Chapter 6
Clinical Use of Botulinum Neurotoxins: Pain

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Abstract Animal data have shown that botulinum neurotoxins (BoNTs) inhibit the release of pain neurotransmitters/neuromodulators (glutamate, substance P, calcitonin-gene-related peptide) and pro-inflammatory agents (prostaglandins, bradykinin, histamine) from peripheral nerve endings and sensory ganglia and reduce the phenomena of peripheral and central sensitization, major factors for pain chronicity. A review of class I and II studies (double blind, placebo controlled) using the criteria set forward by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology shows different levels of efficacy for a large number of human pain disorders: There exists level A evidence (two or more class I studies—established efficacy) for pain of cervical dystonia, chronic migraine and chronic lateral epicondylitis and level-B evidence (one class I or two class II studies—probably effective) for postherpetic and posttraumatic neuralgia, pain of plantar fasciitis, piriformis syndrome and pain in total knee arthroplasty. Level C evidence (one class II study—possibly effective) denotes allodynia of diabetic neuropathy, chronic low back pain, painful knee osteoarthritis, anterior knee pain with vastus lateralis imbalance, pelvic pain, postoperative pain in children with cerebral palsy after adductor hip release surgery, postoperative pain after mastectomy and sphincter spasms and pain after hemorrhoidectomy. The myofascial pain syndrome and chronic daily headaches have level U evidence (efficacy not proven due to controversial results). Results of BoNT treatment trials in episodic migraine and chronic tension headaches justify level A evidence for treatment failure. The end of each assessed category includes a medical comment and suggestions for improvement of future studies. For certain pain syndromes, figures are provided to illustrate the suggested number and site of injections and the appropriate doses.

Keywords Botulinum neurotoxin · Migraine · Neuropathic · Headache · Analgesic · Neuralgia · Plantar fasciitis · Myofascial pain

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6.1 Introduction

Chronic pain is a common medical complaint, and the management of refractory pain is a huge financial burden to the economy. Despite current availability of a large number of analgesic drugs, management of chronic pain is still a challenge for clinicians. Potent analgesics are often helpful, but side effects and drug interactions limit their clinical utility. Therefore, introduction of new drugs with low side-effect profiles, such as botulinum neurotoxins (BoNTs), is welcomed in the arena of chronic pain management.

BoNTs are used widely in clinical medicine for treatment of spasticity, hyperactive movement and autonomic disorders ([1], Chaps. 3–5 of this volume). In these settings, improvements are believed to result from inhibition of acetylcholine release from presynaptic vesicles via the inhibitory effect of BoNTs upon synaptic proteins [2]. In addition to acetylcholine, it is now increasingly recognized that both types A and B toxins (the two in clinical use) inhibit the release of a wide range of neurotransmitters, many of which are essential for initiation and chronicity of pain. Earlier observation of pain relief following treatment of cervical dystonia (CD) with BoNT type A before improvement of neck posture alerted clinicians to an independent analgesic effect for BoNTs. This observation, along with emerging animal data, led to an explosion of clinical trials with BoNTs for pain management in the past two decades. More recently, the discovery of recombinant toxins (chimeras) as a novel analgesic provided a formulation with a potential to retarget, specifically, the sensory neurons for pain treatment [3].

In this chapter, we will first discuss the data derived from animal studies and the mechanisms suggested for the analgesic effect of BoNT administration. Using the efficacy evaluation criteria of the American Academy of Neurology (AAN) [4], we will then review the evidence for efficacy of BoNTs in human pain disorders. To help clinicians regarding the practical aspects of BoNT therapy for pain management, we provide a brief clinical comment after each section. For some indications (common pain disorders), figures are provided to illustrate location and number of injection sites and the suggested doses for treatment.

6.2 Animal Studies

The anatomy of pain includes a complex system of substrates, the activation of which can lead to pain perception. These substrates consist of peripheral pain receptors, pain-conducting c-fibers, sensory cells in peripheral sensory ganglia and sensory spinal, brainstem, thalamic and cortical neurons. Neurotransmitters and neuromodulators at these levels are crucial to the conduction and perception of pain. In addition, pain chronicity and sustenance depends on mechanisms of peripheral and central sensitization. In the former, persistent exposure to a noxious stimulus leads to tissue accumulation of substance P, calcitonin gene-related peptide (CGRP) and glutamate, the pain modulators which coexist in the nerve terminals [5]. The vasodilation and plasma extravasation caused by these agents lead to release of a number of inflammatory

mediators such as histamine, bradykinin, prostaglandin and serotonin, which collectively lead to peripheral sensitization of nerve terminals. Peripheral sensitization enhances the release of glutamate and substance P from spinal cord neurons with resultant central sensitization and heightened perception of pain [6]. At the spinal level, enhanced sensitivity of wide dynamic range (WDR) neurons (caused by peripheral sensitization) is also considered a factor since these sensitized neurons begin to perceive non-nociceptive input as nociceptive [7]. Finally, hyperactivity of the sympathetic nervous system in chronic pain disorders enhances pain and contributes to chronicity (sympathetically maintained pain).

