Effective Pain Palliation in Fibromyalgia Syndrome Patients with Botulinum Toxin Type-A: Case Series of 25

Gordon D. Ko
Scott Whitmore
David Huang
Robert McDonald

ABSTRACT. Background: These case reports document effective treatment using botulinum toxin type-A [BTX-A] in fibromyalgia syndrome [FMS] patients. Outcome measures [including pain scales, Fibromyalgia Impact Questionnaire, algometry] were recorded on 25 FMS patients undergoing repeated BTX-A injections [one to five years duration].

Findings: Pain and function were improved in these patients. Muscles injected with good response included the frontalis, corrugators [for headache], levator scapulae, pectoralis minor [neck/shoulder pain], paraspinals, piriformis and sacroiliac ligaments [low back pain]. The BTX-A worked best with biomechanical approaches incorporating postural correction and core stability strengthening.

Conclusion: Our clinical experience suggests that pain in FMS patients may be effectively managed with BTX-A. doi:10.1300/J094v15n04_07

KEYWORDS. Botulinum toxin type-A, fibromyalgia syndrome, low back pain, migraine headache, whiplash

Gordon D. Ko, MD, CCFP[EM], FRCP[C], DABPM&R, DABPM, Scott Whitmore, BSc[PT], Dip.Manip.PT, MCPA, FCAMT, IFOMT, David Huang, BSc[Hons], DC, FCCRS, and Robert McDonald, BSc, RMT, DAc, Dipl.Osteopathy, Canadian Centre for Integrative Medicine, 12 Main Street North, Markham, Ontario, Canada L3P 1X2.

Address correspondence to: Dr. Gordon D. Ko, University of Toronto, Canadian Centre for Integrative Medicine, 12 Main Street North, Markham, Ontario, Canada L3P 1X2.

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INTRODUCTION

According to the American College of Rheumatology [ACR] criteria for classification, the fibromyalgia syndrome [FMS] is a condition characterized by widespread pain [over three months] with 11 or more of 18 characteristic tender points [TePs] on palpation with four kilograms of digital pressure (1). It affects two percent of the United States general population, predominantly females, with the most common age at presentation of 40 to 50 years (2). Associated syndromes include prolonged morning stiffness, axial skeletal pain [neck and back], temporomandibular joint pain (3), and recurrent headaches [45 percent] (4). The FMS has also been documented after physical trauma (5,6) and whiplash (7), but the causal relationship has not been established according to a consensus report on FMS and disability (8). It has been estimated that the direct medical cost of FMS to the United States economy is in excess of $16 billion annually (9). In 1993 the net cost in Canada was estimated to exceed $700 million (10). Despite such costs, effective long-term treatment remains elusive. A recent review paper documents that the most studied medications to date are the tricyclic derivatives, such as amitriptyline and cyclobenzaprine (11). This same review documented that botulinum toxin-A [BTX-A] treatment is "presently in the early stages of research for fibromyalgia syndrome" (12). One proposed theory for such BTX-A relieving pain is by resolving muscle trigger points [TrPs]. It is important to distinguish TrPs from FMS TePs. The criteria for TrPs are listed in Table 1.

It has been reported that 72 percent of FMS patients have TrPs (14). Tender points do not usually respond to injections of local anesthetic, but TrPs in FMS do (15). Current theories as to the pathophysiology of TrPs include the dysfunctional motor endplate where excessive acetylcholine is released (16). Botulinum toxin type-A is effective for muscle pain and spasticity through its prolonged blockade of acetylcholine. The active moiety, a 150 kDalton protein, is the most potent of the seven neurotoxins produced by the gram-positive anaerobic rod-shaped bacteria *Clostridium botulinum* (17). Its mechanism of action is described in the accompanying diagrams.

