

# The Use of Botulinum Toxins in the Management of Myofascial Pain and other Conditions Associated with Painful Muscle Spasm

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## Objectives

- Discuss the pharmacology and potential side effects of botulinum toxin.
- Discuss traditional approaches to the treatment of myofascial pain syndrome.
- Discuss the potential applicability of botulinum toxin in the treatment of refractory cases of myofascial pain (including a review of currently available literature).
- Discuss injection techniques and dosing of botulinum toxin for myofascial pain.

## Introduction

Botulinum toxins (BTs) are potent neurotoxins produced by *Clostridium botulinum* that are able to block acetylcholine release at the neuromuscular junction producing a flaccid paralysis. The resulting temporary chemodenervation (lasting several months) occurs with minimal risk of systemic adverse effects. BTs can provide symptomatic improvement in a variety of conditions associated with muscle spasm or hypertonicity<sup>1</sup>, including focal dystonia<sup>2</sup>, cervical dystonia (torticollis)<sup>3</sup>, spasmodic dysphonia<sup>4</sup>, oromandibular dystonia (Meige's syndrome)<sup>5</sup>, temporomandibular disorder<sup>6</sup>, tension-type<sup>7</sup> and migraine<sup>8</sup> headache and refractory myofascial pain syndrome<sup>9</sup>. Although the cosmetic use (reducing facial wrinkles<sup>10</sup>) is perhaps the best known application for BTs, there has been tremendous interest and clinical study into their potential for therapeutic efficacy in chronic pain syndromes<sup>11,12,13,14,15,16</sup> though the mechanism of analgesia in such conditions is probably not entirely due to a reduction in focal muscle spasm. This chapter will summarize the clinical studies evaluating botulinum toxins as potential therapeutic agent in refractory cases of myofascial pain or other conditions associated with painful muscle spasm.

The recent addition of the Elan Pharmaceutical product, Myobloc™ (BT<sub>B</sub>) also raises the important issue of choice. Although the net effect of each BT is to block acetylcholine release, one cannot take data derived from clinical studies of BT<sub>A</sub> and apply it to BT<sub>B</sub> by making some adjustment for potency differences. Each BT has a different structure, different mechanism of action (although the net effect may be the same), different formulation, different storage and handling guidelines, different FDA-approved uses, different dosing concerns, and possibly different antibody development concerns. BT<sub>A</sub> has been around much longer and all of the published pain and headache clinical research used BT<sub>A</sub>.

## Myofascial Pain Syndrome

Myofascial pain syndrome (MPS) is a regional pain syndrome<sup>17</sup> defined by the presence of a localized, hyperirritable trigger point, a palpable knot or mass (usually 3-6mm in diameter), in a taut band of muscle associated with tenderness and referred pain into well-defined areas remote from the trigger point area.<sup>18,19</sup> Myofascial pain syndrome (MPS) is characterized by chronic, focal muscle pain, associated with stiffness, tenderness and

fatigue.<sup>20</sup> A myofascial trigger point has been defined as a well-localized, highly irritable taut band of skeletal muscle fibers that responds with a twitch response and referred pain distribution pattern to palpation. Unlike active trigger points, a latent trigger point is clinically silent until activated, typically by trauma, but may cause pain on palpation.<sup>21</sup> Laboratory testing, radiographic studies or other standard tests are not helpful in making a diagnosis of MPS.<sup>22</sup> Diagnostic ultrasound has not been found to be useful.<sup>23</sup> Testing appears only to be useful for excluding other diagnoses.

Just as one should not lump fibromyalgia (FM) and MPS into the same diagnostic basket, myofascial trigger points should be distinguished from fibromyalgia tender points that are in characteristic locations and may be clinically silent unless stimulated by palpation.<sup>24</sup> By the American College of Rheumatology 1990 Criteria<sup>25</sup>, FM is a more widespread pain condition (three or more body regions above and below the waist) lasting for 3 or months associated with pain in at least 11 or 18 tender point sites on digital palpation with a force of approximately 4 kg. Tender points are not associated with a "twitch" on palpation and are usually clinically silent unless stimulated by palpation. Tender points typically do not cause a referred pain pattern on palpation.<sup>26</sup> Patients with FM tend to have more constitutional symptoms than those with MPS.

