Chapter 6
Botulinum Toxin Therapy in Medical Pain Disorders

Delaram Safarpour and Bahman Jabbari

Abstract Animal studies have shown that local injection of botulinum neurotoxins (BoNTs) reduces neuropathic pain. This effect is exerted via interfering with the function of pain transmitters and modulators at peripheral and central levels. Recent studies in humans have demonstrated an analgesic effect in several pain disorders. In this chapter, the effect of BoNT therapy in different medical, human pain syndromes is reviewed. The level of efficacy in each pain syndrome is determined according to the guidelines of the Assessment Subcommittee of the American Academy of Neurology.

Keywords Botulinum toxin · Botulinum neurotoxin · Pain · Neuropathic pain · Pain disorder

Introduction

Over the past 30 years, treatment with botulinum neurotoxins (BoNTs) has established a firm role in many fields of medicine and, most notably, in the treatment of hyperkinetic movement disorders (mainly dystonias), focal spasms, spasticity, autonomic dysfunctions (sialorrhea; hyperhidrosis), and migraine [1]. During the past 15 years, with emergence of data from animal studies, clinical researchers expressed interest in investigating the role of BoNT therapy in human pain disorders. Recent publication of high-quality studies in this field indicates that, in addition to migraine, many pain syndromes are amenable to BoNT therapy.

In this chapter, we describe the current status of BoNT therapy in different human medical pain disorders. In each category, the efficacy of BoNT therapy is defined according to the criteria set forward by the Guideline and Assessment

D. Safarpour
Department of Neurology, Oregon Health &Science University, Portland, OR, USA

B. Jabbari (✉)
Department of Neurology, Yale University School of Medicine, New Haven, CT, USA
e-mail: bahman.jabbari@yale.edu

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Table 6.1 Injection paradigm recommended by the PREEMPT study: injected muscles, muscle location, muscle function, and the dose of onaA (Botox) administered per site(s)

Muscle	Location	Function of muscle	Number of injection sites per muscle	Dose per site
Corrugator	Above the medial edge of eyebrow	Draws the eye brows together and downward	One on each side	5 units
Procerus	Helps to pull the skin between eyebrows downward	Pulling eyebrows together	Single muscle One injection at midline	5 units
Frontalis	Whole forehead	Pulling eyebrows up	Two on each side, total 4	5 units
Temporal	Temple	Closes the mouth	Four on each side, total 8	5 units
Occipitalis	Back of the head	Moves the scalp back	Three on each side, total 6	5 units
Splenius	Upper neck	Turns and tilts the head to the same side	Two on each side, total 4	5 units
Trapezius	Shoulder	Moves the shoulders up and head back	Three on each site, total 6	5 units

From Jabbari [70]

Subcommittee of the American Academy of Neurology [2, 3]. The efficacy levels A, B, C, and U reflect established, probable, possible, and undetermined efficacy, respectively. The level of efficacy depends on the number of certain class of studies available, designated as A, B, C, and D (see Table 6.1 for definition). These levels reflect the strength of available studies. For instance, a level A efficacy requires at least two published class A studies. A level A study is a well-designed, double-blind, placebo-controlled clinical trial that meets all five criteria [2, 3]. This information may be considered complementary to the data that will be presented in the succeeding chapters of this book on the effect of BoNTs on surgical and dental pain as well as pain disorders encountered in veterinary medicine. Detailed information regarding our current knowledge of mechanisms through which BoNTs alleviate pain is described by Lacovik and colleagues in Chap. 4 of this book.

Pain Disorders with Level A efficacy

This category includes five pain disorders in which the efficacy of BoNT injections is considered established (level A) based on two or more class I studies (see Table 6.1 for definition). These disorders are chronic migraine, postherpetic neuralgia, posttraumatic neuralgia, trigeminal neuralgia, and diabetic neuropathy. Among these, only chronic migraine is currently approved by FDA for BoNT therapy.

Level A, FDA-Approved Pain Disorder: Chronic Migraine

Migraine affects over a billion people per year worldwide and is the second cause of workday loss due to disability [4]. It affects 17% of women and 6% of men [5]. Migraine headaches are usually moderate to severe in intensity and last 4–72 hours. The term episodic migraine applies to migraine with headache days of less than 15/month. The term chronic migraine indicates that headache frequency equals or exceeds 15 days per month with at least in 8 of those headache days; headache has characteristics of migraine [6]. High-quality (blinded and placebo-controlled) studies of botulinum toxin therapy in episodic migraine have failed to show positive results. With chronic migraine however, the efficacy has been established via two large-scale, well-designed, high-quality clinical trials (PREEMPT studies) [7, 8]. Each study includes close to 700 patients (total 1384). Each study had a blind arm (24 weeks) followed by an open label arm of 32 weeks. During the blind period, patients were injected either with onabotulinumtoxinA (onaA) or placebo every 3 months. The pooled data of the two PREEEMPT studies showed significant reduction of pain days in the onaA group (8.4 days) compared to the placebo group ($P < 0.001$) [9]. Migraine severity, frequency of migraine days, and migraine duration were also significantly reduced in the onaA injected group ($P < 0.001$). Subsequent studies of PREEMPT patients have shown onaA efficacy in subgroup of patients with medication overuse, improvement of quality of life with onaA therapy, and sustained improvement after five cycles (every three to 4 months) of onaA therapy in migraine [10–12].

Technique and Dosage

A total dose of 165 units is recommended in PREEMPT studies which is distributed over several muscles, each receiving injections at multiple sites (Table 6.1, Fig. 6.1) [13]. The total dose may be increased to 195 units at the discretion of the treating physician. The total number of injections is 31.

Since the publication of PREEMPT studies in 2010, several investigators have attempted to find a technique that provides similar results with fewer sites of injections. Jabbari and his colleagues at Yale University provided evidence that a technique with 21 injection sites can produce comparable results to PREEMPT studies of onaA therapy in chronic migraine. The logic for the Yale technique is based on the following four principles:

1. In the PREEMPT injection scheme, the lower site of injection into temporalis muscle is probably into the tendon and not into the muscle itself. The tendon of temporalis muscle can be quite large and can extend a considerable distance upward [14]. The Yale protocol recommends injections into two sites with 15 units per site (30 units per site) eliminating inferior and superior temporal injections. Such a dose does not cause appreciable weakness of the powerful temporalis muscle.