Experimental animal studies have demonstrated that BoNTs work on many levels of the pain system anatomy and that their actions upon pain transmitters and modulators reduce peripheral and central sensitization.

a. *At the peripheral pain receptor level*: Administration of BoNT type A into rat bladder, along with inhibition of acetylcholine release, inhibits adenosine triphosphate (ATP) and purinergic receptors (mediator of sensory excitation) leading to reduction of painful bladder spasms and actual reduction of pain receptors [8].
b. *At the level of sensory cells in peripheral sensory ganglion*: In the spinal sensory ganglion and the trigeminal ganglion, data demonstrate significant inhibitory action upon release of pain transmitters and modulators. This is particularly shown for glutamate, which is believed to be actively involved in development of neuropathic pain [9] and which accumulates in the tissue after peripheral nerve injury. In an elegant experiment, injection of BoNT type A before formalin into the rat paw resulted in significant reduction of tissue glutamate accumulation, which paralleled marked relief of the inflammation-related pain caused by formalin [10]. This response occurred in a dose-dependent fashion. Martinelli et al. [11] reported a similar effect on pain relief and glutamate accumulation with local BoNT type A injection after ligation of the sciatic nerve. The authors further demonstrated promotion of nerve regeneration in the BoNT type A treated group manifested by a local increase in regeneration-associated proteins [division cycle 2 (cd c2) and growth associated protein 43 (GAP-43)] in the sciatic nerve and glial fibrillary acidic protein (GFAP) in Schwann cells. Animals treated with BoNT type A also demonstrated quicker recovery of walking pattern and weight bearing compared to controls.

   Several lines of evidence demonstrate that BoNTs inhibit the release of pain peptides, substance P, bradykinin, CGRP and glutamate in vitro and in vivo from the dorsal root and trigeminal ganglia and from rat bladder tissue after injury [12]–[14]. Also, BoNT inhibits a family of G proteins including Rho guanosine triphosphatase which is essential for activation of interleukin-1, an important pro-inflammatory cytokine [15]. Intraprostatic injection of BoNT type A inhibits cyclooxygenase-2 expression and suppresses capsaicin-induced prostatitis in the animal model [16]. Collectively, these observations indicate that BoNTs are capable of reducing peripheral sensitization in chronic pain conditions by alleviating neurogenic inflammation. Finally, BoNT type A impairs sympathetic transmission and thus can interfere with maintenance of pain via decreasing sympathetic overactivity (sympathetically maintained pain) [17].

c. *At the spinal cord level*: Inhibition of pain-related neuropeptides and cytokines and peripheral sensitization indirectly reduces central sensitization of spinal cord neurons. Furthermore, injection of BoNT type A into rat jaw muscles decreases the electrical discharge of muscle spindles, a major sensory input which can enhance central sensitization in chronic pain via burdening sensitized WRD neurons [18]. Also, in the aforementioned formalin model of pain in rat paw, it was shown that pretreatment with BoNT type A reduces development of fos-positive neurons in lamina I, II, IV, and V of the spinal cord, regions that receive nociceptive input, following formalin administration [10]. Indirect involvement of spinal cord neurons following peripheral injection was suggested in one study which demonstrated that injection of I^{125}−labeled BoNT into one gastrocnemius muscle resulted in increased radioactivity in the ipsilateral sciatic nerve and hemicord of the cat [19]. In rat paclitaxel-induced neuropathy, unilateral subplantar injection of BoNT type A resulted in bilateral improvement of mechanical hyperalgesia [20]. More recently, Back-Rojecky et al. [21] showed more evidence for the central effect of the toxin after peripheral administration. In diabetic rats with bilateral allodynia, unilateral subcutaneous injection of BoNT type A in the allodynic region of one affected limb improved allodynia in both limbs. Furthermore, intrathecal injection of the toxin with a smaller dose produced the same effect. Lastly, femtomolar concentrations of BoNT type A inhibit membrane Na channels in rat central and peripheral neurons [22]. Overactivity of sodium channels plays a pivotal role in at least one model of chronic neurogenic pain, erythromyalgia [23]. Verderio et al. [24] measured the traffic of botulinum toxin A and E in brain synaptosomes. Inhibitory synapses were found resistant to both toxins, and the toxins preferentially inhibited the excitatory neurotransmitters.