Without a well-understood pathophysiological etiology and the lack of specific diagnostic tests and the paucity of objective physical signs, the diagnosis of MPS has become suspect for some and overly diagnosed for others.<sup>28</sup> The pathogenesis of trigger points is unknown but several hypotheses exist.<sup>29</sup> The energy crisis model proposes that direct injury or repetitive overloading of muscle results in sustained release of intracellular calcium and focal muscle hypercontraction, possibly due to disruption of the sarcoplasmic reticulum.<sup>30</sup> The localized spasm induces release of nociceptive and inflammatory mediators that produces a positive feedback process leading to focal ischemia (depletion of ATP), lactic acidosis and eventual fibrosis. However, pathological and histological analyses do not support this theory.<sup>31</sup>

The dysfunctional muscle spindle and the irritable motor endplate models grew out of different interpretations of electromyographic (EMG) evaluations of trigger points. Durette et al studied 21 patients with MPS and found no evidence of spontaneous fibrillation or positive sharp wave potentials.<sup>32</sup> In contrast, Hubbard and Berkoff examined EMGs in the upper portion of the trapezius muscle in individuals with fibromyalgia or tension-type headaches.<sup>33</sup> Trigger points were identified with digital palpation of the taut muscular band and characteristic pain referral pattern. A monopolar EMG needle was inserted directly over the trigger point and advanced incrementally until the patient described his typical pain and referral pattern. One mm adjustments in the needle were enough to make the pain/referral disappear. A second control needle was placed 1 cm away. Sustained spontaneous EMG activity was found at the trigger point, but not at the control point. This low level electrical activity was not blocked by tubocurarine (blocking cholinergic motor activity) but was by sympatholytics such as phentolamine (blocking muscle spindle afferents). Latent trigger points showed similar findings, but to a lesser degree. No fibrillation potentials or positive sharp wave potentials were noted in trigger points or control points. The authors hypothesized that the EMG activity was generated from sympathetically stimulated intrafusal muscle fibers. Simons et al. used a similar technique and found active loci of spontaneous EMG activity much like that seen in the end plate region.<sup>34</sup> He postulated that the electrical activity was due to abnormally increased motor endplate activity with excessive

release of acetylcholine at the neuromuscular junction resulting in extrafusal muscle contraction in the immediate vicinity of the extrafusal motor endplates.

The peripheral sensitization model proposes that peripheral silent afferents become activated after injury by the release of peripheral nociceptive mediators.<sup>35</sup> Whereas the central sensitization model proposes that the repetitive incoming nociceptive traffic induces neuroplastic changes in the dorsal horn (NMDA-mediated process).<sup>36</sup> It is likely that many of these proposed processes are occurring simultaneously.

Overall treatment goals are directed toward interrupting the pain/spasm cycle, treating underlying conditions if MPS is a secondary process, and working on maladaptive behaviors by using cognitive-behavioral approaches.<sup>37</sup> Travell and Simons popularized the spray and stretch technique as the mainstay of treatment for MPS.<sup>38</sup> The purpose is to desensitize the trigger point and stretch and relax the taut band of muscle. Ice may be used instead of vapocoolant sprays. Authors disagree on how effective the treatment is compared with trigger point injections, but it certainly makes sense to use this noninvasive technique as an adjunct to other therapies especially where the patient and family can be trained in the technique and the patient is cooperative and willing to do the post treatment exercises.

Along with spray and stretch techniques, physical therapy<sup>39</sup> (PT) and PT modalities are probably the most commonly used approaches in early MPS. Therapeutic heat and cold therapy<sup>40</sup>, transcutaneous nerve stimulation, electrical muscle stimulation, ultrasound, iontophoresis, myofascial release, massage, hydrotherapy, stretching and strengthening exercises (passive and active) and acupuncture<sup>41</sup> can be very helpful.

Borg-Stein and Stein reviewed the medical literature of trigger point injections and concluded that although such injections have widespread clinical acceptance, evaluating their efficacy is hindered by difficulties in definitions as well as variations in technique.<sup>42</sup> Gerwin et al. noted that although interrater reliability in identifying trigger points is somewhat suspect, it improves significantly with a few hours of training.<sup>43</sup> Obviously, training in injection technique is important as well in ensuring that whatever is injected is delivered to the trigger point region.