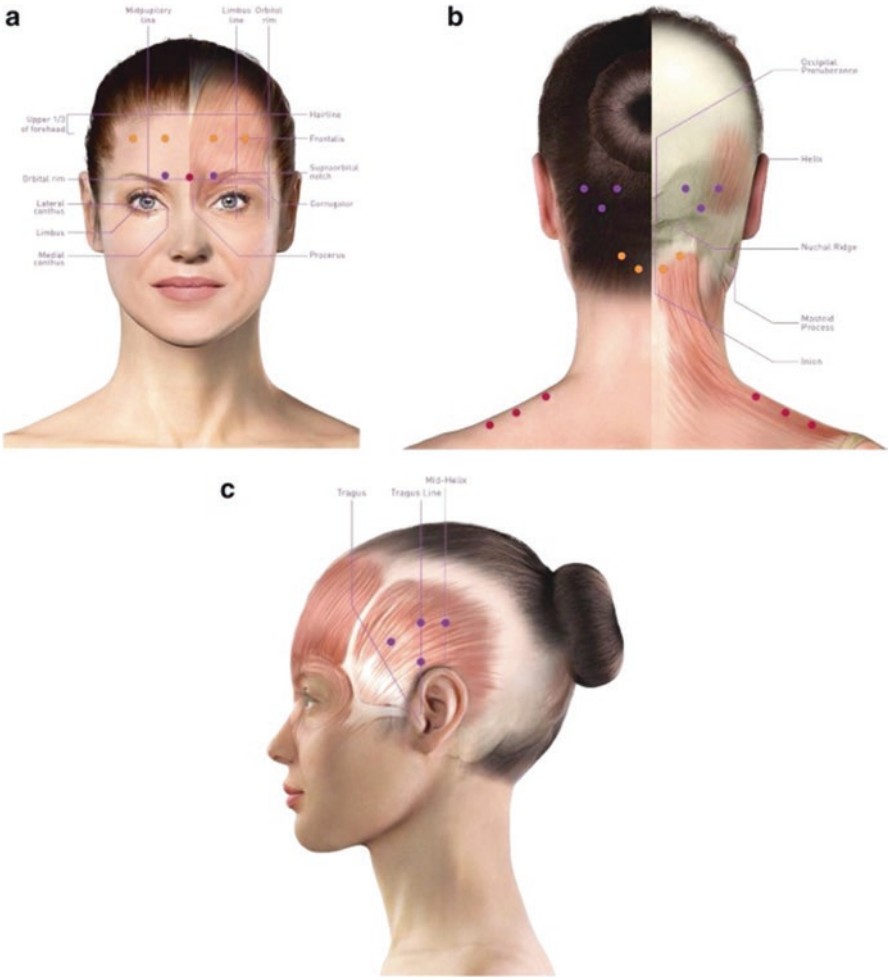

Fig. 6.1 (**a**) Corrugator, as depicted by purple dots; procerus, as depicted by the red dot; frontalis, as depicted by orange dots. (**b**) Occipitalis area, as depicted by purple dots; cervical paraspinal area, as depicted by orange dots; trapezius, as depicted by red dots. (**c**) Temporalis, as depicted by purple dots. Sites of injections in PREEMPT technique. (From Blumenfeld et al. [13]. Printed with permission from Wiley and Sons)

2. The six injections (three on each side) into trapezius muscles are eliminated in the Yale technique as it is unlikely that trapezius muscles contribute significantly to migraine headaches.
3. Occipital injection is reduced from three injections at each side to one injection per site using a larger dose of 10 units. Occipitalis muscle is a small muscle, and a larger dose delivered in one injection is likely to cover the muscle.

Fig. 6.2 The sites of injection in the Yale technique. (From Jabbari [71]. Drawing courtesy of Drs. Tahere Mousavi and Damoun Safarpour)

4. Injection sites into the cervical region are increased from two to three sites (Fig. 6.2) with a larger dose of 15 units per site (10 units/site for small necks). Splenius capitis is also a powerful muscle, and the vast experience of past 30 years with injection into this muscle has shown no appreciable weakness with such doses. In the PREEMPT technique, the medial high cervical site of injection is most likely into semispinalis cervicis. In Yale protocol, the three cervical injections into splenius capitis are not too close to midline.

In an open label study of 50 patients with chronic migraine when using the Yale technique, 72% of the patients after first injection and 85% after third injection reported their experience after onaA injection as "very satisfactory" using Patient Global Impression of Change (PGIC) [15]. No serious side effects were reported over 2–8 years of observation. After the first year of treatment, 73% of the patients reported no more emergency department visit for additional therapy. By 12 months of treatment, 50% of the patients discontinued their daily preventive medications, and 61% had no longer any need for abortive medicine. In a subsequent double-blind, placebo-controlled study of 25 patients [16], injections of onaA, using the Yale technique, reduced the headache days significantly compared to the placebo at 4 and 8 weeks ($P = 0.0031$). Using PGIC, 9 of 11 patients in the onaA group and 3 of 10 patients in the placebo group described their experience very satisfactory ($P = 0.030$). In the open arm of the study, 58.8% of the patients reported 50% or more reduction of pain days at 4 weeks postinjection, and 88.2% demonstrated reduction of HIT scores compared to baseline. Larger blinded and placebo-controlled studies are necessary to establish the Yale technique as an alternative to the technique of PREEMPT.

Pain Disorders with Level A Efficacy (Effective), Not FDA Approved: Postherpetic Neuralgia, Post-traumatic Neuralgia, Trigeminal Neuralgia (Table 6.2)

Postherpetic Neuralgia (PN)

Postherpetic neuralgia is one of the most painful human pain disorders. It is a complication of herpes zoster infection. In adults, herpes zoster infection is due to reactivation of inactive varicella zoster virus acquired during childhood. Elderly and immunocompromised individuals are more susceptible to zoster reactivation [23]. Zoster infection can involve face, limbs, or trunk with distribution of vesicles, while in the latter regions follow the distribution of skin eruptions following the course of peripheral nerves. Spontaneous pain cessation may occur, but, in many patients, continued pain (for months even years) despite antiviral and analgesic therapy handicaps the patient. Two double-blind and placebo-controlled class I studies [17, 18] have reported significant improvement of pain in PN after administration of local botulinum toxin injections (Table 6.2). In one study [17], pain improvement was associated with significant reduction of opioid use when BoNT treatment was compared to lidocaine and placebo groups (toxin, 78%; lidocaine, 48%; placebo, 34%).