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

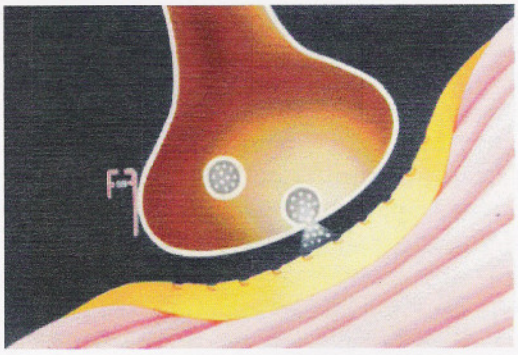
When injected into muscle, BTX-A is taken up at the neuromuscular junction [NMJ].

The light chain then cleaves the 25 kDalton synaptosome-associated protein and inhibits calcium activated release of acetylcholine [see Figure 1c]. Prolonged muscle relaxation/paralysis occurs as a result of this block. Collateral terminal sprouting will occur to attempt reinnervation of the neuromuscular junction [NMJ]. By day 63, these sprouts will stop growing. They then retract back as the original NMJ function returns around three months (18). Patients are usually advised that the onset of action occurs around day 3, and the peak effect after three weeks. The average duration of response is three months. Injections are spaced out a minimum of three months to minimize the risk of antibody formation to the protein [which would prevent BTX-A from working the next time].

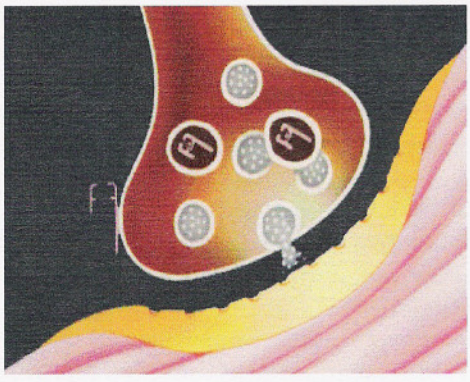
Botulinum toxin type-A comes in vials of 100 units. A unit of BTX-A is defined as the lethal dose for 50 percent of a colony of 20 gm Swiss-Webster mice. Extrapolated to the 70 kg human, the lethal dose would be about 2,700 units. The typical maximum dose at one injection setting is 400 units [higher doses up to 600 units have been reported]. 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 mus-

FIGURE 1. a. A heavy chain [100 kD] attaches it to the pre-synaptic membrane of the nerve terminal. b. Endocytosis of the BTX-A molecule then occurs. c. After endocytosis, the disulphide bond is broken, allowing the light chain to move to the presynaptic terminal. [reprinted with permission, Allergan Inc.]

a.



b.



c.

cle injections]. Such incidences are largely dependent on operator technique and dose used. One recent meta-analysis documents the overall safety of BTX-A (19). Relative contra-indications to BTX-A include generalized muscular weakness [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 (20). 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 (21).

It has been reported that 67 percent of FMS patients had migraine headaches prior to onset of their FMS (22) and that 25 percent of chronic low back pain [LBP] patients will evolve into FMS (23,24). After reviewing the studies on BTX-A working in migraines and LBP, we proceeded with showing effective treatment in FMS patients with these conditions (25,26).

MATERIALS AND METHODS

This paper presents 25 patients (with 4 earliest treated patients in greater detail) who underwent repeated BTX-A injections with outcome measurements reported pre-injection and one to two months following their latest injections. Measurements included the visual analogue scale for pain [PVAS], the short-form McGill Pain Questionnaire [SFM], the Fibromyalgia Impact Questionnaire [FIQ[and tender points pain thresholds (Fischer algometer by one author). These patients were referred from family physicians and specialists [rheumatologists and neurologists] and were seen at both academic [tertiary care hospital-based] and community clinic settings.

Patients provided signed informed consent for undergoing all injection treatments and participating in this uncontrolled study. The consent forms followed the guidelines laid out by the ethics review board and the Canadian Medical Protective Association.

RESULTS

Detailed Case Reports [Followed Since 2000]

Case Study #1

A 33-year-old married disabled customer service worker was seen in 2000 with widespread pain and right sciatica for five years. Her medical history included childhood sexual abuse (27,28), major depressive disorder (29), panic disorder, agoraphobia, abnormal sleep electroencephalogram [restless legs (30), alpha-delta intrusion (31)], slip-and-fall trauma [October 1998], and a car accident (32) [January 1999] with two-week hospitalization, subsequent home care, and wheelchair use.