Short-term efficacy has been demonstrated with dry needling,<sup>44</sup> sterile water,<sup>45</sup> lidocaine (plain 1 and 2%),<sup>46</sup> bupivacaine,<sup>47</sup> diclofenac,<sup>48</sup> and prednisone. It appears that the nature of the injected substance is not a critical factor and it is unclear whether any therapeutic substance injected provides more benefit than dry needling alone.<sup>49</sup> The needle is presumed to cause a mechanical disruption of the trigger point zone and stretch of adjacent muscle fibers. Local anesthetics when injected do reduce post injection soreness and for that reason are most commonly used. All local anesthetics have the potential for myotoxicity with lidocaine 0.5-1.0% having less potential for this than bupivacaine 0.25-0.5%, but the problem rarely occurs absent excessive use of this modality. Epinephrine may prolong the block from the local anesthetic, but is not necessary for trigger point release. Most authors feel that steroids are not needed unless there is an associated inflammatory process such as bursitis, tendonitis, or scar neuroma. Trigger point injections should be part of a comprehensive treatment program and not a sole treatment initiative.

Pharmacotherapy for MPS has included skeletal muscle relaxants (although many of these produce unwanted sedation and side effects), antispastic agents (such as baclofen and tizanidine), antidepressants (especially tricyclic antidepressants), anticonvulsants (especially those producing reduction in muscle spasm such as the benzodiazepines clonazepam and diazepam and gabapentin), and traditional analgesics.<sup>50</sup> None of these agents are particularly

effective, but may be useful as adjuncts to other treatments. Unfortunately, much of the published literature discussing pharmacotherapy options lumped MPS and FM together and does not speak specifically to the response of MPS.

### **Botulinum Toxins in Myofascial Pain and Conditions with Muscle Spasm: Clinical Developments**

When conservative therapies fail to improve refractory myofascial pain, BTs may be quite helpful in reducing the spasm to a point where conservative measures can be reinstated with greater effect to resolve the process. There seems little doubt that BT injections can produce a much longer duration response than local anesthetic or steroid + local anesthetic trigger point injections. However, it was only relatively recently that this fact was firmly established.

Lalli et al. looked at lidocaine vs. BT<sub>A</sub> in the treatment of myofascial pain in a double-blind randomized trial of 20 patients (15 female) who received 50 units of BT<sub>A</sub>(Botox®) or 1% lidocaine.<sup>51</sup> Botulinum toxin-treated patients showed statistically significant improvement at 2 and 4 weeks as measured by visual analog scales and palpable muscle spasm. No major side effects were seen.

Porta et al. looked at lidocaine/methylprednisolone versus BT<sub>A</sub> (Botox®) in 40 patients with MPS in the psoas, piriformis, and scalenus anterior muscles in a single-blind, randomized trial.<sup>52</sup> Patients received BT (80-150 units) or similar volume of steroid/local anesthetic as a compartment injection into the affected muscle. The reduction in pain scores was better in the BT-treated group at 30 days (p=0.0598) but did not reach significance until 60 days (p=0.0001). No major side effects were observed.

Patel et al. presented their preliminary results from a randomized double-blind, placebo controlled study comparing trigger point injections with saline, bupivacaine or BT<sub>A</sub> (Botox®).<sup>53</sup> Twelve patients had completed the study at the time of the poster presentation. The preliminary data with this small number of patients showed a trend toward significance for the BT<sub>A</sub> group.

It was in 1994 that initial clinical reports hinted at the potential of BT in improving myofascial pain. As seems to be the case in other new areas for use of a product, initial reports were either anecdotal case reports or flawed by small numbers of patient participants.

Acquadro and Borodic reported on the use of BT<sub>A</sub> (Botox®) in 2 female patients with refractory trapezius and splenius capitis myofascial pain.<sup>54</sup> The first injection of 50 units provided the patients with slight improvement and the second of 150 units 4 weeks later provided what was reported as dramatic improvement.

Cheshire et al. described responses to BT<sub>A</sub> (Botox®) trigger point injections in six patients with chronic myofascial pain in a randomized double-blind, placebo controlled study.<sup>55</sup> Cervical paraspinal or shoulder girdle trigger points were injected with either saline or 50 units of BT<sub>A</sub> reconstituted in 4 ml of preservative-free saline injected equally into two or three sites. Responses were measured over 8 weeks by verbal pain descriptors, visual analog scales, pressure algometer and palpable muscle spasm or firmness. Four of six subjects experienced reduction in pain and spasm following BT, but not saline, injections. Onset of responses occurred within the first week following BT injections with a mean duration of 5-6 weeks.