Post-traumatic Neuralgia

Ranoux et al. [19] studied the effect effects of onabotulinumtoxinA on post-traumatic neuralgia. Twenty patients were investigated via a double-blind, placebo-controlled clinical trial. Injections were given into the areas of skin affected by pain and allodynia. The injections were administered intradermally, 1.5 centimeters apart. The dose varied from 20 to 190 units based on the area involvement. The magnitude of pain was measured by VAS using a 0 to10 scale. The authors found significant reduction of pain intensity during the second week following injection ($P = 0.02$), and this positive effect lasted 14 weeks ($P = 0.03$). In the area of involvement, allodynia to brush was also improved significantly. Authors reported no side effects.

More recently, Attal et al. [20] described similar responses to BoNT therapy in a double-blind, placebo-controlled clinical trial conducted on 46 patients with post-traumatic neuralgia. The percentage of pain relief, their primary outcome, was significantly higher in the toxin group (26.4 versus 10.6 for the placebo) ($P = 0.008$). The two secondary outcome measures, reduction of pain frequency and improvement of sleep, also significantly improved in the toxin-treated group ($P = 0.001$ and $P = 0.02$).

Trigeminal Neuralgia

Trigeminal neuralgia (TN) has an estimated lifetime prevalence of 0.3% and usually affects individuals over age 50 years of age [24]. Secondary TN can be seen in patients with multiple sclerosis and has an earlier age of onset. TN is characterized by severe, brief bouts of pain, usually lasting a few seconds. Patient may experience

Table 6.2 Pain syndromes with level A efficacy (effective) based on two or more class I randomized double-blind, placebo-controlled clinical trials

Authors	Pain syndrome	AAN class	Number of Patients in Study	Type of toxin	Total dose units	Injection site	Primary outcome (PO)	Secondary outcome (SO)	Results
Xiao et al. (2010) [17]	Postherpetic neuralgia	I	60	Prosigne	100 U	Subcutaneous Multiple sites Grid-like	Pain intensity (VAS), days 7 and 90	Sleep hours	Both PO and SO were met ($P < 0.01$)
Apalla et al. (2013) [18]	Postherpetic neuralgia	I	30	onaA	100 U	Subcutaneous Administered in five sites	50% reduction in pain intensity (VAS)	Quality of sleep on 5-point scale	Pain intensity and quality of sleep improved ($P < 0.0001$)
Ranoux et al. (2008) [19]	Post-traumatic neuralgia	I	24	onaA	20 to 190 U	Intradermal 1.5 cm apart Number based on extent of skin involvement	Pain intensity (VAS)	Allodynia to brush	Significant improvement of VAS – week 2 ($P = 0.02$), week 14 ($P = 0.03$)
Attal et al. (2016) [20]	Post-traumatic neuralgia	I	46	onaA	20–190 U	Intradermal 1.5 cm apart Number based on extent of skin involvement	Percentage of pain intensity relief	Pain frequency and sleep	Pain intensity improved ($P = 0.008$). SOs ($P = 0.001$) and ($P = 0.01$), respectively
Wu et al. (2012) [21]	Trigeminal neuralgia	I	40	Prosigne	75 U	Subcutaneous/ epidermal 16 sites on the face	50% reduction in pain intensity (VAS)	Patient Global Impression of Change (PGIC)	Both PO and SO improved ($P < 000.1$)
Zhang et al. (2014) [22]	Trigeminal neuralgia	I	84	Prosigne	25 versus 75 U group	Subcutaneous/ epidermal 16 sites on the face	50% reduction in pain intensity (VAS)	Patient Global Impression of Change (PGIC)	Both PO and SO improved ($P < 0.05$) No difference between two dose groups

onabA onabotulinumtoxinA(Botox), *Prosigne* Chinese type A toxin from Lanzhou Institute, *PO* primary outcome, *SO* secondary outcome, *PGIC* Patient Global Expression of Change, *VAS* Visual Analogue Scale

many (tens to hundreds) of pain bouts per day. Medical treatment consisting of treatment with anticonvulsants (carbamazepine, phenytoin, and valproic acid) provides limited relief. Patients with advanced age often poorly tolerate high doses of such medications which may be required for satisfactory pain relief. Microvascular surgery and the Gamma Knife procedure offer relief in some patients, but recurrence of pain is not uncommon after these interventions.

Two class I, randomized, double-blind, placebo-controlled clinical trials evaluated the efficacy of BoNT therapy in trigeminal neuralgia [21, 22] (the last two studies listed in Table 6.2). Both studies reported that intradermal and subcutaneous injections of BoNT-A into the area of the face affected by pain improves pain of TN significantly. Injections were carried out using a grid-like pattern (8–16 sites) (Fig. 6.3). The toxin used in these studies was Prosigne. Prosigne is a Chinese type A toxin with suggested unit comparability to onabotulinumtoxinA (Botox). One of the two abovementioned studies compared 25 and 75 units of Prosigne in TN and found the low dose of the toxin to be equally effective as the high dose [22]. In this study, seven patients developed mild facial asymmetry, and three developed mild facial swelling after injections; all side effects disappeared within a week.

A prospective study on 88 patients with TN demonstrated that repeated injections of onabotulinumA over 14 months sustained pain relief efficacy and continued to reduce anxiety and depression along with improving the patients' sleep and the quality of life [25].

In our experience, more than 50% of the patients with refractory TN respond to BoNT injections. Injections are done subcutaneously in a grid-like pattern covering the region(s) of pain. With onabotulinumtoxinA (Botox), we use 2.5 units/site (Fig. 6.3).

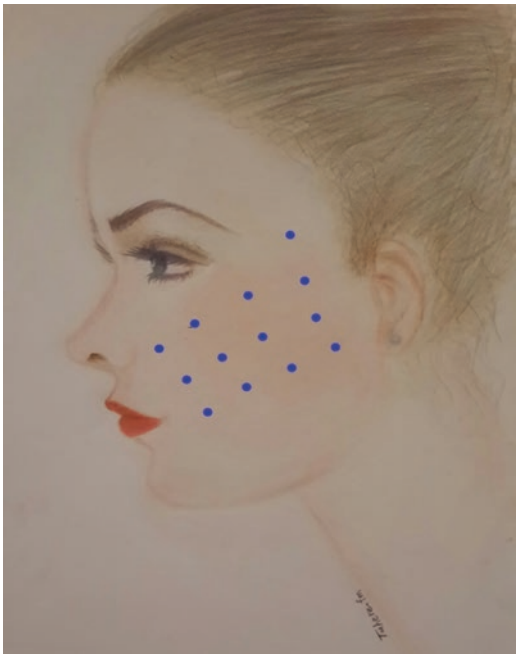

Fig. 6.3 Subcutaneous grid-like BoNT injections in trigeminal neuralgia covering the distribution of pain. (Drawing courtesy of Tahere Mousavi M.D.)