Previous treatments included physiotherapy [with modalities such as laser and attempts at active exercise, hydrotherapy, and core training], chiropractic, massage, Chan-Gunn acupuncture, podiatry orthotics, and psychotherapy. Medications used were oxycontin, cyclobenzaprine, relafen, gabapentin, rivotril, stadol, and imovane. She did not improve with epidural corticosteroids [computerized tomography scan: L_5S_1 bulging disc, but EMG study was normal] and facet joint injections/nerve blocks.

Pre-injection [in March 2000] outcome measures are listed in Table 2. Physical exam findings also included: height = 70 inches, weight = 320 pounds, TeP index = 54, and Fischer algometry average pain threshold < 2 kg [3 + tender].

TABLE 2. Data from Case Study #1

Outcome Measure	Pre-Injection	Post-Injection
	March 2000	May 2000
PVAS	10/10	4/10
SFM	37/45	2/45
OLBP	23/50	1/50
FIQ	69.4/90	11.3/90
TeP Count	18/18	5/18

PVAS = Pain visual analog scale, SFM = Short-Form McGill Pain Questionnaire, OLBP = Oswestry Low Back Pain Questionnaire, FIQ = Fibromyalgia Impact Questionnaire, TeP = tender point

An initial procaine injection into the most painful TrPs provided good but short-term relief. In April 2000, 200 units of BTX-A were injected into the right piriformis [3.5 inches 22 gauge needle with EMG guidance], right T11 erector spinae, and both upper trapezii. One month later, she reported for the first time in years that she was able to walk several blocks, make beds without help, do laundry, dishes, and most yard work. She also joined a weight loss program.

In August 2000, after the second series of BTX-A [400 units] in the same muscles and levator scapulae, she weaned off oxycontin and relafen completely. On the third series BTX-A [400 units], she began vocational retraining. She had lost 34 pounds.

Further injections were carried out in April 2001 [300 units], October 2001 [250 units], and February 2002 [200 units]. She improved to the point where she could exercise regularly, lose weight [she had lost 68 pounds], and work part-time. Two years later, she returned in February 2004 and had 200 units of BTX-A administered to recurrent TrPs in the left levator scapula, left pectoral, and right gluteal areas. Her latest injections were done in February 2006 [400 units] with continued good pain relief.

Case Study #2

A 46-year-old married mother of two and church worker was seen with FMS, irritable bowel syndrome, and migraines 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 [hepatitis C diagnosed in 1995] (33). She was in a car accident in 1989, incurring whiplash and a right frozen shoulder.

Initial examination [June 2000] findings included: height = 64 inches, weight = 114 pounds, no anemia or jaundice, and BP134/99 mmHg. She was treated with hydrotherapy [in addition to active physiotherapy] and gabapentin [slowly up to 2400 mg/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 injec-

tions were 25 units for headaches [with supraorbital 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 fewer wrinkles!] [see Table 3].

She returned in March 2001 for an injection of 300 units of BTX-A. Her 15th set of injections was done in February 2006 with 400 units. She continues to work full-time and requires no oral analgesic agents.

Case Study #3

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 110/70 mmHg [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 [left] and 95 pounds [right] (34). The 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-spine [minimal disc bulge C5-6] were all unremarkable.

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 [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 [Childers' protocol]. At one month post-BTX-A, there was definite improvement [see Table 4]. 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 re-

TABLE 3. Data from Case Study #2

Outcome Measure	Pre-Injection	Post-Injection	
	June 2000	September 2000	January 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

PVAS = Pain visual analog scale, SFM = Short-Form McGill Questionnaire, PDI = Pain Disability Index, FIQ = Fibromyalgia Impact Questionnaire, TeP = tender point

TABLE 4. Data from Case Study #3

Outcome Measure	Pre-Injection	Post-Injection
	December 1999	December 2000
PVAS	4/10	1/10
PDI	25/70	5/70
TeP Count	12/18	5/18
Jamar grip [left hand]	75 lbs.	100 lbs.

