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Chapter

# MS Progress Notes...

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## **BOTOX: POISON OR PANACEA?**

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Whoever first thought to use botulinum toxin (BTX) as a therapeutic intervention should be congratulated - or institutionalized.

In the past, people died from botulism as a result of toxin exposure from poor food canning techniques. Over time however, the potent botulinum toxin was isolated and purified. It was FDA approved for the treatment of blepharospasm, cervical dystonia, axillary hyperhidrosis, strabismus, and wrinkles. Botulinum toxin is not FDA approved for use in spasticity or in the bladder, however it is usually a covered treatment for patients with MS.

**Mechanism of Action:** BTX neurotoxins are produced by the anaerobic bacterium *Clostridium botulinum*, and prevent acetylcholine release at the neuromuscular junctions of skeletal muscles and muscle spindles, reducing spasticity. Of the seven serotypes of BTX (A-G), A and B are the only serotypes clinically available. In this country, botulinum toxin A is available as Botox® and Dysport®, and botulinum toxin B is available as Myobloc®.

Botulinum toxin treatment is temporary. Neuromuscular junctions can regenerate over time, reducing the effect of BTX, which must be repeated periodically. Antibodies to BTX proteins may form, and more frequent treatment is associated with an increased risk for the development of antibodies.

Contraindications to BTX therapy include bleeding disorders, pregnancy (category c), an underlying neuromuscular junction disorder such as myasthenia gravis, infection or device at the injection site, and allergy or religious objection to albumin.

**Urological Uses:** Although BTX A was initially used for skeletal muscle indications, experience in the lower urinary tract soon followed. The first urological benefit of BTX A was demonstrated in a small group of patients with neurogenic overactive bladders. Schurch and colleagues (2000) injected Botox into the bladder. This was found to restore continence as well as to reduce or eliminate the use of antimuscarinics. Since this study, intravesical BTX A has been used as a salvage therapy for both idiopathic and neurogenic overactive bladder patients who failed oral medications.

While the injection technique continues to evolve, current treatment depends on direct cystoscopic visualization of the bladder. Aliquots of BTX are injected into the smooth muscle of the bladder wall, avoiding

the trigone. Treatment benefit is usually noted within one week, but up to one month may be required before optimal response is seen. Benefit usually persists for six months, although as long as twelve months has been reported. There is also evidence to support that injection requirement decreases over time, so that the treatment needs to be given less frequently for sustained effect. Repetitive injections have not been associated with adverse events and multiple injections do not appear to reduce the effect of BTX.

In overactive bladder, BTX injections result in improvements in urgency, frequency, incontinence and quality of life. These subjective responses have also been confirmed objectively with urodynamic testing. There have been increases in maximal cystometric bladder capacity, improved bladder compliance and decreased bladder filling pressures.

There are a few potential side effects of BTX injections into the bladder wall, including localized pain, bleeding and temporary urinary retention. A very rare side effect of BTX injection into the detrusor is transient generalized muscle weakness, lasting from 2-4 weeks.

**Botulinum Toxins for Spasticity:** Botulinum toxin can be useful in managing spasticity due to MS. Before approving BTX use, many insurers will insist that oral medications such as Baclofen and Tizanidine be tried first, with either an inadequate response or an inability to tolerate the medication due to allergy or side effects. Bracing and conventional nerve blocks should also be considered prior to BTX. Unfortunately, conventional nerve blocks destroy both the sensory and the motor nerves, which can result in painful dysesthesias in the distribution of the treated sensory nerves. This severely limits their use in the upper extremity, and to a lesser extent, in the lower extremity.

Botulinum toxin is especially helpful when the spasticity is fairly focal, so that the spasticity can be addressed with a safe amount of toxin. Some toxin does diffuse away from the injection sites and when large doses are given, BTX may cause some generalized weakness. For Botox® the maximum amount recommended for use at one time is 400 units, and the amount of Myobloc® recommended is 5000 units for large muscles, or muscles that are very deep or difficult to treat. In the former, the issue is the amount of toxin required to reduce the tone in the large volume of muscle, and in the latter the issue is localizing the toxin to the correct muscle.

