated in rat spinal motoneurons after chemodenervation with botulinum toxin.** Exp Neurol 2000; 161: 361-72.

7. ANTI-INFLAMMATORY EFFECT:

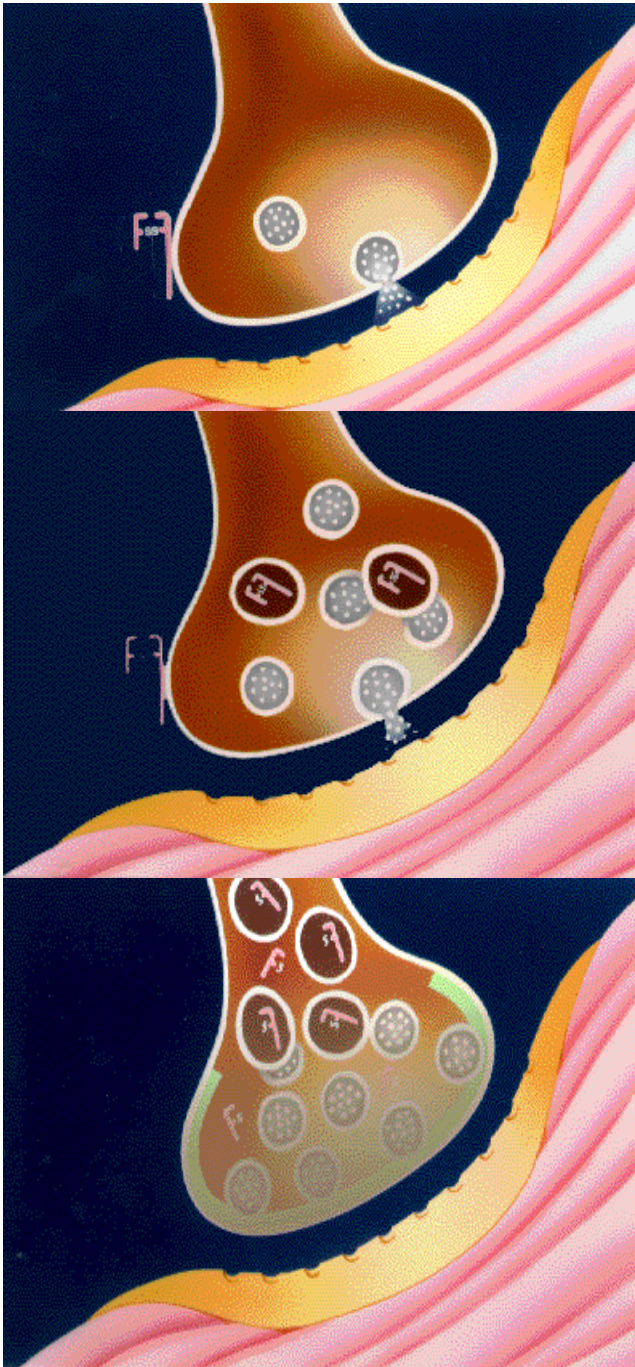
Cui M, Aoki KR. **Botulinum toxin A reduces inflammatory pain in the rat formalin model.** Cephalalgia 2000; 20: 414.

WHAT IS BOTOX AND HOW DOES IT WORK ? Dr. G. Ko

BOTOX is Botulinum Toxin –A (manufactured by Allergan Inc.).

It is the most potent of eight neurotoxins produced by the gram-positive anaerobic rod bacteria *Clostridium Botulinum*.

This 150 kDalton protein when injected into muscle is taken up at the neuromuscular junction.



It's heavy chain (100kD) attaches it to the presynaptic membrane of the nerve terminal.

Endocytosis of the BOTOX molecule then occurs.

After endocytosis, the disulphide bond is broken, allowing the light chain to move to the presynaptic terminal.

The light chain then binds to the 25 kDalton synaptosome-associated-protein (SNAP-25) and results in the inhibition of calcium activated release of acetylcholine.

Prolonged muscle relaxation / paralysis occurs as a result of this acetylcholine block.

The nerve-muscle junction returns back to normal function after 3-4 months.

The ONSET of this occurs around 3-4 days

3-4

PEAK effect around 3-4 weeks

Average DURATION of response 3-4 months.

Should be injected less than 3-4 hours after reconstitution.

Maximum dose of injection is 400 units.

The cost of one vial is about \$400

BOTOX comes in vials of 100 units. A unit of BOTOX is defined as the LD50 for a colony of 20 gm swiss-webster mice. Extrapolated to the 70 kg human, the lethal dose would be about 2700 units. The typical maximum dose at one injection setting is 400 units (higher doses up to 600 units have been reported).

Injections are spaced out a minimum of 3 months to minimize the risk of antibody formation to the protein (which would prevent BOTOX from working the next time).

Reported side-effects include a flu-like illness which may last a few days. Rare post-injection muscle soreness and stiffness may last 1-2 weeks. Inadvertent weakness depends on the site of injection (e.g. eyelid ptosis for injections in the pericranial frontal muscles, swallowing difficulty for anterior neck muscle injections). Such incidences are largely dependent on operator technique and dosage used.

Relative contraindications to BOTOX include generalized muscular weakness (myopathies, neuromuscular junction diseases such as myasthenia gravis), profound atrophy of the target muscle, aminoglycoside antibiotic therapy and pregnancy.

BOTOX should be refrigerated. After reconstitution with preservative-free normal saline, it ideally should be injected right away for optimal effect. Post-injection electrical stimulation/ contraction of the injected muscle(s) has been reported to augment the response.

Other uses for BOTOX at our clinic include:

- hyperhidrosis (sweaty palms, armpits)
- excessive salivation in ALS, CP patients
- focal spasticity (stroke, Multiple Sclerosis, cerebral palsy): OHIP covered
- focal dystonias (writer's cramp, cervical dystonia)
- essential tremor

Surface EMG assessment is also helpful in identifying which facial muscles are hypertonic and dysfunctional (synkinesis) for BOTOX. (with physiotherapist Sylvia Loong BScPT CFB)

We also use specialized equipment as needed to more accurately inject. This includes:

- EMG guided injections (with the NeuroMax 1004)
- Peripheral nerve stimulator (NS 272)
- Ultrasound guided injections (including the Canadian Centre for MSK ultrasound)

MD Injectors (Botox Therapeutic) at the CCIM:

Dr. Gordon Ko, Dr. Kinga Koprowicz, Dr. Tom Han