PVAS = Pain visual analog scale, PDI = Pain Disability Index, TeP = tender point, lbs. = pounds

turned 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 continues to work full-time.

Case Study #4

A 53-year-old woman had post-traumatic head/upper facial pain after a car accident in 1989. Computerized tomography and magnetic resonance imaging scans were normal. Over the subsequent 10 years, she had 12 surgical procedures including open cervical level two ganglionectomy, cervical facet rhizolyses on three occasions, cervical C2 neurotomy [dorsal ramus medial branch], right temporal artery excision, bilateral supraorbital nerve resections, and percutaneous microballoon compression of the gasserian ganglion. Attempts with active physiotherapy and exercise were severely limited by her chronic daily pain.

Despite palliative nerve blocks from the referring anesthesiologist, she still complained of daily bifrontal headaches radiating to the upper shoulders and the dorsal area of her neck. Topamax was added to her medications which included paxil, oxycontin, stemetil, amitriptyline, ibuprofen, and losec.

Physical examination revealed hypoesthesia in the forehead and the second cervical distribution. Tenderness was most noted on the upper trapezii, frontalis, and paracervical muscles. She had 18 out of 18 TePs and fulfilled the ACR criteria for FMS.

Botulinum toxin-A injections administered to the pericranial [frontalis, corrugator, procerus, temporalis] and trapezii muscles showed good response, supported by outcome measures and surface EMG recordings [see Table 5].

Further injections have been carried out every three to four months. Her 14th set of injections were carried out in December 2005 [with 300 units]. She estimated it alleviated pain by 75 percent, allowing her to reduce her use of oxycontin [10 mg, twice daily]. Her FIQ score before BTX-A was 51.4/ 90. One month after her BTX-A injection [in December 2003], the FIQ was down to 14.8. With BTX-A, she reported that she can go shopping and carry 10 pounds of groceries. Her husband observed that she can do ironing without complaining of pain. She can do laundry, dishwashing, and can stand one hour to cook.

TABLE 5. Data From Case Study #4

Outcome Measure	Pre-Injection		One Month Post-Third Injection	
PVAS	7/10		4/10	
Headache Disability index	92/100		84/100	
Headache Impact test	68/78		58/78	
Vernon-Mior questionnaire	33/50		28/50	
Surface EMG RMS amplitudes [μV]	left	right	left	right
Frontalis				
-sitting at rest	2.24	3.99	1.44	0.96
-cervical lateral flexion	6.97	4.54	1.51	0.98
-cervical rotation	6.84	6.73	1.90	1.34
Trapezius				
-standing at rest	15.07	5.47	5.20	2.24
-cervical rotation	5.36	4.12	2.44	3.10

PVAS = pain visual analog scale, EMG = electromyogram, RMS = root mean square

Table 6 shows data from a total of 25 cases of FMS patients who had repeat BTX-A injections in the past six months [as of December 2004]. Prior to these injections, all patients had been prescribed traditional analgesic medications [mostly by their family doctor] and were always recommended to first go through a course of active physiotherapy [including stretching and core stabilization training]. Several patients dissatisfied with the lack of symptom relief also pursued complementary and alternative medicine therapies.

DISCUSSION

Though most patients were referred with a diagnosis of FMS, a detailed clinical evaluation was necessary to confirm that their findings fol-

TABLE 6. Case Series of 25 Fibromyalgia Syndrome Patients with Botulimum Toxin Type-A Injections for Pain