6.3 Clinical Evidence in Human Subjects

The clinical evidence in this chapter is defined according to the guidelines of the Therapeutics and Technology Assessment Subcommittee of the AAN [25]. In these guidelines, level A comprises two or more class I studies, B indicates at least one class I or two class II studies and C comprises one class II or two consistent class III studies. Level U refers to unproven evidence, inconsistent results (Table 6.1).

6.3.1 Design of the Review

Class I and class II articles were searched online through PubMed (1966 to the end of March 2011) and OvidSP including ahead-of-print manuscripts.

Currently, five forms of BoNTs are widely marketed and are used for treatment of human subjects. Botox (onabotulinumtoxinA), Xeomin (incobotulinumtoxinA), Dysport (abobotulinumtoxinA), and Prosigne (Chinese toxin) are type A toxins. Myobloc (rimabotulinumtoxinB) is type B. Prosigne is not approved by the Food and Drug Administration (FDA) for use in the USA.

Table 6.1 American Academy of Neurology classification of evidence for therapeutic trials [4]

Class I: A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

The following are also required:

a. Concealed allocation
b. Primary outcome(s) clearly defined
c. Exclusion/inclusion criteria clearly defined
d. Adequate accounting for dropouts (with at least 80 % of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias
e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required[a]:

    1. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g., for a drug, the mode of administration, dose, and dosage adjustments are similar to those previously shown to be effective)
    2. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment
    3. The interpretation of the results of the study is based on an observed-cases analysis

Class II: A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e class I, above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class III: All other controlled trials (including well-defined natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements

Class IV: Studies not meeting class I, II, or III criteria including consensus or expert opinion

[a]Note that numbers 1–3 in class I are required for class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to a class III

6.3.2 Pain Disorders with Level A Evidence (Two or More Class I Studies, Efficacy Established)

6.3.2.1 Neck Pain Associated with CD (Eight Class I Studies)

CD is a late-onset focal dystonia characterized by twisting and twitching of the neck and shoulder muscles. There is often limitation of head movement leading to different head postures: over-rotation (torticollis), lateral tilt (laterocollis), over-flexion (anterocollis) and extension (retrocollis) or a combination thereof. Neck pain is often the most disabling symptom experienced by a majority of the patients (68–75 %) [26].

Eight class I studies evaluated the issue of pain in CD in relation to BoNT treatment. Four investigated type A [27]–[30] and four investigated type B BoNTs [31]–[34]. One other study compared efficacy and safety of abobotulinumtoxinA with trihexyphenidyl [35]. In these studies, the response to pain was measured by different means including a simple pain scoring scale (severe, moderate, mild, none), the visual analog scale (VAS), and the pain subscale of Toronto Western Spasmotic Torticollis Rating Scale (TWSTRS). The results uniformly show that treatment of CD with type A (Botox, Dysport, Xeomin) or type B (Myobloc) BoNTs results in significant reduction of neck pain ($p < 0.05$). For example, in the study of Truong et al. [30] comparing abobotulinumtoxinA with placebo at 4 weeks, the level of pain reduction measured by VAS was 13.4 mm (on a 100-mm scale) for abobotulinumtoxinA versus 1.9 mm for the placebo ($p < 0.002$). AbobotulinumtoxinA is also superior to trihexyphenidyl in terms of efficacy and better tolerance [35].

Additionally, six prospective, blinded, multicenter studies compared two serotypes of BoNTs with each other in terms of safety and efficacy and response to pain [34], [36], [37], [38], [39], [40]. The comparison studies of onabotulinumtoxinA with rimabotulinumtoxinB [34], [36], [37] and incobotulinumtoxinA [38] showed that both serotypes effectively reduced pain and there was no significant difference between the two except in the study of Lew et al. [34], which demonstrated a significantly higher response rate of pain relief for type B (59 % versus 36 %; $p < 0.05$). The comparison study of abobotulinumtoxinA with onabotulinumtoxinA reported slightly more pain improvement in the abobotulinumtoxinA group, but this difference was not statistically significant. In one report, abobotulinumtoxinA group demonstrated more side effects [39]. A recent double-blind class II study compared pain efficacy of onabotulinumtoxinA with Prosigne (using 300 units of each) in patients with CD. Pain efficacy was the same for both toxins at 4 and 16 weeks [40].