In 1997, Alo and colleagues reported on their prospective but uncontrolled study of 52 patients (29-83 years old) with refractory MPS (cervicothoracic 33, low back/gluteal 19)

who received fluoroscopically-directed injections of BT<sub>A</sub> (Botox®) 10u/cc in preservative-free saline (10-300 units BTA were used in the cervicothoracic MPS patients and 90-300 units BT<sub>A</sub> were used in the low back/gluteal MPS patients).<sup>56</sup> Up to 3 treatments were given 4 weeks apart if persistent spasm and pain were noted.<sup>57</sup> Greater than 50% reduction in spasm and symptoms were achieved in 63% of the cervicothoracic and 43% of the lumbar/gluteal patients. A very mild, short-lived flu-like syndrome was seen in 62% of patients with the first injection and not observed subsequently to this extent and only one patient suffered transient dysphagia. The rather high incidence of flu-like syndrome has not been reported by other authors and may have been due to the use of contrast for targeting the injections under fluoroscopy.

Grana reported on 5 patients with cervical MPS who received BT<sub>A</sub> (Botox®)50 units in 4cc preservative-free normal saline in divided doses into the upper and middle trapezius, scalene, levator scapulae and sternocleidomastoid muscles after achieving less than a week of relief with standard trigger point injections with local anesthetics.<sup>58</sup> All 5 patients reported improved VAS pain scores 2 weeks post BT<sub>A</sub> and 4/5 still had VAS reductions at 3 months.

In the first large controlled study of BT<sub>A</sub> in muscular pain, Knusel et al. presented data on the use of BT<sub>A</sub> (Botox®) in chronic low back muscular pain (without prior surgery or other identifiable spine pathology) in 70 patients randomized into four groups (placebo, 120, 180 or 240 units of BT<sub>A</sub>).<sup>59</sup> Patients in all groups improved in all outcome measures. The BT<sub>A</sub> 240 unit group showed statistical significance over placebo at weeks 6, 9 and 12 for muscle spasm and weeks 6 and 12 for physician global assessment. No adverse events of significance were noted.

These data and subsequent unpublished data derived from other studies conducted by Allergan on low back pain point to the difficulty of assessing a new modality of treatment in a rather amorphous condition. Low back pain is a rather broad diagnostic category that makes it difficult to be sure that any patient group is relatively homogenous. Additionally, recruiting patients who have not had surgery, have no spine pathology, have no pending litigation, disability or workers' compensation claims and have had no significant interventions whatsoever will recruit a group of patients that pain physicians see infrequently and such patients are likely to respond to even simple modalities, such as trigger point injections, creating the potential for high placebo response rates. Perhaps if different inclusion/exclusion criteria and a higher total dose were used similar to that used by Jabbari et al. (see below), better results might have been seen.

Porta et al. performed a preliminary trial of BTA (Botox®) and physical therapy on 38 patients (24 women, 14 men; age range 18-73 years; 3 with fibromyalgia) with piriformis (27), iliopsoas (9) and scalenus (2) myofascial pain.<sup>60</sup> Injections into the piriformis and iliopsoas were performed with CT-guidance while other injections were done by palpation alone. Efficacy and safety were evaluated at 1 month. Seventeen patients (45%) reported pain relief and 6 (16%) reported improvement. Eight of the 15 who had no improvement admitted to failing to comply with the therapy requirements showing that BT treatments do not work in a vacuum but must be part of a treatment continuum.

Wheeler et al. reported the lack of efficacy of BT<sub>A</sub> (Botox®) over placebo in when injected into trigger points in 33 patients with cervicothoracic myofascial pain in a randomized, double-blind study.<sup>61</sup> Participants were divided into 3 groups receiving 50 or 100 units of BT<sub>A</sub> diluted in 2 ml of preservative-free normal saline or normal saline and were evaluated over a 4 month period in a standard fashion. The most tender trigger point (if there

were several) was chosen as the injection site. Participants were followed regularly and algometer measurements of the trigger point injected as well as subjective assessment of improvement, visual analog scale measurements, and physical examinations were performed. A second injection of 100 units of BT in 2 ml of normal saline was given to 11 patients in the same site and to 2 patients in an adjacent symptomatic site.