Level B Efficacy (Probably Effective) Based on Availability of Class I and II Studies: Diabetic Neuropathy, Chronic Low Back Pain, Plantar Fasciitis, Piriformis Syndrome, Lateral Epicondylitis, Neuropathic Pain After Spinal Cord Injury, and Male Pelvic Pain (Table 6.3)

Diabetic Neuropathy

Peripheral neuropathy is a common finding in diabetic patients. Painful diabetic neuropathy is more common in type 2 diabetes and often seen in older individuals (25–26% in type 2 versus 16% in type 1) [50, 51]. The type of pain is usually neuropathic, characterized by burning, tingling, pricking, and sometimes electric-shock sensation. Affected regions of skin (usually feet) demonstrate allodynia (touch perceived as pain). The second type of pain is muscle cramps which are often associated with the neuropathic pain. There is now strong evidence from randomized clinical trials that local injection of botulinum toxins can alleviate both neuropathic pain and muscle cramps in diabetic neuropathy.

Yuan et al. [26], in a double-blind, placebo-controlled study, investigated the effect of onabotulinumtoxinA (Botox) in 20 patients with painful diabetic neuropathy. The study had a crossover design. A total dose of 50 units was used. Injections were administered on the dorsum of the foot at 12 sites. Outcomes were measures by Visual Analogue Scale (VAS), depicting pain intensity at a 0–10 scale and by CPSQI, a Chinese version of the Pittsburgh Sleep Quality Index. There was significant improvement of VAS in the toxin group compared to the placebo group at weeks 1, 4, 8, and 12 ($P < 0.05$). CPSQI, measured at week 4, also demonstrated significant improvement compared to the placebo ($P < 0.05$). One patient in the toxin group developed mild local skin infection at the site of injection that cleared up within days.

Ghasemi et al. [27] studied 40 patients with painful diabetic neuropathy. Twenty patients were assigned to aboA toxin group (100 units) and 20 to saline (placebo) group. The study was blinded and had a parallel design. The outcomes were evaluated 3 weeks after injections. In the toxin group, 30% experienced no pain after treatment, while 0% reported no pain in the placebo group ($P = 0.01$). After treatment, diabetic neuropathy scores (DPN4) in the toxin group were significantly reduced for electric shocks, burning, pins and needles, and brushing ($P < 0.005$). In neuropathic pain scale (NPS), all items, except cold sensation, improved ($P = 0.05$). No side effects were reported.

Salehi et al. [29] also studied the effect of aboA toxin injections (100 units) on pain relief in diabetic painful neuropathy. The protocol studied 32 patients and had a parallel, placebo-controlled, double-blind design. The injection pattern was similar to the two abovementioned studies. Outcome measures included VAS for pain, PSQI for sleep, and SF-36 for quality of life. At 12 weeks, all measures improved for the toxin group: VAS and PSQI, $P < 0.001$, and SF-32, $P = 0.050$. The duration of study was 3 months. No side effects were reported.

Table 6.3 Pain disorders with level B efficacy (probably effective) based on one class I or two class II studies. All studies are double-blind and placebo-controlled

Authors	Diagnosis	Class	Number of Patients in Study	BoNT type	Total dose in units	Site(s) of injection	Outcome measure	Results
Yuan et al. (2009) [26]	Diabetic neuropathy Neuropathic pain	II Crossover	20	onaA	50 U	Intradermal – dorsum of the foot 12 sites	Pain intensity (VAS), sleep CPSQI	VAS improved at 1, 4, 8, 12 wks ($P < 0.05$); CPSQI improved ($P < 0.05$)
Ghasemi et al. (2014) [27]	Diabetic neuropathy Neuropathic pain	I Parallel	40	aboA	100 U	Intradermal – dorsum of the foot 12 sites	Pain intensity (VAS); NPS	Both VAS and NPS improved ($P < 0.05$)
Restivo et al. (2018) [28]	Diabetic neuropathy Painful cramps	I Parallel	50	incoA	100 U 30 U	Gastrocnemius small flexor of the foot	PO: pain intensity (VAS); SO: QoL	VAS and cramp frequency improved: ($P = 0.037$) and ($P = 0.004$)
Salehi et al. (2019) [29]	Diabetic neuropathy Neuropathic pain	II Parallel	32	aboA	100 U	Foot surface, 12 points	Pain (VAS) Sleep (PSQI) Quality of life (SF-36)	VAS improved at 12 wks ($P < 0.001$) PSQI ($P < 0.001$) SF-36 psychological Scale ($P = 0.050$)
Foster et al. (2001) [30]	Low back pain	II Parallel	31	onaA	200 U	Unilateral Erector spinae at all five lumbar levels (40 U/level)	Pain (VAS); ADL (Oswestry)	VAS improved 3 wks:($P = 0.012$ 8 wks: ($P = 0.009$) Oswestry improved 8 wks: P (0.011)
Machado et al. (2016) [31]	Low back pain	II Parallel	37	aboA	500 U 1000 U	Unilateral bilateral Erector spinae at all five lumbar levels (40 U/level)	Pain (VAS); Oswestry; PGIC	VAS improved 8 weeks: (0.048) Oswestry improved 8 weeks: (0.040) PGIC improved 8 weeks: (0.029)