Three prospective long-term studies of abobotulinumtoxinA with six or more injections (performed every 3 months) demonstrated sustained responses following repeated treatments with mild side effects (local pain, subtle weakness, dysphagia) [30], [41], [42] Approximately 20 % of the patients chose not to continue the treatment due to high cost, dislike of injections and loss of efficacy [41], [42]

Clinical Comment BoNTs are an effective and established treatment for pain in CD. The degree of pain relief in CD is comparable among type A toxins and is similar between type A and type B toxins (with the exception of one study which reported type B being more effective [34]).

6.3.2.2 Chronic Migraine (Two Class I Studies)

Chronic migraine (CM) is defined as headache with a frequency of 15 or more headache days per month (at least eight migraine type), for more than 3 months, lasting more than four hours per day [43]. Freitag et al. [44], in a double-blind, placebo-controlled study, compared the effect of a fixed dose (100 units), fixed site (glabella, frontalis, temporal, trapezius, suboccipital) paradigm treatment of onabotulinumtoxinA (20 patients) with placebo (21 patients). All patients with medication

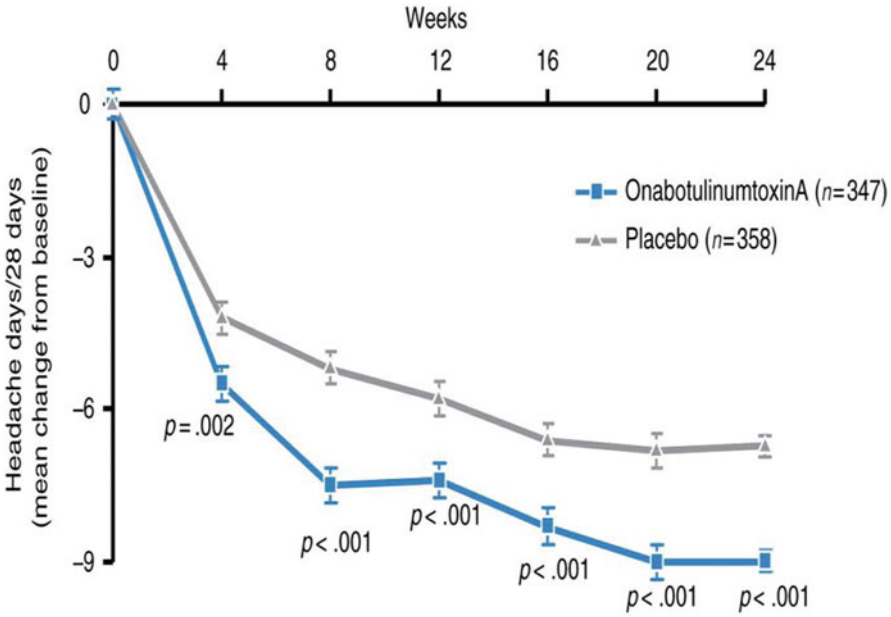

Fig. 6.1 PREEMPT 2: showing significant improvement of pain days from botulinum toxin group compared to placebo group over all time points of the 24-month blinded arm of the study. (From Cephalalgia July 2010 with permission)

overuse were excluded. The primary outcome was the number of migraine episodes experienced over each 4 weeks of the study. The secondary outcomes were number of headache days and headache index (HI; measure of both intensity and frequency). OnabotulinumtoxinA was statistically superior to placebo for both primary ($p < 0.01$) and secondary outcomes (frequency of pain days $p = 0.041$ at 4 weeks and $p = 0.046$ at 16 weeks, and HI, $p = 0.003$ at 16 weeks).

In the summer of 2010, the results of Phase 3 Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) 1 and PREEMPT 2 [45], [46], two large class I, multicenter studies assessing efficacy of onabotulinumtoxinA in CM, were published. Each study included approximately 700 patients, with comparable and close numbers of subjects in both the toxin and placebo groups, evaluated over a 24-week blinded arm study followed by a 32-week open arm study. Both studies included patients with medication overuse. The primary outcome for PREEMPT 1 was the number of headaches episodes, and for PREEMPT 2, the number of headache days, both evaluated at 24 weeks. A number of secondary outcomes were also evaluated at the 24-week time point. PREEMT 2 met its primary and secondary outcomes at all time points (Fig. 6.1 and Table 6.2). For the primary outcome, the change in headache days was 9 for onabotulinumtoxinA versus 6.7 for the placebo ($p < 0.001$). The pooled data [47] of the two studies also showed significant change from the baseline in favor of onabotulinumtoxinA regarding the primary and secondary parameters (Table 6.2).

