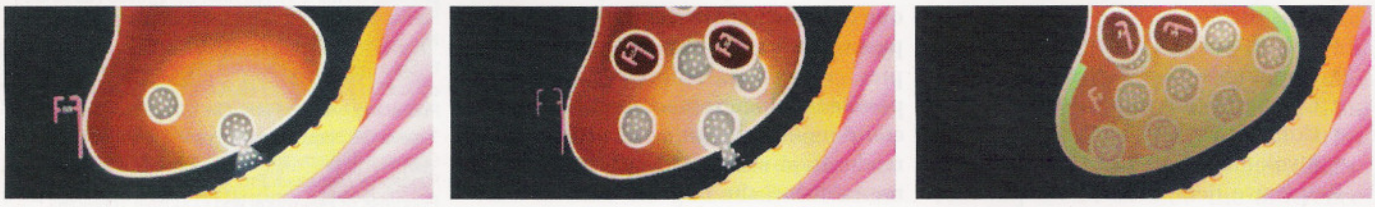
Botulinum Toxin Type-A in Pain Management

A review of of BTX-A including a discussion of its mode of action and case studies illustrating its use in treatment of a variety of pain presentations.



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Botulinum toxins were first developed in the 1950's by ophthalmologist Dr. Alan Scott (and subsequently approved by the FDA in 1989) for the treatment of eye movement disorders such as strabismus and blepharospasm.[1] Its uses have subsequently expanded to include neurological movement disorders, including focal muscle dystonia[2,3] and spasticity.[4,5]

Botulinum toxin type-A (BTX-A) is effective for muscle spasticity through its prolonged blockade of acetylcholine. The active moiety, a 150 kDalton protein, is the most potent of seven neurotoxins (A, B, C1, D, E, F, G) produced by the gram-positive anaerobic rod-shaped bacteria Clostridium botulinum.[6] (See Appendix A for a summary of botulinum toxin products). BTX-A's mechanism of action is described in the following section.

How Botulinum Toxins Work

When injected into muscle, BTX-A binds with high specificity and affinity to presynaptic cholinergic axon terminals. Its heavy chain (100kD) attaches it to the presynaptic membrane of the nerve terminal (see Figure 1a). Current research indicates that the attachment site is the SV2 neuronal acceptor protein located on the synaptic vesicle itself.[7]

Endocytosis of the BTX-A molecule then occurs (see Figure 1b). Current research indicates that this occurs through the same vesicles where acetycholine is released.[8] After endocytosis, the disulphide bond is broken, allowing the light chain to move to the presynaptic terminal. The light chain actually migrates through the channel created by the heavy chain.[9] The light chain then cleaves nine aminoacid residues from the 25 kDalton synaptosome-associated protein (which has 205 residues). This inhibits calcium-activated release of acetylcholine (see Figure 1c).

Current research also indicates that the products of SNAP-25 cleavage are also inhibitory. This leads to retraction of the endplate nerve terminals and subsequent loss of endplate organization. Muscle relaxation/paralysis occurs as a result of this block. Within four days, collateral terminal sprouting will occur to attempt re-innervation of the neuromuscular junction (NMJ). These temporary functional synapses result in partial recovery of muscle function after about 28 days. Within about two months after injection, the original nerve terminals will begin to recover their ability to release acetylcholine and original endplate connections are restored. Sprouting then stops and the temporary synapses lose their function. Within approximately three months, the original neuromuscular junctions recover full function and are normalized.[10,11] Cholinergic parasympathetic and postganglionic sympathetic nerve synapses of the autonomic nervous system are also potential targets. For example, intradermal injections of BTX-A leads to denervation of eccrine glands (useful for hyperhidrosis and sialorrhea).[12]

Patients are usually advised that the onset of action occurs around day three,

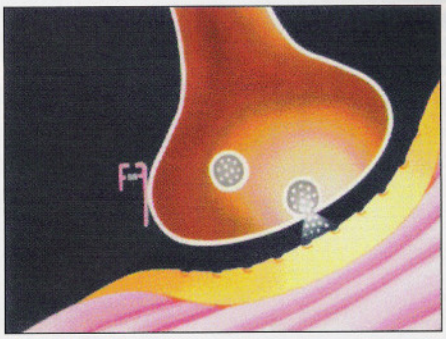

FIGURE 1A. *BTX-A attaches to the pre-synaptic membrane of the nerve terminal. (Reprinted courtesy of Allergan Inc.)*