De Andres et al. (2010) [32]	Low back pain	II	27	onaA	50 U	Quadratus lumborum Psoas major	Pain (VAS)	More patients showed VAS improvement in the aboA group but statistically not significant
Cogne et al. (2017) [33]	Low back pain	II Crossover	17	onaA	200 U	Bilateral Erector spinae lumbar region (20 U/level)	PO: pain (VAS) SO: Quebec Back Pain Disability Scale, QoL scale	No significant difference between toxin and placebo in either PO or SO
Babcock et al. (2005) [34]	Plantar fasciitis	II Parallel	27	onaA	70 U	Medial heal Midfoot into plantar fascia	Pain (VAS) MFS Pressure algometry (PA)	All improved significantly VAS: $P < 0.0005$ MFS: $P = 0.001$ PA: $P = 0.003$
Huang et al. (2010) [35]	Plantar fasciitis	II Parallel	50	onaA	50 U	Below calcaneus into plantar fascia	Pain (VAS) Thickness of fascia	VAS improved Thickness of fascia reduced ($P < 0.001$)
Peterlein et al. (2012) [36]	Plantar fasciitis	II Parallel	40	aboA	200 U	Fan shape from the origin of PF	Pain (VAS) proportion of responders	AboA 25% versus saline 5% Statistically not significant
Rodriguez et al. (2013) [37]	Plantar fasciitis	II[a] Parallel	40	aboA	250 U	Gastrocnemius Soleus	Pain (VAS) MFS FADI	More improvement of VAS, MFS, and FADI in aboA group compared to steroid group ($P < 0.05$)
Ahmad et al. (2017) [38]	Plantar fasciitis	II Parallel	50	incoA	100 U	Single injection into plantar – medial aspect of calcaneus	Pain (VAS) Foot and Ankle Ability Measure (FAAM)	Both VAS and FAAM improved $P = 0.01$

(continued)

Table 6.3 (continued)

Authors	Diagnosis	Class	Number of Patients in Study	BoNT type	Total dose in units	Site(s) of injection	Outcome measure	Results
Abbasian et al. (2020) [39]	Plantar fasciitis	II Parallel	32	BoNT-A?	70 U	Medial gastrocnemius	Pain (VAS) AOFAS score Patient satisfaction	Improvement of VAS and AOFAS significant compared to placebo $P < 0.01$
Fishman et al. (2002) [40]	Piriformis syndrome	II Parallel	36	onaA	200 U	Into piriformis muscle	Pain (VAS)	65% of onaA and 6% of placebo improved in VAS ($P = 0.001$)
Childers et al. (2002) [41]	Piriformis syndrome	II Crossover	9	onaA	100 U	Into piriformis muscle	Pain (VAS)	Significant improvement of VAS and daily activity ($P < 0.05$)
Fishman et al. (2017) [42]	Piriformis syndrome	II Parallel	56	incoA	300 U	Into piriformis muscle	Pain (VAS) FAIR physical score	VAS improved $P < 0001$; FAIR: improvement varied from $P = 0.003$ to $P = 0.046$
Wong et al. (2005) [43]	Lateral epicondylitis	II Parallel	60	aboA	60 U	Deep into SC tissue and muscle, 1 cm from lateral epicondyle (LE)	Pain (VAS) Grip strength	VAS improved, Wk 4: $P < 0.01$ Wk 12: $P < 0.006$ Finger strength (ns)
Hyton et al. (2005) [44]	Lateral epicondylitis	II Parallel	40	aboA	50 U	Into muscle, 5 cm distal to the tender epicondyle	Pain (VAS) SF-12 Hand grip	No significant difference between aboA and placebo in those measures

Placzek et al. (2007) [45]	Lateral epicondylitis	I Parallel	130	aboA	60 U	3–4 cm distal to the tender epicondyle, at two points	Pain (VAS) Patient and physician satisfaction	VAS improved ($P < 0.05$) Physician satisfied
Espandar et al. (2012) [46]	Lateral epicondylitis	II Parallel	48	aboA	60 U	33% of arm's length, below epicondyle	Pain (VAS) Maximum pinch pain	VAS improved $P = 0.01$ Maximum pinch $P = 0.004$
Han et al. (2016) [47]	Neuropathic pain after spinal cord surgery	I Parallel	40	Meditox	200 U	Subcutaneous Multiple sites	Pain (VAS) WHO-QoL	VAS improved ($P < 005$) WHO-QoL: trend $P = 0.052$
Gottsch et al. (2011) [48]	Male pelvic pain – prostatitis	II Parallel	13	onaA	100 U	Into bulbospongiosus muscle	Pain (VAS) Chronic pain syndrome index (CPSI)	VAS improvement 30% (toxin)versus 13% (placebo) $P < 0.0002$) CPSI pain subset also improved ($P = 0.05$)
Falahatkar et al. (2015) [49]	Male pelvic pain – prostatitis	I Parallel	60	aboA	100 U 200 U	Into lateral lobe of prostate, three sites	Pain (VAS) NIH-CPSI	Significantly improved pain (VAS) and quality of life (CPSI)

Prosigne, Chinese type A toxin from Lanzhou Institute, *PGIC* Patient Global Impression of Change, *VAS* Visual Analogue Scale, *PSQI* Pittsburgh Sleep Quality Index, *CPSQI* Chinese version of Pittsburgh Sleep Quality Index, *onaA* onabotulinumtoxinA (Botox), *incoA* incobotulinumtoxinA (Xeomin), *aboA* abobotulinumtoxin (Dysport), *NPS* neuropathic pain scale, *MFS* Maryland Foot Score, *aboA* abobotulinumtoxin/A (Dysport), *FADI* Foot and Ankle Disability Index, *FAAM* Foot and Ankle Ability Measure, *CPSI* Chronic Prostatitis Symptom Index

[a]Comparator study (toxin versus steroid)

Restivo et al. [28] assessed the efficacy of intramuscular injections of onaA on painful cramps associated with diabetic neuropathy. Fifty patients were studied in a clinical trial with a parallel, double-blind, placebo-controlled design. Injections of either 30 or 100 units of onaA into medial gastrocnemius or small foot flexors muscles were compared with placebo (saline) injections. A decrease of 50% or more of cramp frequency and cramp intensity was taken as primary outcome which was met in the toxin group after one week and lasted for 14 weeks (*P* values 0.037 and 0.04, respectively). The maximum effect was at week 6. Mild pain at the site of injection occurred in 25 patients in the toxin group which disappeared within 2–3 days.

Comment
The level of evidence for analgesic effect of BoNT therapy in neuropathic pain of diabetic neuropathy is B (probably effective) based on one class I and two class II studies. The level of efficacy is also B for BoNT therapy for muscle cramps in diabetic neuropathy. All three type A toxins (ona, abo, and inco) have demonstrated analgesic effects. Larger controlled studies are needed to support these encouraging findings. No serious side effects were reported in these studies with the applied doses of BoNTs.