Although by their strict criteria for improvement (absence of pain simultaneously on three different measures - Neck Pain and Disability Scale, pressure algometer, and patient's global assessment), similar clinical improvement rates across the 3 groups were seen, there were notable differences among the groups in response to the second injection. The number of patients determined to be asymptomatic was higher in the BT groups. The authors noted that further investigation with higher doses and sequential injections might have reached clinical significance. Certainly the use of 50 units while reasonable for a single injection site, is not sufficient if several muscles are involved. Additionally, the the study design of injecting only the most tender trigger point even if several active trigger points were identified seems to run counter to typical approaches to myofascial pain treatment of trying to "deactivate" all of the active trigger points in order to give the patient better relief.

Royal et al. presented their retrospective data on 81 patients (age range 21 to 84 years old) with cervical (73 injections), thoracic (17 injections), lumbar and/or gluteal (20 injections) and extremity (4 injections) MPS who had previously failed traditional conservative measures and had only short-term improvement with standard trigger point injections.<sup>62</sup> The 81 patients received 109 BT<sub>A</sub> (Botox®) injections (average of 131 units per session) over an approximately 18-month period. Six patients were excluded from analysis due to insufficient follow up information. Sixty-three patients (84 injections; 21 male, 42 female) experienced a fair to excellent response. Areas of MPS involvement were: cervical-73, thoracic-17, lumbar/gluteal-20, and extremity-4. BT<sub>A</sub> dosing ranges for specific muscle groups were as follows: Trapezius: 20-100 units; Levator scapulae: 15-40 units; Splenius capitis: 20-50 units; Sternocleidomastoid: 25-100 units; Quadratus lumborum: 20-60 units; Piriformis: 30-100 units; Rhomboid: 20-120 units; Thoracic and lumbar paraspinals: 20-40 per segment.

The BT<sub>A</sub> injections were performed as standard trigger point injections with the Botox® reconstituted in local anesthetic, typically bupivacaine 0.5%, in a final concentration of 10 units per cc. Each trigger point received 2-4 cc of total volume infiltrated in a standard fashion under direct digital palpation using a 25 Ga 1.5 inch needle with 1-2 cc directly into the trigger point and additional amounts in the surrounding taut band of muscle. Patients received 100 to 300 units of BTA (the majority received 100 units for unilateral pain and 200 for bilateral) at any injection session with the dosing amount determined by the number of involved muscles and severity of spasm. Only patients with a good to excellent response were offered repeat BT<sub>A</sub> injections when the first wore off. The complication rate was exceedingly low. One patient had transient neck muscle weakness within the first week that resolved completely after a few days. One patient developed transient tension-type headache symptoms in the first few days of the injection that was felt to be due to the injection itself.

A positive response was defined as at least a 30% reduction in symptoms from baseline. An excellent response was defined as at least 70% reduction from baseline. A good response was defined as 50-69% reduction and a fair response as 30-49% reduction. No relief or minimal relief was defined as a response less than 30% from baseline. The breakdown of responses are reflected in [Table 2](#). Ten percent of the patients injected were "cures" with

complete resolution of symptoms at one year follow up. The breakdown for patient insurance coverage was workers compensation (34%), private insurance (30.5%), medicare (19%) and personal injury (16.5%).

Freund and Schwartz reported on the treatment of whiplash-associated neck pain with botulinum toxin in a randomized, double-blind, placebo controlled trial of 26 patients. Fourteen of the patients received 100 units of BT<sub>A</sub> (Botox®) in 1ml of saline while twelve received placebo (1ml of saline). Five trigger points received 0.2ml each via a 30 Ga needle. The treatment group showed a trend toward improvement in range of motion and reduction in pain at 2 weeks post injection. At 4 weeks post, the treatment group was significantly improved ( $p < 0.01$ ).

Bahman Jabbari and colleagues at the Department of Neurology, Uniformed Services University, Bethesda, MD have studied the use of 200 units of BT<sub>A</sub> (Botox®), 40 units/site, versus saline placebo at five lumbar paravertebral levels on 28 patients with chronic unilateral low back pain using a randomized, double blind design.<sup>64</sup> Visual analogue scores (VAS) and the Oswestry's Low Back Pain Questionnaire (OLBPQ) were used to follow the patients. At three weeks, 11 of 14 patients who received BT<sub>A</sub> (78%) showed significant (>50%) pain relief versus 4 of 14 (28%) in the NS group ( $p = 0.021$ ). At eight weeks, 9 of 14 in the BT<sub>A</sub> group (61%) and 2 of 14 (14%) of NS group reported relief ( $P = 0.018$ ). Repeat OLBPQ at eight weeks showed improvement in 10 of 14 (70%) in the BT<sub>A</sub> group versus 3 of 14 (21%) in the NS group ( $P = 0.022$ ). No patient experienced side effects