Botulinum toxins can also be used as an adjunct to more global treatments, such as oral agents or intrathecal Baclofen (ITB). For

example, when a patient on ITB has asymmetrical tone and requires some spasticity in order to remain ambulatory, BTX can be helpful to reduce tone focally in the more spastic leg. Another adjunctive use is for upper extremity spasticity in a patient whose lower extremity spasticity is well controlled on ITB. Fortunately, if BTX worsens function, the effects are time-limited because the neuromuscular junctions will regenerate. However, this can worsen disability for several months. Patient and dose selection is the key issue in reducing unwanted weakness.

Some physicians inject the patient in the position that brings out the most tone, but we find it is more comfortable and safer to have the patient in a relaxed position when the medication is injected. In general the procedure is carried out using electromyographic guidance. The dose is injected via a monopolar needle electrode, using surface electrodes for the reference and ground. Surface landmarks like those used in electromyography guide needle insertion and expertise in anatomy and kinesiology of the involved muscles assists both in selecting the correct muscles and their localization. The dose is divided among several injection sites in larger muscles in order to spread the BTX effect over a larger volume of muscle.

MS Spasticity patterns that are amenable to BTX are listed in Table 1.

**Table 1: Uses of Botulinum Toxin in Limb Spasticity**

Problem	Potential complications	Muscles involved
Equino-varus foot	Toe walking, poor brace fit. Genu recurvatum, poor balance, hip hiking & circumduction, falls, ankle sprains	Gastrocnemius/soleus Tibialis Posterior Toe flexors (long and short)
Adducted Thighs	Limits base of support and balance, falls; Limits perineal hygiene, toileting, sexuality and self catheterization	Adductor longus Adductor brevis Adductor magnus
Striatal Toe	Pain from contact with shoes, Ingrown toenail	Extensor Hallucis Longus
Shoulder Adduction/Internal Rotation	Shoulder pain from joint capsule stretch or fibrosis, Limits axillary hygiene; Limits reach and function of arm	Pectoralis Major Latissimus dorsi Teres major
Flexed Elbow	Limits reach, dressing. Limits balance while walking due to asymmetrical arm swing; Maceration of skin in antecubital fossa if severe.	Biceps Brachioradialis Brachialis
Flexed Wrist	Limits hand use by mechanical block and weakening finger flexors. Pain in wrist. Limits hygiene; skin maceration at wrist; promotes development of Carpal Tunnel Syndrome	Flexor Carpi Radialis Flexor Carpi Ulnaris (Finger Flexors)
Thumb-in-palm	Prevent use of hand for gross grasp; Stimulates reflex grasping by fingers; maceration of skin of palm; odor.	Flexor Pollicis longus Adductor Pollicis Opponens Pollicis Flexor Pollicis Brevis
Fisting	Limits use of hand for	Flexor Digitorum

	functional tasks; Limits hand hygiene; potential skin maceration; odor; makes dressing more difficult; pain in hand	Superficialis Flexor Digitorum Profundus
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There are a limited number of controlled trials documenting the efficacy of BTX in spasticity. Studies have shown that there is an improvement in the Ashworth score (by 2 points), or an improvement in the distance between the knees following BTX treatment to the hip adductors, without any change in the Ashworth scale of spasticity. A decrease in the Ashworth scale or amount of pain caused by flexor or extensor spasms of the arm or leg, or an improvement in the ability to maintain proper hygiene have been documented in small studies.

There are several other potential uses of BTX in symptom management for patients with MS. In patients with tremor, judicious use of BTX (again an off-label use) can reduce the amplitude of the tremor which can be functionally beneficial. In rubral tremor, treating the pectoralis major, teres major and sometime the biceps can produce such a result. When tremor is the reason for injection, doses must be adjusted downward to avoid weakening the shoulder girdle so much that the patient cannot lift the limb to a potential target. Oral agents for tremor should be considered before BTX, as in treatment of spasticity. For patients with severe sialorrhea, BTX injection of some of the salivary glands can reduce the volume of saliva, if anticholinergic medications are not tolerated.

The many uses for Botox continue to evolve. Only time and imagination will test the limit of its full potential.

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