Chronic Low Back Pain

"Chronic back pain is defined as pain that persists for 12 weeks or longer, even after an initial injury or underlying cause of acute low back pain has been treated." Approximately 20 percent of people affected by acute low back pain develop chronic low back pain [52]. The anatomic basis of low back pain is complex; hence, the pain can originate from malfunction of several structures among the low back muscles, vertebral column, facet joints, and nerve roots. Potent analgesics such as narcotics can provide pain relieve in chronic low back pain, but their use is associated with side effects, and there is always a potential for addition. Spinal stimulation, a relatively new treatment modality for low back pain, is often more effective than conventional therapy but has higher risk of complications.

Botulinum Toxin Treatment

BoNT therapy aims to alleviate low back pain through several mechanisms:

1. Relaxing tense and contracted muscles via blocking the release of acetylcholine from presynaptic vesicles in neuromuscular junction.
2. Reducing arrival of pain signals to the spinal cord by influencing peripheral pain neurotransmitters.
3. A central analgesic effect due to retrograde transfer of the toxin from periphery to the spinal cord [53]. This would reduce the phenomenon of central sensitization which is a part of pathophysiology of any chronic pain disorders.

4. By reducing the activity of muscle spindles after intramuscular injection [54] cuts down a powerful excitatory input to the spinal cord.
5. When a tight compartment in the back is playing a role in the pathophysiology of low back pain (tight compartment syndrome [55]), injection of BoNT into the tight muscles may alleviate pain by causing reversible atrophy tense back muscles.

Botulinum Toxin Studies of Low Back Pain Targeting Erector Spinae (ES) Muscles

This category includes three controlled clinical trials. Two of these trials reported significant improvement of low back pain in patients with no history of prior surgery using an identical technique of injection and dosage. In one study [30], conducted at Walter Reed Army Medical Center, authors studied 31 patients with predominately unilateral chronic low back pain comparing the effects of onaA injections blindly with placebo. In the onaA group, each patient received 40 units injected into ES muscle at each of the five lumbar levels ipsilateral to the side of pain. The outcome measures included VAS for pain and Oswestry Low Back Pain Questionnaire (OLBPQ) for the activities of daily living. Three weeks following injection, 11 of 15 patients (73.8%) in the onaA group and 4 of 16 (25%) patients in the placebo group had 50% or more reduction of pain intensity ($P = 0.012$) which remained reduced at 8 weeks only in the onaA group ($P = 0.0009$). At 8 weeks, OLBPQ demonstrated significant improvement of activities of daily living in 10 of 15 patients in the onaA group and 3 of 16 in the saline group, respectively ($P = 0.011$). No patient reported any side effects. In the second study [32], investigators at Yale University blindly studied the effects of aboA injection into ES muscles in 37 patients with unilateral and bilateral chronic low back pain (no history of surgery). The technique was identical to that of the first study – injection into ES muscle at four lumbar levels. A total dose of 500 units was used for unilateral and 1000 units for bilateral injections. Although the units of different toxins are not truly interchangeable, a conversion ratio of 1:2.5 is used between onaA and aboA often in clinical trials which makes the dose of the two studies comparable. The second study found significant improvements by VAS (proportion of responders), activities of daily living, and Patient Global Impression of Change in the aboA group compared to the placebo group (P values of 0.008, 0.048, and 0.0930, respectively). Three patients in the toxin group and two patients in the placebo group developed local pain at the site of injection lasting a few days. In contrast to the two abovementioned studies, another study which used the same technique and onaA toxin did not find a significant difference between the toxin and placebo group in any of the outcome measures (VAS, Quebec Back Pain Disability Scale) [33]. The authors stated that the response failure might have been related to the lower dose of the toxin used in their study (half compared the other two studies).

Botulinum Toxin Study Targeting Quadratus Lumborum and Iliopsoas Muscles

De Andres et al. [32] compared the effect of a single injection of 100 units of onaA with placebo and lidocaine in a blinded study of 27 patients with myofascial pain at lumbar area.

The onaA was injected into quadratus lumborum and iliopsoas major muscles at one side (27 patients) and compared with the effect of saline (14 patients) and lidocaine (13 patients) injected into the same muscles on the other side. The pain outcome was measured by VAS. Patient activities of daily living were assessed through five different questionnaires including OLBPQ. At the end of the study, a trend for significant VAS improvement was noted only on the side that patients had received onaA injection.

Comment
Injection of botulinum toxin A (ona or inco) into the erector spinae muscles using Walter Reed-Yale protocol (injecting 40 units of abo or inco A per each lumbar level) significantly improves low back pain in patients with no surgical history. The level of efficacy for this protocol in chronic low back pain is B (probably effective) based on publication of two class II (placebo-controlled and blinded) studies. The failure of another study that was conducted under a very similar protocol [33] most likely reflects using a much lower dose (half of that of prior studies) as suggested by authors. The short-term positive results of the Walter Reed-Yale protocol in chronic low back pain need to be confirmed in clinical trials with larger number of patients and conducted over longer periods of time.

Plantar Fasciitis (Plantar Fasciopathy)

Plantar fasciitis (PF) is a common pain problem that affects 10% of runners [56]. Plantar fascia is a layer of fibrous tissue that connects the base of the toes to the medial part of the calcaneum. It is believed that repeated trauma to plantar fascia during running, playing football, or jobs that require heavy labor causes microtears in the PF. In some patients, the pathology also involves local inflammation. The main symptom of PF is pain that is often felt at or close to the heel. Patients with mild symptoms respond to stretching, night splint, orthosis, and nonsteroidal, anti-inflammatory medications. Injection of steroids into the plantar fascia, acupuncture, ultrasound therapy, cryosurgery, and application of shock waves is often used to achieve pain relief in more severe cases. These remedies, however, are not without complications; steroid injections may cause rupture of plantar fascia, and application of shock waves may be hard to tolerate due to its painful nature. Because of these issues, many patients with severe PF are unsatisfied with their management.