Lang published her data on 72 patients receiving 95 BT<sub>A</sub> (Botox®) injections for MPS using a novel grid pattern into the mid belly of the muscles. The median BT<sub>A</sub> dose was 200 units. Outcomes were good to excellent in 65%, fair in 24% and poor in 12%. There were 2 cases of transient weakness and 1 case of transient flu-like syndrome. Insurance type seemed not to be predictive of outcome.

Inhahl and Holm injected 36 patients (19-78 years) many of whom had undergone surgery with BT<sub>A</sub> (Botox®) into painful or tender muscles (iliopsoas, quadratus lumborum, multifidus, and piriformis) based upon palpation.<sup>66</sup> Injections were performed with CT (iliopsoas and piriformis) or EMG-guidance (quadratus and multifidus). Twenty percent of patients reported excellent pain reduction, 40% were good and 25% fair.

Although the data on BT use in myofascial pain and conditions associated with painful muscular spasm can be challenged on the basis that most of the studies were retrospective or uncontrolled, the sheer number of studies showing positive results along with similar findings in the few controlled prospective studies that have been done suggest that there is something of value to consider.

### **Antinociceptive Mechanisms**

Brin proposed that the mechanism of action for BT in migraine is less likely to be due to blocking muscle contraction and thus removing a migraine trigger and more likely to be due to blocking release of pain-mediating neurotransmitters or peptides or some other central effect. There is considerable supporting data from the cervical dystonia and spasticity literature for the position that BTs reduce pain from some mechanism other than effects on alpha motor neurons even before the chemodenervation effects occur. Jankovic and Schwartz noted that pain consistently improved, often within hours after the BT<sub>A</sub> injection, well before any reduction in muscle spasm could be detected in their large series of cervical dystonia patients.<sup>67</sup> Most clinicians treating cervical dystonia with BT<sub>A</sub> have observed that pain relief

typically outweighs the degree of spasm reduction seen.<sup>68</sup> Fillippi et al. demonstrated that gamma motor endings of isolated rat masseter muscles could be blocked within 80 minutes by BT thereby reducing the Ia afferent signal from the muscle spindles and muscle tone via a reflex mechanism.<sup>69</sup> Subsequent intrafusal and extrafusal atrophy from chemodenervation prolongs the effect.<sup>70</sup> Giladi also postulates that a central reorganization takes place due to the prolonged reduced spindle feedback.<sup>71</sup>

In the 1970s, Wiegand et al. demonstrated retrograde axonal spread of radiolabeled BT injected near the sciatic nerve within 48 hours.<sup>72</sup> The authors noted that they could not confirm whether the retrograde radioactivity was unchanged toxin or breakdown products. Aoki confirmed the findings of Wiegand et al. in a study in which rats were injected unilaterally in the gastrocnemius muscle with radiolabeled BT<sub>A</sub>.<sup>73</sup> Radioactivity remained at the injection site for at least 2 hours and disappeared by 48 hours, having appeared in the sciatic nerve and spinal cord. However, Aoki was able to show that the retrograde radioactive spread was due to breakdown products and not intact toxin transport.

Since co-localization of vasoactive intestinal peptide and neuropeptide Y with acetylcholine has been demonstrated in parasympathetic neurons, inhibition of SNAP-25 or VAMP by BT could block neurotransmitter exocytosis and reduce pain.<sup>74</sup> In a study of rat dorsal root ganglia neurons and isolated rabbit iris spincter and dilatory muscles, BT<sub>A</sub> was shown to inhibit neuropeptide release.<sup>75</sup> Additionally, BT<sub>A</sub> can block the in vitro release of substance P and acetylcholine but not norepinphrine from rabbit ocular tissue.<sup>76</sup> Aoki and Cui demonstrated that BT<sub>A</sub> (3.5 or 7.0 units/kg/paw) blocked the neuropathic pain component (rat hind paw formalin model) in a dose-dependent fashion.<sup>77</sup> Rats were challenged with subcutaneous 5% formalin in one hind paw at 5 days and in the opposite hind paw at 12 days post BT<sub>A</sub>. BT<sub>A</sub> efficacy was slightly less at day 12 than 5. The animals showed no obvious motor weakness or weight loss. These data provide interesting topics for discussion, but answers must await further study.