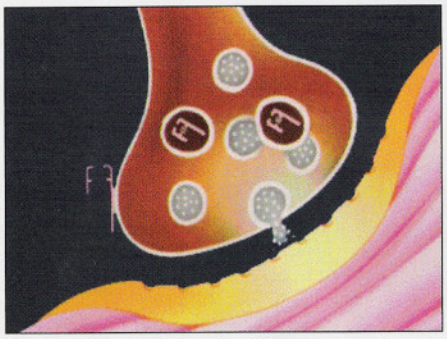

FIGURE 1B. *Endocytosis of the BTX-A molecule. (Reprinted courtesy of Allergan Inc.)*

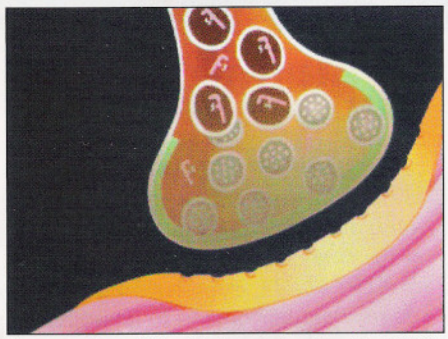

FIGURE 1C. *After Endocytosis, the disulphide bond is broken and allows the light chain to move to the presynaptic terminal. (Reprinted courtesy of Allergan Inc.)*

and the peak effect (in muscle relaxation) after three weeks. The average duration of response is three months. Pain relief, however, may last longer than the effects of muscle relaxation.[13] Injections are spaced out a minimum of three months to minimize the rare risk of antibody formation to the protein[14] which would prevent BTX-A from working the next time.

Safety of Botulinum Toxins

Botulinum toxin type-A comes in vials of 100 units. A unit of BTX-A is defined as the lethal dose for 50 percent (LD-50) of a colony of 20 gm Swiss-Webster mice. The LD-50 for monkeys is 39U/kg. Extrapolated to a 70 kg human, a lethal dose would be about 2,700 units. The typical maximum dose at one injection setting is 400 units. Reported side effects include post-injection muscle soreness, stiffness typically lasting a week and, rarely, a flu-like illness which may last a few days to a month. Inadvertent weakness depends on the site of injection (e.g. eyelid ptosis for injections in the pericranial frontal muscles, and difficulty with swallowing for anterior neck muscle injections).

Case reports of serious adverse effects have led to recent FDA and Health Canada safety reviews. Such incidences are largely dependent on operator technique (e.g. concomitant general anesthetic) and dose used. A retrospective review of 929 cerebral palsy children patient encounters documented no severe adverse effects or botulism.[15] Other supportive studies document safety[16,17] and a meta-analysis supported the overall safety of BTX-A.[18] Relative contra-indications to BTX-A include generalized muscular weakness (e.g., myopathies and NMJ diseases such as myasthenia gravis), profound atrophy of the target muscle, aminoglycoside antibiotic therapy, and pregnancy. Post-injection electrical stimulation/contraction of the injected muscle(s) has been reported to augment the response. Endplate targeted injections—with electromyographic (EMG) guidance—appear to be more effective than anatomical approaches.[19] BTX-A should be stored in the freezer and reconstituted with preservative-free normal saline. When stored in saline, it loses potency by 35 percent after one week and 44 percent after two weeks.[20] A recent rat study suggests that there are retrograde effects when BTX-A is injected into the brain and may provide implications for novel uses.[21]

Botulinum Toxin and Headache

A noticeable reduction in pain using BTX-A was first observed by Jankovic in work on cervical dystonia.[22] Subsequent reports by the Carruthers, who were the first to report the cosmetic benefits from blepharospasm treatment,[23] documented relief of headaches with injections done for wrinkles.[24]

Though there were earlier supportive studies for the use of botulinum toxin type-A for headache treatment (specifically, migraine, tension, and cervicogenic types),[25-28] more recent larger multi-centre trials did not find evidence for tension-type headache.[29,30] Results were more positive in specific subgroups of migraine and chronic daily headaches.[31-34] A recent neurology consensus panel did not find sufficient evidence at this time for headache.[35] The results of a large multi-centre phase three trial for migraine (PREEMPT) will be available later this year. The preliminary word on the PREMMPT migraine study is positive. This heralds good news in eventually getting BTX-A approved for pain.