BoNT Therapy in Plantar Fasciitis

The senior author of this chapter and his colleagues first studied the effect of local BoNT injection in patients with PF under a double-blind, placebo-controlled protocol [34]. Twenty-seven patients were randomized into toxin and placebo groups. In the toxin group, onabotulinumtoxinA (Botox) was injected into the medial aspect of the heel (40 units) and into the plantar fascia between the anterior part of the heel and midfoot (30 units). A thin needle, gauge 27.5, was used for injections to avoid injury to PF. Treatment outcome was assessed by VAS, Maryland Foot Score (MFS), and pressure algometry at 3 and 8 weeks after injection. All measures were significantly improved at 3 and 8 weeks (P values at week 3: < 0.005, < 0.0005, $P = 0.003$, respectively). Except for mild local pain at the site of injection for a few minutes, no other side effects were reported. A later blinded study conducted in 50 patients with PF [35] also reported significant improvement of VAS in the toxin group compared to placebo ($P = 0.001$). The toxin group also demonstrated significant reduced thickness of plantar fascia. The authors injected 50 units of onaA into the plantar fascia via posterior calcaneal approach under ultrasound guidance. No side effects were reported. Two other blinded, placebo-controlled studies have shown similar results using different techniques [38, 39]. In one of the two studies [38] which included 50 patients, a single injection with 100 units of incoA or saline was administered into the most tender part of plantar fascia at the distal aspect of plantar-medial aspect of calcaneus where the plantar fascia is adjacent to flexor digitorum brevis. Pain (VAS) and function (ankle ability measure – FAAM) outcomes were measured at 6 and 12 months. Both VAS and FAAM improved in the toxin group at 6 and 12 months ($P = 0.01$ and <0.005, respectively). Three patients in the saline group, but none in the toxin group, required surgery after 12 months. No side effects were reported. In a very recent publication [39], authors have provided evidence from a controlled clinical trial that a single injection of 70 units of onaA into the medial gastrocnemius under ultrasound guidance can significantly improve the symptoms of PF. Improvement of pain (measured by VAS) and the improved score from the American Orthopedic Foot and Ankle Society Scale (AOFAS) were both statistically significant compared to the placebo at 12 months ($P < 0.01$). Two patients in the toxin group and one in the placebo group reported mild, transient "local inflammation" at the site of injection. Elizondo-Rodriguez et al. [37] blindly compared the effect of abobotulinumA (aboA) injection with steroid and lidocaine injections in 40 patients with PF. BoNT injection was superior to steroid in terms of long-term pain relief and foot function (Table 6.3).

Comment

Five controlled clinical trials (blinded and placebo-controlled) have shown injection of BoNT-A improves pain and foot function in plantar fasciitis both short term and up to at least 12 months. All three marketed types of type A toxin (onaA, incoA, and aboA) have demonstrated a positive effect. Side effects are mild, infrequent, and transient. These studies (all class II) provide a B level of evidence (probably effective) for efficacy of BoNT-As in PF. The optimal location of injection (into the

plantar fascia or gastrocnemius/soleus muscles) remains to be determined by future studies. Larger clinical trials are needed in order to raise the level of significance for this indication from B to A (see chapter supplement).

Piriformis Syndrome (PS)

Piriformis syndrome is caused by a tense and overactive piriformis muscle and its pressure against the adjacent sciatic nerve. Pain is the major symptom of PS, often felt deep in the buttock; it occasionally radiates to the thigh. Pain of PS is mainly felt during sitting and squatting. Piriformis muscle is a deep triangular muscle, located behind gluteus maximus with attachments to the sacrum and the greater trochanter. The true incidence of PS is not known, but one investigator reported that 6% of patients diagnosed with sciatica represent piriformis syndrome [57].

Treatment of Piriformis Syndrome

Treatment begins with physical therapy alone or combined with oral analgesics. A special stretching technique which lengthens the piriformis muscle is sometimes helpful [58]. Heat application and ultrasound therapy may promote the positive effects of physical therapy [59]. One retrospective study in 500 patients over a 10-year period reported that injection of 1.5–2% lidocaine mixed with 20 mg of triamcinolone into the piriformis muscle improves pain in 70% of patients [60]. Sustained pain relief using current medical managements is uncommon in many PS patients.

BoNT Therapy in Piriformis Syndrome

In 2002, two groups of investigators reported the results of blinded, placebo-controlled studies that have assessed the efficacy of onabotulinumtoxinA (Botox) in piriformis syndrome. Childers et al. [41] in a crossover study of nine patients reported that injection of 100 units of onaA into the piriformis muscle (PM) relieved pain significantly (measured by VAS) ($P < 0.05$). In a larger parallel study of 36 patients, 25 patients were injected with 200 U of onaA, and 15 patients were injected with the same volume of saline into PM [42]. In blinded assessments of the results, 65% of the patients in the onaA group and 6% of the patients in the saline group demonstrated >50% decrease in pain intensity as measured by VAS ($P = 0.001$). Furthermore, flexion, adduction, and internal rotation of the affected leg (FAIR test) produced less pain in the onaA group compared to the placebo group. In both studies, piriformis muscle injection was performed under electromyogrphic guidance using a long needle (3.5 cm or longer) in order to reach the deep piriformis muscle located behind gluteus maximus. In 2017, 15 years later, the same senior investigator published a controlled study [44] in which the results

of incobotulinumtoxinA (Xeomin) injection were blindly compared with that of placebo injections into the piriformis muscle in patients with PS. Following injection of 200 units, pain (measured by VAS) was significantly reduced in the incoA group at 2, 4, 8, 10, and 12 postinjection weeks ($P < 0.0001$). The FAIR test also significantly improved in the incoA group compared to placebo over 2, 4, 6, and 8 postinjection weeks ($P < 0.05$). In addition to clinical features of pain, the authors have used specific abnormalities of H-reflex, elicited from posterior tibialis muscle to support the diagnosis of piriformis syndrome. Side effects were reported to be mild and transient in the toxin group consisted of pain at the site of injection (2), flue-like symptoms (1), neck pain (1), and wobbly neck (1). Similar side effects were reported in the placebo group.

Comment

Although piriformis syndrome as the cause of sciatic pain remains controversial [61], three class II studies have provided evidence that injection of BoNT into piriformis muscle can reduce sciatic pain in the affected patients. The larger studies used an injection dose of 200 units of BoNT-A (onaA or inco-A) which did not cause any serious side effects. The data indicates that injection of BoNT-A into the piriformis muscle is probably effective (level B evidence, two class II studies) in relieving sciatic pain in piriformis syndrome.

Chronic Lateral Epicondylitis (CLE)

Chronic lateral epicondylitis is a common pain disorder affecting 1–3% of general population each year [62]. It is an overuse injury that is caused by repeated wrist extension against resistance. Heavy works requiring elbow extension and sports, particularly tennis, that often requires overextension of the elbow commonly cause CLE. Up to 50% of tennis players, especially those with poor or heavy swings, may develop this complication [62]. Although most acute cases improve with time if repeated elbow overextension is avoided, close to 20% develop CLE a year after the onset of their symptoms [63]. The lateral epicondyle is often tender to touch, and extension of the elbow generates pain. The pathology consists of degeneration of extensor tendons which is demonstrated well on in ultrasound examination, sometimes associated with inflammation [64]. Physical therapy avoiding elbow overuse and bracing helps in mild cases. Pharmacotherapy with nonsteroidal analgesics and GABAergic drugs such as pregabalin and gabapentin offers help. Local injection of steroids and anesthetic agents is reserved for more severe cases.