Patient number	Age/Sex	Occupation	N	First Injection [d/m/yr]	Latest Injection [d/m/yr]	Scores before BTX-A		Scores 4-6 weeks after last BTX-A	
						FIQ	PVAS	FIQ	PVAS
1 ∀	45/F	Material Handler	12	11/12/00 100 units	04/02/04 300 units	81.6/100	8/10	50.2/100	4/10
2 details in case #1	39/F	Personal support worker	7	03/04/00 200 units	24/02/04 [after 2 yr. gap] 200 units	69.4/90	10/10	11.3/90 [after 1st BTX-A]	4/10
3 mva	30/F	Asst. crown attorney	4	04/02/03 100 units	18/11/03 400 units	79.2/100	10/10	56.5/100	4/10
4	44/F	ICU Nurse	8	21/01/02 100 units	20/04/04 500 units	89/100	7/10	44.3/100	4/10
5 mva	47/F	Chiropractor	3	04/02/03 50 units	20/04/04 100 units	46.4/100	3/10	13.7/100	1/10
6	66/F	Legal secretary	6	30/09/02 100 units	06/04/04 200 units	84.7/100	10/10	17.1/100	2/10
7	39/F	Part-time clerical	8	08/04/03 100 units	27/04/04 500 units	83.2/100	10/10	68.7/100	4/10
8 ∀	50/F	Homemaker	4	31/07/03 200 units	27/04/04 300 units	72.7/80	8/10	51.4/80	4/10
9 crohn's	47/F	Banker on LTD	4	07/07/03 100 units	20/04/04 400 units	78.1/90	10/10	55.8/90	5/10
10	51/F	Banker	3	28/05/01 100 units	29/10/03 200 units	57.5/100	8/10	22/100	4/10
11 ∀	35/F	Public Health Clerk	5	25/02/03 100 units	20/04/04 500 units	82.9/100	7/10	18.5/100	3/10
12 ∀	31/F	Office Worker	4	10/03/03 100 units	17/09/03 200 units	66.2/100	8/10	41.8/100	4/10
13	44/F	French Tutor	2	27/05/03 100 units	28/10/03 100 units	21/45*	6.5/10	11/45*	2/10
14	49/F	Nurse	4	24/10/02 100 units	26/08/03 300 units	27/45*	6/10	21/45*	4/10
15	44/F	Social Worker	2	17/03/03 100 units	26/08/03 100 units	42/45*	9/10	14/45*	6/10
16 ∀	44/F	Admin. Asst.	6	27/05/03 100 units	02/03/04 200 units	55/100	9/10	39/100	5/10
17 ∀	31/F	Dentist	3	26/08/03 100 units	18/11/03 200 units	3/45*	5/10	2/45*	2/10
18	42/F	Healthcare worker	3	13/04/03 100 units	13/01/04 200 units	76.9/100	8/10	32.7/90	3/10
19	28/M	Financial advisor on LTD	6	25/11/02 100 units	09/02/04 500 units	40/45*	10/10	32/45*	4/10
20 ∀ details in case #4 mva	53/F	Homemaker	8	17/07/01 100 units	15/12/03 400 units	51.4/90	6/10	14.7/90	2/10
21 details in case #2	46/F	Clerical Work	9	10/12/01 100 units	06/04/04 400 units	57.0/100	5/10	6.7/100	2/10
22	44/F	Financial Advisor	3	12/05/03 200 units	15/12/03 400 units	27/45*	9/10	6/45*	6/10
23 ∀	55/M	I.T. Manager	7	27/06/02 100 units	20/04/04 200 units	80.3/90	9/10	34.9/90	2/10
24 mva	45/F	Social worker	7	27/04/01 100 units	16/03/04 300 units	77.2/100	8/10	7.7/100	1/10
25 mva	45/F	Accountant	5	14/01/03 100 units	13/01/04 500 units	66.9/90	10/10	42.5/90	2/10

* patients who completed only the short-form McGill pain questionnaire

N = number of botulinum toxin type-A injections, BTX-A = botulinum toxin type-A
d = day, m = month, y = year, FIQ = Fibromyalgia Impact Questionnaire, PVAS = pain visual analog scale, ∀ = had surgery, F = female, M = male, ICU = intensive care unit, LTD = long term disability, IT = information technology, mva = pain after motor vehicle accident

lowed the ACR criteria for FMS. Algometry was always carried out to confirm the TeP count [pain threshold less than 4 kg]. The Travell-Simons approach was used for MPS [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, though overlap was noted to occur in some patients [muscles such as the midpoint trapezius and extensor carpi radialis brevis].