Botulinum Toxin for Pain

Randomized trials were also published for chronic piriformis pain syndrome[36-38] and chronic mechanical back pain.[39] We have also found this effective in FMS patients who suffer from migraine headaches[40] and LBP.[41] More recent laboratory research has also indicated that BTX-A may also have a more central effect in pain control by blocking calcium-mediated release of substance P in dorsal root ganglion neurons,[42] as well as in the brain and trigeminal nerve ending.[43,44] Botulinum

TABLE 1. Trigger Points and Myofascial Pain Syndrome Criteria

Major Criteria

1. Pain localized to region, usually unilateral, asymmetric tenderness
2. Taut band is palpable
3. Pain in known referred zone
4. Exquisite spot tenderness
5. Restricted range of motion due to tight muscle

Minor Criteria

1. Reproduction of pain/altered sensation by pressure on TrP
2. Local twitch response on snapping the taut band
3. Pain alleviated by stretching muscle or by injecting TrP

Diagnosis requires all the major criteria and at least one minor criteria.[13]
TrP=trigger point

toxin type-A also works in pain through inhibition of other pain neurotransmitters (e.g., calcitonin gene-related peptide,[45] vasoactive intestinal polypeptide,[46] and by elevation of enkephalins at the dorsal horn of the spinal cord).[47] In a rat formalin model, BTX-A was found to have dose-dependent anti-inflammatory effects[48] with the mediator likely to be glutamate.[49] Fos expression in the dorsal horn was also inhibited.[50] BTX-A, by an action on TRPV1 receptors, also reduces capsaicin-evoked pain and neurogenic vasodilation in human skin.[51,52]

Based on this finding, we have observed effectiveness in focal neuropathic pain control with intradermal injections of BTX-A.[53,54] This may also apply for the 27 to 38 percent of FMS patients with marked skin allodynia in which there are higher levels of cytokines in the skin.[55] Patients with marked hypersensitivity should first try intradermal injections using a 4:1 dilution. Such patients may actually have generalized complex regional pain disorder and are more likely to flare up if injected too aggressively. We have also published on using BTX-A for fibromyalgia.[56]

One proposed theory for BTX-A relieving pain is by resolving muscle trigger points (TrPs). It is important to distinguish TrPs from FMS tender points (TePs). The criteria for TrPs are listed in Table 1. Studies, however, are both supportive[57-60] and non-supportive[61-63] in its use for myofascial pain.

It has been reported that 72 percent of FMS patients have TrPs.[64] Tender points do not usually respond to injections of local anesthetic, but TrPs in FMS do.[65] Current theories as to the pathophysiology of TrPs include the dysfunctional motor endplate where excessive acetylcholine is released[66] and where higher levels of inflammatory mediators have been found.[67]

It has also been reported that 67 percent of FMS patients had migraine headaches prior to onset of their FMS[68] and that 25 percent of chronic low back pain (LBP) patients will evolve into FMS.[69,70] After reviewing the studies on BTX-A working in migraines and LBP, we proceeded with showing effective treatment in FMS patients having these conditions.[71,72]

Studies of BTX-A have been published on demonstrating effectiveness for other conditions including:

- TMJ pain syndrome[73,74]
- Tendinopathies (tennis elbow)[75-78]
- Plantar fasciitis[79,80]
- Osteoarthritis, rheumatoid and psoriatic arthritis[81]
- Post-motor vehicle accident whiplash syndrome[82,83]
- Cancer pain, including post-radical neck dissection[84] and radiation fibrosis syndrome[85]
- Surgical wound healing[86]
- Post-amputation and phantom limb pain[87,88]
- Sports overuse injuries[89]

Illustrative cases involving each of these will now be presented (from each author):

Case Study #1: BK—Long-Term Safe Pain Palliation in Fibromyalgia

A 46-year-old married mother of two and church worker was seen with FMS, irritable bowel syndrome, and migraine headaches. She was taking bellergal, codeine, and dicetel. Supplements included ginger, echinacea, milk thistle, garlic, vitamin E, and coenzyme Q10. She had been abused in childhood by alcoholic parents and was an intravenous drug abuser with hepatitis C diagnosed in 1995.[33] She was in a car accident in 1989, incurring whiplash and a frozen right shoulder.

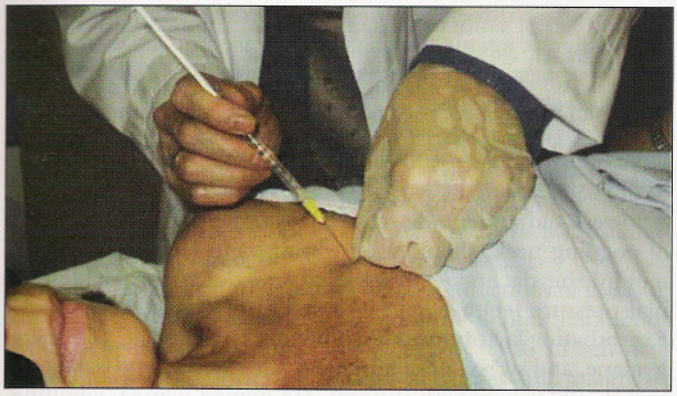

FIGURE 2. *Case Study 1. Pectoral muscle injection done in a supine position with Botox. Careful placement of needle is needed to avoid pulmonary and brachial plexus structures.*