BoNT Therapy for Chronic Lateral Epicondylitis (CLE)

Four groups of investigators [43–46] conducted double-blind, placebo-controlled studies assessing the efficacy of BoNT injections in CLE (Table 6.3). All studies used abobotulinumtoxinA (Dysport) injections. The injection site was along the

course of the extensor muscles. The dose varied from 50 to 60 units. Different investigators chose different distances from lateral epicondyle as the site of BoNT injection. One group injected into extensors 1 cm below the tender epicondyle [43], two groups injected between 3 and 5 cm below the epicondyle [44, 45], and one group injected 33% of the arm's length below the epicondyle [46]. Three studies [43, 45, 46] with larger group of patients and employing a larger dose of toxin (60 units) reported improvement of pain ($P < 0.05$, measured by VAS) and physician satisfaction scale, whereas one study with smaller number of patients, injected close to epicondyle (cm) and employing a smaller dose of the toxin (50 units), did not report significant difference between the toxin and placebo groups [44]. Unfortunately, up to one-third of the patients after BoNT injection developed weakness of finger extensors that in some patients lasted up to 3 months.

Comment
Injection of abobotulinumtoxinA (Dysport) below the tender lateral epicondyle into elbow extensors is probably effective in CLE (level B: one class I and two class II studies). Development of finger weakness is a bothersome side effect. Hopefully, future studies may reduce the frequency of this complication via refinement of injection technique and BoNT dose adjustment.

Neuropathic Pain After Spinal Cord Injury

Han and coworkers [47] evaluated the analgesic effect of botulinum toxin type A (BTX-A) in 40 patients who experienced neuropathic pain after spinal cord injury. The study was randomized, double-blind, placebo-controlled, and parallel in design. In the toxin group, each patient received 200 units of Meditox (Korean toxin) injected subcutaneously into the area of skin affected by the neuropathic pain. The total dose of 200 U was distributed into several injection sites. The outcome measures consisted of Visual Analogue Scale for pain assessment (VAS), the Korean version of the short-form McGill Pain Questionnaire, and the World Health Organization WHOQOL-BREF quality of life. The patients' response to the injected toxin or placebo was evaluated at 4 and 8 weeks postinjection. At 4 and 8 weeks following injection, the VAS score was significantly reduced in the toxin group (18.6 ± 16.8 and 21.3 ± 26.8, respectively) compared to the placebo group (2.6 ± 14.6 and 0.3 ± 19.5, respectively) ($P < 0.05$). There was a trend toward significance in WHOQOL-BREF for the BONT-A group at 4 weeks ($P = 0.0521$). No side effects were reported.

Comment
This class I study provides a level B evidence (probably effective) for efficacy of subcutaneous injection of Meditoxin (type A, Korean BoNT) in neuropathic pain incurred in patients with spinal cord injury.

Chronic Pelvic Pain (CPP)

Chronic pelvic pain is defined as a noncyclic pain in the pelvic region of more than 6 months' duration. It is a common disorder in both genders. In one prospective study of a large number of women (n = >5000), 14.7% met the criteria for chronic pelvic pain [65]. There is evidence from blinded, placebo-controlled studies that both male and female pelvic pain may benefit from BoNT treatment. For male pelvic pain, these studies, one class I and one class II, provide a level B efficacy (probably effective), whereas for female pelvic pain, availability of one class II study denotes a possible level of efficacy (C level).

Gottsch el al. [48] have studied 11 male patients with CPP related to prostatitis in a randomized, placebo-controlled, double-blind protocol. A total of 100 units of BoNT-A was injected into the bulbospongiosus muscle. One month following treatment, the response measured by Global Response Assessment (GRA) was significantly better in the BoNT-A group compared to the placebo group (30% vs. 13%, p = 0.0002). The NIH-CPSI pain subdomain of NIH-CPSI score also significantly improved in the BoNT group. Another group of investigators injected 100 and 200 units of abobotulinumtoxinA (Dysport) into the lateral lobe of the prostate (at three sites) of 60 patients with prostatitis and CPP [49]. Pain was evaluated by VAS, American Urological Symptom Score (AUA-SS), NIH-CPSI, and frequency of diurnal and nocturnal urination. Injections and assessments were performed under a double-blind, placebo-controlled protocol. All measures improved following BoNT treatment. NIH-CPSI pain subdomain and the VAS scores showed the most significant improvements (scores were decreased by 79.9% and 82.1% at 6-month follow-up, respectively).

Recently, the beneficial effect of BoNT therapy in male chronic pelvic pain was supported by a class III study in that the effect of transurethral injection of 200 units of onaA into prostate was compared in 43 patients with no treatment over 12 months [66]. All patients had chronic pelvic pain due to chronic prostatitis (mean duration of 7 years). The outcome measures consisted of VAS for pain and NIH-CPSI total score. The toxin-injected group demonstrated a significant reduction of VAS (P < 0.0001 and significant improvement of NIH-CPSI score (P < 0.0001) at 3 months.

There are several other pain disorders in which efficacy of botulinum toxins for pain relief is suggested based on limited (one class II study) and small double-blind, placebo-controlled clinical trials. These conditions which by AAN guidelines will currently have a C level evidence (possibly effective) include female pelvic pain syndrome, painful knee osteoarthritis, pain in children with cerebral palsy after adductor release surgery, and vastus lateralis imbalance syndrome [67].

The level of efficacy of BoNT therapy in myofascial pain syndrome (MFPS) has been designated as U (undetermined) by AAN's assessment and guideline committee due to contradicting results from two large, class I clinical trials. However, the two studies employed different injection techniques: Gobel et al. [68] who reported statistically significant pain relief used a flexible injection pattern and injected 10 trigger points, whereas Ferrante et al. [69] who reported failure of BoNT to relieve

pain in MPS injected less than five trigger points (in many patients one trigger point). The authors of this chapter feel that MFPS with Gobel et al.'s method should have a level B efficacy (probably effective) based on one well-designed and conducted class I study.

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