Table 6.2 Results (*p* values) of PREEMPT studies and pooled data comparing botulinum toxin and placebo with baseline

Parameters	PREEMPT 1	PREEMPT 2	Pooled data
Number of HD days	0.006	< 0.001 (primary outcome)	< 0.001
Number of HD episodes	0.34 (primary outcome)	< 0.003	< 0.001
Number of migraine days	0.002	< 0.001	< 0.001
Number of moderate to severe HD days	0.004	< 0.001	< 0.001
Change in total HIT-6 score	0.001	< 0.001	< 0.001
Total accumulative HD hours in HD days	< 0.001	< 0.001	< 0.001
Frequency of triptane intake	0.23	< 0.001	< 0.001

HD headache, *PREEMPT* phase 3 research evaluating migraine prophylaxis therapy

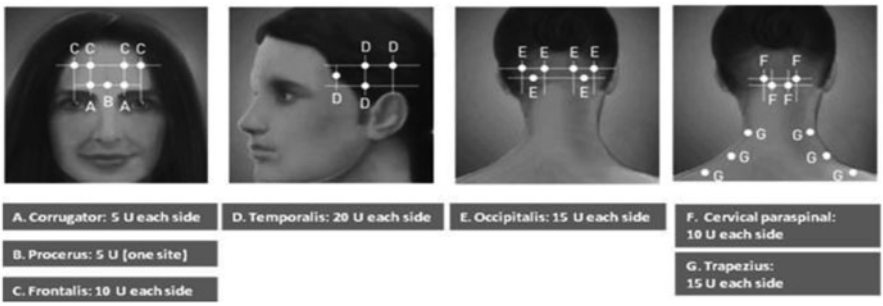

Fig. 6.2 Sites of onabotulinum toxin injection for treatment of chronic migraine based on PREEMPT studies (from Blumenfeldt et al Headache 2010;50:146). The recommended dose varies between 155–195 units. With permission Wiley publishers

Although PREEMPT 1 did not meet the primary outcome, it met its secondary outcomes (Table 6.2). The FDA considered headache days a better outcome measure than headache episodes for the study of CM (PREEMPT 2). OnabotulinumtoxinA was approved for treatment of CM in the UK and Canada in the summer of 2010 and in the USA in October 2010. Figure 6.2 shows the site of injections and doses used in the PREEEMPT studies of CM.

Clinical Comment CM is a major health problem and is believed to account for the majority of the cases of chronic daily headaches (CDHs). Many clinicians consider the number of moderate and severe headaches (most troublesome to the patient) a true measure of patient discomfort and a better primary outcome compared to either total number of pain days or headaches episodes. This measure was significant for the toxin group in all three studies (the two PREEMPT studies and the pooled data) (Table 6.2). Clinical evidence in agreement with PREEMPT data (Fig. 6.1) indicates that the analgesic effect of botulinum toxin therapy in CM improves with repeated treatments. Inclusion of patients with medication overuse is considered a weakness of the PREEMPT studies.