TABLE 2. Data From Case Study #1: BK

Outcome Measure	Pre-Injection	Post-Injection	
(see key below)	June 2000	Sept 2000	Jan 2001
PVAS	5/10	4/10	3/10
SFM	25/45	13/ 45	7/45
PDI	30/70	18/70	11/70
FIQ	57/100	-	14/100
TeP Count	18/18	18/18	8/18

Key: PVAS=Pain visual analog scale, SFM=short-form McGill Questionnaire, PDI=Pain Disability Index, FIQ=Fibromyalgia Impact Questionnaire, TeP=tender point

In her initial examination in June 2000, findings included: height=64 inches, weight=114 pounds, no anemia or jaundice, and BP 134/99mmHg. In addition to active physiotherapy, she was treated with hydrotherapy and gabapentin titrated slowly up to 2400mg/day. She was weaned off codeine and bellergal.

On her September 2000 visit, she had a better appetite and her weight had increased to 119 pounds. In December 2000, the BTX-A injections were 25 units for headaches (with supra-orbital nerve blocks) and 75 units for upper trapezii and splenii cervicis. At the post-injection in January 2001 she described "an excellent response." Her headaches resolved with, as a bonus, fewer wrinkles! (see Table 2).

She returned in March 2001 for an injection of 300 units of BTX-A. Her 22nd set of injections was done on January 15, 2008 (similar outcome measures to 2001) with 400 units as follows: 25 units (2:1 dilution) into bilateral pectoralis minor, pectoralis major, levator scapulae, upper trapezius muscles (see Figure 1). 50 units (4:1 dilution) into bilateral subscapularis muscles; 10 units (2:1) into bilateral masseters, splenius capitus muscles and 60 units total into the frontalis, procerus, corrugator, occipitalis muscles (following the Silberstein protocol for migraine). With these treatments, she continues to work full-

time, exercise three times/week at the YMCA. She requires no oral analgesic agents. She has experienced no adverse effects over these past seven years with regards to cardiac, liver, renal, or endocrine function.

Case Study #2: TC—Long-Term Relief After One Injection With Postural Corrrection

A 20-year-old student was referred to our clinic for management of ongoing neck, shoulder and head pain. He complained of multiple headaches per month that were described as a holocranial pressure feeling that was rated at 6/10 on the VAS scale. Exacerbating factors included rapid neck movement, poor sleep hygiene, and stress. He complained of moderate and daily neck and shoulder pain with stiffness. He denied nausea, vomiting, photophonophobia, or aura. Family history was negative for headache. There was no history of motor vehicle accident or trauma to the head and neck. CT scan and MRI of the head and cervical spine were normal. He treated the pain with judicious use of Tylenol with Codeine, approximately twice per month. He denied daily use of analgesic medications. He had been tried on a number of medications which included: Amitriptyline, Propranolol, Epival, Topamax, Sandomigraine, Gabapentin, Naproxen, Baclofen, Zanaflex, and various Triptans. He had undergone various treatments that included physiotherapy, chiropractic, acupuncture, naturopathy, massage therapy, and occipital nerve blocks. None of these modalities offered him long term relief. He was attending University and required time off from classes when his headaches became severe.

His examination revealed a tall (6'2") and thin (135 lbs) male (BMI=17.3) with a 2-3 finger breadth forward head posture and protracted shoulders. Muscle tenderness and spasm was evident in the pectoralis, subscapularis, upper trapezius, levator scapulae, and subclavius muscles, as well as the suboccipital muscle group. There was weakness in the lower trapezius, infraspinatus, and rhomboid muscles. There was an exaggerated hyperkyphosis of the thoracic spine with an apex at the T6 vertebrae in a sitting position. Hyperlordosis of the cervical spine was also present. The erector spinae muscles were elongated, as well as hypertonic, and there was weakness noted in testing of the latissimus dorsi muscle. His neurological examination was entirely normal.

Two weeks prior to BTX-A injection, he was given a stretching protocol aimed at the sternocleidomastoid (SCM), pectoralis major, suboccipitals and levator scapulae. To compliment this regime, strengthening exercises were given for the rhomboids, lower trapezius, infraspinatus, and longus colli.