In general, patients with MPS alone responded more readily to simpler treatments incorporating manual therapy, spray-and-stretch, and local procaine/lidocaine injections. Resistant localized MPS cases appeared to respond well to BTX-A and, in general, required fewer treatments than FMS patients. During the course of this study, there were five to six MPS patients seen for every one FMS patient. A higher proportion of the more recalcitrant FMS patients were seen in the tertiary care hospital clinic than in the community setting.

One previous published study (35) on BTX-A for FMS found it to be ineffective. 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. On the other hand, several earlier studies (36-39) have demonstrated clinical effectiveness for myofascial pain, including more recently published randomized double-blinded placebo controlled trials (40,41). Another recently presented paper suggested no difference compared to bupivacaine (42).

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 [strengthening the trapezii and rhomboids] result in a much better clinical response.

Botulinum toxin type-A has also been demonstrated to be effective in headache [migraine, tension, and cervicogenic types] treatment (43-46) and for chronic mechanical back pain (47). We have also found this effective in FMS patients who suffer from migraine headaches (25) and LBP (26). 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 (48), as well as in the brain and trigeminal nerve ending (49,50). Botulinum toxin type-A also works in pain through inhibition of other pain neurotransmitters [calcitonin gene related peptide (51), vasoactive intestinal polypeptide (52)] and by elevation of enkephalins at the dorsal horn of the spinal cord (53). In a rat formalin model, BTX-A was found to have dose-dependent anti-inflammatory effects (54) with the mediator likely to be glutamate (55, 56). Fos expression in the dorsal horn was also inhibited (57).

Based on this finding, we have observed effectiveness in neuropathic pain control with intradermal injections of BTX-A (58,59). This also applies for the 27 to 38 percent of FMS patients with marked skin allodynia in which there are higher levels of cytokines in the skin (60). 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. Other options include a trial of gabapentin slowly titrated up to 2,400 to 3,600 mg/day, pregabalin up to 450 mg/day (61), and/or tizandine 2 to 4 mg at night titrated up to 12 mg/day (62). Tramacet may also be used for pain control (63). Cannabinoids combined with opioids have also been published as helpful for severe neuropathic pain in FMS (64,65).

When injecting BTX-A for pain, we advise the ABCD recommendations, found in Table 7.

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 [migraine], a 1:1 dilu-

TABLE 7. 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 guidance (66).

Recent consensus in the Canadian Society for Neurotoxins in Pain recommend a 4:1 dilution for most muscles and a 2:1 dilution [to minimize diffusion] in pericranial, scalene, sternocleidomastoid, and piriformis muscles.

tion [with a 0.5 inch 30 gauge needle] appears to work best with least side-effect [ptosis]. The Silberstein approach [one horizontal row in the frontalis muscles] is preferred over the Blumenfeld technique [two rows] as the former involves fewer injection sites and less pain. If there is marked skin hyperalgesia, injections should be done quickly [no needling or fanning out technique] with smaller gauge needles [27.5 inch or 30 gauge 1 inch] and followed by topical local anesthetic or ice [as tolerated]. Longer needles [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.

Clinical experience suggested that the duration of pain relief outlasts the muscle relaxation effect (67). In this study, disuse atrophy [especially the temporalis muscle] did not occur in any patient as high doses were avoided in non-dystonic muscles. Auto-immunity was also not observed [where BTX-A then stopped working]. Rare post-injection pain flare-ups did occur, requiring additional local anesthetic injections, but did not deter patients from coming back. Patients who complied well with their exercises, could often go for longer periods in between BTX-A injections. All treatments also need to be integrated with lifestyle changes including adequate physical activity level (68), coping skills (69), detoxification (70), sleep hygiene (71), and an interdisciplinary approach (72-74). Excess major negative life events and permanent disability pensions were associated with a negative outcome (75). Perhaps BTX-A, shown to be effective in migraine and back pain, could also be used earlier to prevent the development of FMS and its ensuing disability.

From an evidence-based perspective, there is obviously a need to do a proper randomized controlled double-blinded study for BTX-A in FMS. It is hoped that this report will stimulate further research in FMS management.

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