## **Dosing Considerations**

Once the decision is made to consider BT for the treatment of MPS or other muscle spasm conditions, the key questions are which patient will best benefit from this therapy, what dose to administer (in what concentration and in what diluent) and how to do it. Unfortunately, the answers to many of these questions are still uncertain. Until more studies are performed, only general guidelines are available from the currently available literature.

### **1. Whom to inject?**

As with any new therapy, especially one that is expensive, it makes sense to use BTs only in more refractory cases until the treatment becomes established and pharmacoeconomic data is supportive. In MPS, especially in the cervical and thoracic region, the potential for significant reduction in medication use and complete resolution of symptoms in a substantial portion of refractory cases is a strong argument in support of BT use. Quality of life and functional improvement can be measurably improved in many patients. In the lower back, conditions that "look" more like spasticity or focal dystonia, such as piriformis syndrome or unilateral back spasm, seem to respond better than more diffuse amorphous conditions. Several researchers are conducting additional studies on the use of BT in low back pain and

we should have better guidelines on patient selection soon

**1. Where to inject?**

With MPS, most investigators have injected active trigger points directly or used a grid pattern (Lang's method) around them to get more diffuse spread through the involved muscle. Yue also has demonstrated that scalene or psoas compartment injections under fluoroscopic guidance can be used with success to target adjacent muscles. In the lower back, trigger points in deeper paraspinals are not as easily felt and the limited studies that have been published have either chased tenderness or spasm as their guide for which muscles to inject.

**1. How much to inject?**

Cervical and VII<sup>th</sup> nerve dystonia data has been used as a starting point for BT<sub>A</sub> dose calculations with adjustments depending upon the size of the muscle and degree of spasm. Clinical experience with BT<sub>A</sub> would seem to support this extrapolation to MPS/headache, but with BT<sub>B</sub> it will be important to be cautious at first and start at a maximum of 2,500 to 5,000 units and move upward depending upon clinical response until data from current studies provides dose-response information.<sup>79</sup>

The total maximum dose per visit for BT<sub>A</sub> (Botox®) typically should not exceed 300-400 unit range (although many have gone as high as 600-700 safely for numerous involved muscles as in diffuse spasticity/dystonia) and intervals between doses should be no more frequent than every 3 months. Following these general guidelines will reduce adverse events (primarily weakness) and antibody formation. Little data is available to help one decide on BT<sub>B</sub> dosing outside of cervical dystonia. It appears to be about 40-50 times less potent than BT<sub>A</sub> with very few patients having received doses at or above 20,000 units, though these doses appear to be well tolerated. In the cervical dystonia data, BT<sub>B</sub> produced a duration of action between 12 and 16 weeks similar to that seen with BT<sub>A</sub>.

Larger volumes of injectate and doses of neurotoxin may influence the tendency for excess BT to diffuse to nontargeted sites (adjacent muscles or remote sites). This becomes a concern especially with anterior neck injections where EMG guidance and low volumes of injectate (BT<sub>A</sub> 100 units/cc or BT<sub>B</sub> 5,000 units/cc) should be used. The technique of using multiple injection sites (grid pattern) within the muscle appears to reduce unwanted side effects as does using EMG guidance to target motor end plates thus allowing one to use less toxin.

**1. What to use as diluent?**

Allergan recommends that only preservative-free saline (PFNS) be used as the diluent and once it is added to reconstitute Botox® it should be used within 4 hours due to dual concerns of protein denaturation and infection risk. Elan Pharmaceuticals also recommends that PFNS be used if one desires a more dilute concentration of Myobloc™ than 5,000 units/cc and, although the toxin is stable for months at room temperature, if the vial is violated, the toxin should be used within 4 hours due to infection concern. Since the pH of 5.6 in the Myobloc™ preparation might cause local injection discomfort, perhaps more than that seen with the more neutral pH of BT<sub>A</sub>, the author recommends that preservative free lidocaine be used to dilute the BT

to provide a local anesthetic effect.