He underwent bilateral BTX-A injections to the upper trapezius (50 units at 2 injection sites), levator scapulae (50 units at 1 injection site) and pectoralis major (25 units at 1 injection site) and minor (25 units at 1 injection site). The total dose was 300 units given in a 4:1 dilution. The diluent was 0.9% non-preserved saline.

His exercise program continued post BTX-A injection and the resistance used in the strengthening protocol was increased as tolerated. As resistance continued to increase, the strengthening exercises were performed every other day. His treatment plan also consisted of mobilization of the right C2/3 facet joint and myofascial release of the pectoralis major and subclavius muscles bilaterally. His posture markedly improved (see Figure 3).

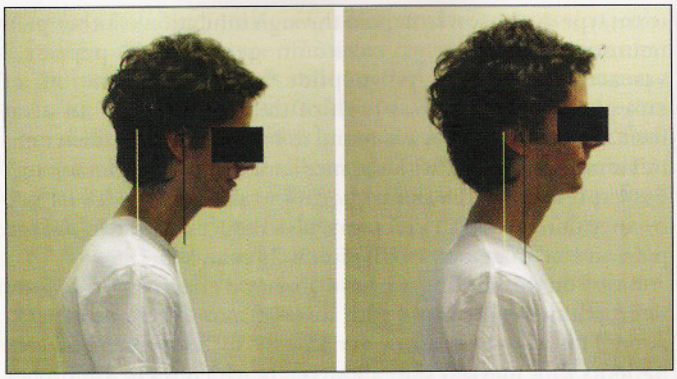

FIGURE 3. *Case Study 2. Before: note head forward position. After: improved head position.*

TABLE 3. Data From Case Study #2: TC

Outcome Measure	Pre-injection	Post-inj (12 wks)
Headache days	45	8
VAS pain	6/10	2/10
Vernon Mior	23/50	8/50
HIT-6	64	40

There were no complications or side effects from the BTX-A injections. He is now three years post BTX-A injection and has very mild, intermittent neck pain and his headaches are rare (see Table 3). He continues with his active rehab program and takes no further medications. His headaches and pain are having little, if any, impact on his day to day functioning. He has not required re-injection with BTX-A.

Case Study #3: HA—Vascular Doppler Technique for Injecting BTX-A

A 42-year-old otherwise well woman with an eight-year history of left-sided facial pain—initially intermittent, now constant. Her pain is most intense in the left jaw joint and left temple. She has difficulty opening wide and chewing. She sleeps poorly and awakens with stiff jaw, sore teeth, and temple pain despite a night guard. She gets right sided migraines with aura once to twice per week which last from 12 to 24 hours with treatment. Examination reveals tender masticatory muscles and jaw joints bilaterally on palpation, CT scan negative for masses or other soft tissue pathology, and her left jaw joint shows mild degenerative changes.

Current medications include Demerol, T3, Flexeril and Sumatriptan with diminishing effect. She has been treated with BTX-A three times in the past with good effect on jaw pain but only modest relief from headaches. Overall medication use drops for 4 weeks after injections with 150U of Botox (Allergan, Inc.)

History and exam suggest headaches are secondary to TMD. Alternative injection technique for BTX-A includes targeting peri-vascular areas in the temples and forehead for a more profound effect on the trigemino-vascular structures. An 8 MHz Doppler stethoscope is used to map local blood vessels (see

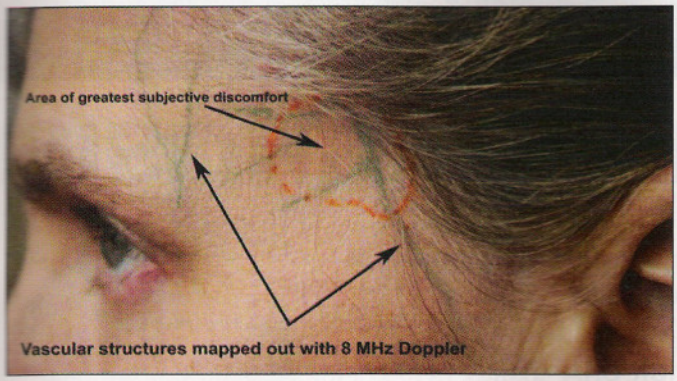

FIGURE 4. *Case Study 3. Mapping of peri-vascular areas in the temples for subcutaneous injections of BTX-A.*

Figure 4). BTX-A is injected subcutaneously over the course of each vessel in the areas of greatest subjective tenderness. Masseters are injected based on muscle bulk.

Outcome in this case is improved post injection in terms of intensity of temple pain and frequency of migraines which diminish to once every two weeks. Reduction in medication use extends to six weeks. No adverse effects are noted.

Case Study #4: DM—Combined Approach for Whiplash

A 50-year-old female accountant, disabled since a 2000 MVA, presented two years ago with six year history of right-sided headache, neck pain, dizziness, TMD, fullness and pressure in right ear, numbness in right face, tongue, roof of mouth on right, and right arm. She suffered from depression and trouble sleeping. She had a history of abuse in her childhood. NSAID, muscle relaxers, extensive physiotherapy, massage, chiropractic, and acupuncture failed. No pending litigation.

On exam, tender right C2-C6 facets, tight and tender muscles as mentioned below, positive right thoracic outlet syndrome (TOS) tests, depressed.

Treated with Celexa, Amitryptiline, gabapentine, tramadol, right C2-C6 facet blocks, and Botox in right splenius capitus, right SCM, right scalene, right levator scapulae, masseters, temporalis, and pectoralis minor at three month intervals. Sent for rehab with personal trainer. Within six months (two treatments of BTX-A), she was off Celexa, gabapentin, and tramadol. She was only on 20 mg Elavil, in school planning to work within six months. She was also doing yoga and meditation with her VAS pain 2-3/10. Now received fourth Botox, still recurrence of symptoms after three months. Working with personal trainer for postural re-alignment, core strength, stretches and cardio. Overall very pleased.

Case Study #5: EMG-Guided Injection of BTX-A

A 45-year-old right-handed psychiatrist developed bilateral arm pain and numbness after he got lost hiking while carrying his children. After 18 months of unsuccessful active physiotherapy with daily stretching, craniosacral osteopathy, acupuncture, non-steroidal anti-inflammatory drugs, and cortisone injections, he was referred with "medial epicondylitis, thoracic outlet syndrome (TOS), FMS." His past health history included migraines, anxiety, and irritable bowel syndrome. Family history included alcoholism, thyroid disease, lung cancer, and polio (in two siblings).

The initial examination findings in December 1999 included: height=70 inches, weight=155 pounds, BP 110/70mmHg (both arms), tender epicondyles with positive Cozen's sign, TTP=1-2+ 12/18, normal motor, sensory, and reflex testing. There was positive left brachial plexus tension and Adson's and Allen's tests using portable doppler. No subclavian bruit was detected. The Jamar grip strength was 75 pounds on the left and 95 pounds on the right. His Pain Disability Index was 25/70, with limitations in writing, recreation, and gardening.

Investigations included normal nerve conductions of median, ulnar (including F-wave), medial antebrachial cutaneous motor/sensory nerves, and normal needle EMG of left arm myotomes. Blood work, ultrasound of elbows, and magnetic resonance imaging of the C-spinewere all unremarkable with a minimal disc bulge C5-6.

His arm doppler photoplethysmography confirmed vasculogenic TOS: severely decreased amplitudes bilaterally with 180° hyperabduction and moderate decrease with left costoclavicular and Adson's maneuvers. Color duplex imaging failed to document a thrombus. Subsequent therapy with spray-and-stretch, EMG biofeedback, and home exercises, alleviated his right arm pain only temporarily.

A persistent left scalene medius TrP was then injected with one percent preservative-free procaine. His pain diary recorded a reduction of PVAS from 4/10 to 1/10 for a few hours. By the next morning, his pain returned to 4/10. Further injections with procaine, combined with therapy, provided only one to two weeks of relief.

EMG-guided injection with 35 units of BTX-A was done in November 2000, followed by electromuscular stimulation using Childers' protocol. See figure 5 for an example of EMG and ultrasound guided injection of BTX-A. At one month post-BTX-A, there was definite improvement. At three months, he described his left arm as being 90 percent improved. A second injection in March 2001 with 50 units BTX-A resulted in 95 percent improvement. A year later, he returned for TrP lidocaine injections into the trapezii. He returned in April 2004 for consultation on a right rotator cuff tendonitis and reported no ongoing TOS symptoms provided he kept up his daily stretching.