The use of preservative-free local anesthetic as a diluent, though outside of labeling from the manufacturers, does not denature the protein (as long as bicarbonate is not added to neutralize the acidic pH of the local anesthetic) and certainly seems to help with local injection pain with the BT<sub>B</sub> formulation.<sup>80</sup> In MPS, numerous studies have documented that local anesthetics seem not to interfere with toxin efficacy, although studies comparing local anesthetics versus PFNS have not been done. Additionally, whether volume of diluent makes a difference in efficacy is not known, although studies are in progress to answer this question.<sup>81</sup>

### 1. Is targeting of injections needed?

The use of fluoroscopic or EMG guidance to identify the muscle or localize the motor endplate prior to injections appears to be a benefit in some situations (particularly in the anterior neck and the deep paraspinal muscles and possibly to reduce unwanted remote spread by targeting motor end plates with lower toxin doses), but other clinicians have not shown that this technique is necessary when the muscles and trigger points are easily palpable. Fluoroscopic or CT guidance with or without EMG can be very helpful for injections of the piriformis, multifidus or psoas muscles. EMG guidance is typically used when targeting extremity muscles or neck muscles that cannot reliably be identified with palpation.

## Conclusion

BTs appear to be a useful treatment in refractory MPS and other conditions with muscle spasm. Presumably BTs work by breaking the spasm/pain cycle giving the patient a "window of opportunity" for traditional conservative measures to have a greater beneficial impact, but several studies suggest that a direct antinociceptive effect distinct from any reduction in muscle spasm may be at play. The major benefit of BTs compared with standard therapies is duration of response. We do not advocate that BTs be used as a first line treatment for MPS. However, in refractory cases where nothing else has worked, it may offer a chance for improvement or cure not otherwise available. In the year 2001 we should have some very good data from studies presently being conducted to help us decide where to place BT in our pain treatment continuum. For now, it remains an off-label, but increasingly accepted, approach in patients with refractory myofascial or muscular pain, who despite multidisciplinary approaches, continue to suffer.

## References

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1. Data on file, Allergan, Inc.
1. The author is currently performing a prospective, double-blinded, randomized clinical trial evaluating the effects of different volumes of diluent in cervicothoracic MPS patients with support from Allergan.

# Table 1

## Distinguishing Fibromyalgia from Myofascial Pain Syndrome

Characteristic

Fibromyalgia syndrome

Myofascial Pain Syndrome

Prevalence

4-6% of general medical patients

30-60% of pain clinic patients

Sex

10:1 female

1:1

Onset

50% idiopathic;20% physical trauma;20% viral;10% emotional

Trauma or strain

Sleep disorder, fatigue

Always

Often

Pain

Diffuse

Localized

Pain referral (trigger point)

?

Localized

Tenderness (tender point)

Multiple spots at tendon insertion, in muscle belly or over bone

Few spots in muscle belly only

Palpable taut band with twitch response

?

Present

Interrater reliability

Good for palpation or algometry

Good for tenderness to palpation, poor for other features

Fatigue

Common

Uncommon

Irritable bowels syptoms

Common

Uncommon

Treatment

Medication, exercise

Loca myofascial release

Local injections

Uncertain

Good results in case series

Outcome

Usually chronic

Usually self-limited

## Table 2

Table

**103 injections in**

**# of injections**

**%**

**M:F**

**Response**

**76 patients**

**(# patients)**

**durations**

**(months)**

Excellent

56

54.4

25:10

3.6

Good

16

15.5

12:4

2.4

Fair

12

11.7

5:7

2.4

No/minimal

19

18.4

6:7

### Table 3

#### Recommended Dose Ranges for BTA (Botox®)

Frontalis: 6-10

Trapezius: 25-100

Iliopsoas: 50-100

Corrugator: 3-5

Levator scapulae: 25-50

Lumbar paraspinals: 50/segment (300-400)

Procerus: 3-5

Latissimus dorsi: 50-100

Quadratus lumborum: 50-100

Obicularis (crows feet): 3-5

Teres major: 25-75

Piriformis 50-100

Temporalis: 6-10

Brachioradialis: 25-75

Medial hamstrings: 50-150

Sternocleidomastoid: 50-100

Biceps: 75-125

Gastrocnemius: 50-100

Scalene: 25-50

Brachialis: 25-50

Lateral hamstrings: 75-150

Splenius capitis: 10-30

Flexor carpi radialis: 10-50

Soleus: 25-75

Semispinalis capitis: 10-30

Flexor carpi ulnaris: 10-50

Tibialis posterior: 75-125

Splenius cervicis: 10-30

Iliocostalis thoracis: 100-200

Tibialis anterior: 50-100