In June 2005, he underwent BTX-A injections for painful tight piriformis and hamstring muscles with good results. With daily stretching exercises, sleep, and stress management, he contin-

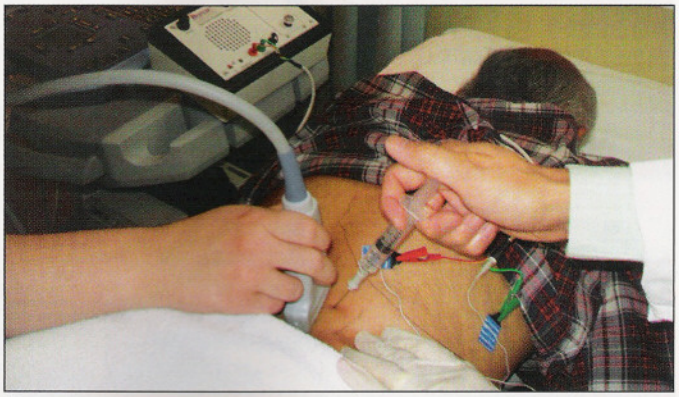

FIGURE 5. *Case Study 5. Example of EMG and Ultrasound guided injection of Botox for painful tight psoas muscle. This approach is also used for thoracic outlet compression (scalenes) and for piriformis compression (in thin individuals).*

Table 4. ABCD Starting Dose Recommended Guidelines

Active Trigger Point: Five to 10 units (if local anesthetic provides just short-term relief).
Biomechanical approach: 25 to 50 units (e.g. injecting tight pectorals to correct anterior shoulder protraction and head forward posture). Dosing may be titrated up higher for larger muscles (e.g. piriformis with 100 units, iliopsoas with 150 units).
Combination of the above: Care must be taken to not over-inject trigger points that are in weakened muscles under biomechanical tension.
Dystonia: Higher starting doses are administered and often with electromyographic and/or ultrasound guidance.

ues to work full-time. His latest injections were carried out in June 2008 with continued good efficacy.

Discussion

For the patients referred with a diagnosis of FMS, a detailed clinical evaluation was necessary to confirm that their findings followed the American College of Rheumatology criteria.[90] Algometry was always carried out to confirm the TeP count based on a pain threshold less than 4 kg. The Travell-Simons approach (see Table 1) was used for Myofascial Pain Syndrome (MPS) having all major criteria and at least one minor criterion. Myofascial pain syndrome TrPs—with their characteristic taut band, referred pain zone, and twitch response on needling or snapping palpation—differed from FMS TePs, although overlap was noted to occur in some patients (e.g., muscles such as the midpoint trapezius and extensor carpi radialis brevis).

One previous published study on BTX-A for FMS found it to be ineffective.[91] This was a small study of 10 patients who underwent alternate injections of lidocaine or BTX-A solely into the upper trapezii muscles. Only one patient reported relief of pain for two weeks with lidocaine. In our experience, injections into the trapezius may exacerbate pain in FMS patients, particularly in the presence of a head-forward posture with depressed scapula and TOS symptoms (painful paresthesias in the arm). Weakening this scapula elevator will aggravate the tension on the brachial plexus. Instead, injections into the tight pectoralis minor/levator scapulae muscles combined with daily stretching of these muscles and scapular stabilization exercises to strengthen the trapezii and rhomboids result in a much better clinical response.[92]

For myofascial pain, studies however are both supportive[93-96] and non-supportive.[97-99] Successful randomized trials were published for chronic piriformis pain syndrome[100-102] and chronic mechanical back pain.[103]

When there is co-existent neuropathic pain, pharmaceutical management is often necessary. Options include a trial of gabapentin slowly titrated up to 2,400 to 3,600 mg/day, pregabalin up to 450 mg/day,[104] and/or tizandine 2 to 4 mg at night titrated up to 12 mg/day.[105] Tramadol may also be used for pain control.[106] Cannabinoids combined with opioids have also been published as helpful for severe neuropathic pain in FMS.[107,108]

When injecting BTX-A for pain, we recommend using the ABCD recommendations found in Table 4.

In general, for FMS patients, BTX-A injections should be done "low and slow" and work best incorporating the biomechanical approach. With the exception of headaches, a maximum of two to four sites should be infiltrated initially—usually the levator scapulae and/or pectorals. If the patient has a good partial response, then other sites may be injected later. A 2:1 dilution is recommended. A 1.5 inch 27 or 25 gauge needle is used for the neck/shoulder girdle muscles. For pericranial muscles associated with migraine, a 1:1 dilution using a 0.5 inch 30 gauge needle appears to work best with least ptosis side-effect. The Silberstein approach of one horizontal row in the frontalis muscles is preferred over the Blumenfeld technique of two rows—as the former involves fewer injection sites and less pain. If there is marked skin hyperalgesia, injections should be done quickly with no needling or fanning out technique and using smaller gauge needles (e.g., 30 gauge 1 inch) followed by topical local anesthetic or ice, as tolerated. Longer needles (e.g., 2 inch 25 gauge and 3.5 inch 22 gauge) are needed to access deeper muscles such as the piriformis. Electromyographic guidance is often used for the first session to help in localizing such deep muscles. With good clinical results and depth recording, subsequent injections could then be done effectively without the need for EMG. Higher risk muscles such as the scalenes were almost always injected via EMG. An interdisciplinary model augments clinical results where each patient gets examined concurrently by both the manual therapist localizing the shortened muscles/TrPs and the physiatrist doing the injections. Post-injection physiotherapy should always be done emphasizing stretching of shortened muscles and core stability strengthening.

Conclusion

In our experience, disuse atrophy—especially of the temporalis muscle—did not occur in any patient as high doses were avoided in non-dystonic muscles. Autoimmunity (where BTX-A then stops working) was also not observed. Rare post-injection pain flare-ups did occur, requiring additional local anesthetic injections, but it did not deter patients from coming back. Patients who complied well with their exercises could often go for longer periods between BTX-A injections. Better results are obtained when treatments are integrated with lifestyle changes including adequate physical activity level,[109] good nutrition with detoxification,[110] sleep hygiene, and coping skills in an interdisciplinary approach.[111]

From an evidence-based perspective, there is obviously a need to do further randomized controlled double-blinded studies for BTX-A using a biomechanical approach for treating pain. It is hoped that this report will stimulate further research in this area.

APPENDIX A. BOTULINUM TOXIN PRODUCTS

	Xeomin®	Botox®	Botox–Cosmetic™/ Vistabel®	Dysport®/ Reloxin®	Dysport® Cosmetics®	Neurobloc®/ Myobloc®
Company	Merz Pharmaceuticals	Allergan	Allergan	Ipsen / Medicis	Ipsen / Medicis	Solstice Neuroscience
Type	Type A-Hall Strain	Type A-Hall Strain	Type A-Hall Strain	Type A	Type A	Type B
Approvals	European Union, Mexico, Argentina, Brazil	In over 75 countries all over the world including USA and Canada	In 16 countries, including USA, Canada, Italy, France	Dysport: In over 65 countries, not in USA or Canada	Germany, some other european countries	Europe and USA
Active substance	Botulinum neurotoxin type A (150 kd), free from complexing proteins	Botulinum toxin type A complex (900 kd)	Botulinum toxin type A complex (900 kd)	Botulinum toxin type A complex (900 kd)	Botulinum toxin type A complex (900 kd)	Botulinum toxin type B complex
Comparison of strength of action	1	1:1	1:1	Approx. 1:3 – 1:4	Approx. 1:3 – 1:4	1:1000
Indications	Blepharospasm Cervical dystonia	Many indications including blepharospasm and cervical dystonia	Glabellar lines	Many indications including blepharospasm and cervical dystonia	Glabellar lines	Cervical dystonia only
Mode of action	SNAP 25	SNAP 25	SNAP 25	SNAP 25	SNAP 25	VAMP
Pharmaceutical form	Powder for solution for injection	Powder for solution for injection	Powder for solution for injection	Powder for solution for injection	Powder for solution for injection	Solution
Units/vial	100	100	50	500	500	2.500/5.000/10.000
Volume	Max. 8 ml	Max. 10 ml	1,25 ml	Max. 2,5 ml	Max. 5 ml	0,5 ml; 1 ml; 2 ml; max. 3,5ml
Re-constitution	0,9 % nacl Solution	0,9 % nacl Solution	0,9 % nacl Solution	0,9 % nacl Solution	0,9 % nacl Solution	Prepared solution, dilutable
Storage	25 °C	2-8 °C <-5 °C	2-8 °C <-5 °C	2-8 °C	2-8 °C	2-8 °C, do not freeze
Shelf life (unopened)	36 months	36 months	36 months	24 months	24 months	24 months
Shelf life reconstituted	24 h	4 h	4 h	8 h	9 h	24 months (closed)
Auxilliary substances	Albumin 1 mg Sucrose 4,7 mg	Albumin 0,5 mg Nacl 0,9 mg	Albumin 0,5 mg Nacl 0,9 mg	Albumin 0,125 mg Lactose 2,5 mg	Albumin 0,125 mg Lactose 2,5 mg	Albumin, nacl, succinat, octanolat, tryptophan
Ph-Wert	5-7	5-7	5-7	5-7	5-7	5,6
Foreign protein load in dose-equivalence range	0,6 ng/100 U	5 ng/100 U	2,5 ng/50 U	4 ng/400 U	4 ng/400 U	100 ng/10.000 U
Specific activity (MU per ng protein)	166 MU/ng	20 MU/ng	20 MU/ng	100 MU/ng	100 MU/ng	100 MU/ng

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