6.3.2.3 Chronic Lateral Epicondylitis (Three Class I Studies and One Class II Study)

Wong et al. [48] conducted a prospective, double-blind study in 60 patients with chronic lateral epicondylitis (CLE). In the toxin group, abobotulinumtoxinA (60 units) was injected into subcutaneous tissue and underlying muscle, 1 cm from the lateral epicondyle aimed toward the tender spot. Pain intensity was evaluated by VAS (primary outcome) at 4 and 12 weeks. In the toxin group, pain measured by VAS improved significantly ($p < 0.001$ and $p = 0.006$) for 4- and 12-week time points. One patient developed weakness of fingers, which lasted for 3 months. However, a blinded study of 40 patients with CLE by Hayton et al. [49] found no significant change in VAS or quality of life (measured by the 12-Item Short Form Health Survey or SF-12) 3 months after injection of abobotulinumtoxinA intramuscularly 5 cm distal to the maximum point of tenderness at the lateral epicondyle, in line with the middle of the wrist. In another class I study [50] of 130 patient in 16 centers, BoNT type A was injected in the painful origin of forearm extensor muscle and the results were compared with placebo at 2, 6, 12, and 18 weeks. Both VAS and global assessments improved significantly from week 2 to week 18 at different time points ($p = 0.003$ and 0.001, respectively). Weakness of the third finger developed in the number of patients but it did not interfere with work. In a recent class I study, 48 patients randomly received abobotulinumtoxinA (60 units) or placebo under a double-blind, prospective protocol [51]. The site of injection was one-third of the way down the length of the forearm from the tip of the lateral epicondyle along the course of the posterior interosseous nerve. Primary outcome was improvement of pain at rest (measured by VAS) and secondary outcomes were improvement of pain at maximum grip and maximum pinch. Outcomes were measured at 4, 8 and 16 weeks. Significant improvement of pain at rest and pain at maximum pinch was noted in the BoNT group ($p < 0.01$). Approximately half of the patients in the BoNT group developed pain and muscle spasms in the injected site. One patient developed significant weakness of the third and the fourth finger which lasted for 2 months.

Clinical Comment The three class I studies with larger number of patients depicted efficacy of BoNT treatment in CLE. The study of Hayton et al., which disclosed negative results, had two possible design problems: (1) The first assessment was done at 3 months, which may be too late since most patients who receive BoNT treatment show fading of improvement by 3 months. (2) The small sample size of the study could have led to type II error in statistical assessment. The side effects, weakness of fingers and wrist extension, limit the practical value of BoNT therapy in CLE. Future studies may consider smaller doses and more refined techniques to avoid this side effect.

6.3.3 *Pain Disorders with Level-B Evidence (One Class I or Two Class II Studies): Probably Effective, Should Be Considered for Treatment*

6.3.3.1 Postherpetic and Posttraumatic Neuralgia with Allodynia (Each One Class I Study)

Neuropathic pain is a symptom of damage or dysfunction of the peripheral or central nervous systems, and in some cases it may result from nociceptive injury [52]. The pain often has a burning quality and may be associated with dermal hypersensitivity and allodynia. Xiao et al. [53] assessed pain relief by VAS at 1, 7 and 90 days in a class I study in 60 patients with postherpetic neuralgia (PHN) after administering BoNT type A, lidocaine or a placebo (20 patients in each group). Pain relief and improvement of sleep in the BoNT group were superior to that in the lidocaine and placebo groups ($p < 0.05$). Patients in the BoNT group also used significantly less opioids (22 % versus 52 % and 66 %). Ranoux et al. [54] conducted a double-blind, placebo-controlled study on 29 patients with refractory neuropathic pain, 25 with posttraumatic neuralgia (PTN)/allodynia and 4 with PHN. OnabotulinumtoxinA (20–190 units) and placebo were injected once intradermally in the painful area after baseline assessments. Outcomes were evaluated at 4, 12 and 14 weeks with measurement of pain intensity, thermal and mechanical perception, allodynia to skin brushing and quality of life. Patients who received BoNT type A had diminished pain intensity, neuropathic symptoms and allodynic brush sensitivity and reduced number of pain paroxysms along with improvement of certain quality-of-life markers (general activity, mood) compared to the placebo group ($p < 0.05$).

6.3.3.2 Plantar Faciitis (Two Class II Studies)

Pantar faciitis (PF) is the most common cause of heel pain caused by micro-tears and inflammation as a result of repeated injury. In severe cases, treatment with posterior night splints, ultrasound, iontophoresis, phonophoresis, extracorporal shock therapy or local corticosteroid injections can help, but failures are not uncommon. Babcock et al. [55] investigated the efficacy of onabotulinumtoxinA in 27 patients (43 heels) with chronic PF (class II). Injection of 40 and 30 units of onabotulinumtoxinA, one medial to the heel and the other about 1–3 inches anterior to the heel (tender area in PF) (Fig. 6.3), resulted in significant improvement of the pain in the onabotulinumtoxinA group. Two months post injection, the study met all three primary outcomes (reduction of pain intensity measured by pressure algometry, pain frequency and the Maryland Foot Score) ($p < 0.05$).

Huang et al. [56] conducted a prospective, double-blind study in 50 patients with PF and refractory pain. In the toxin group, 50 units of onabotulinumtoxinA were administered into the heel under ultrasonic guidance. At 3 weeks and 3 months, the toxin-injected group showed significant pain relief (measures by VAS) compared to

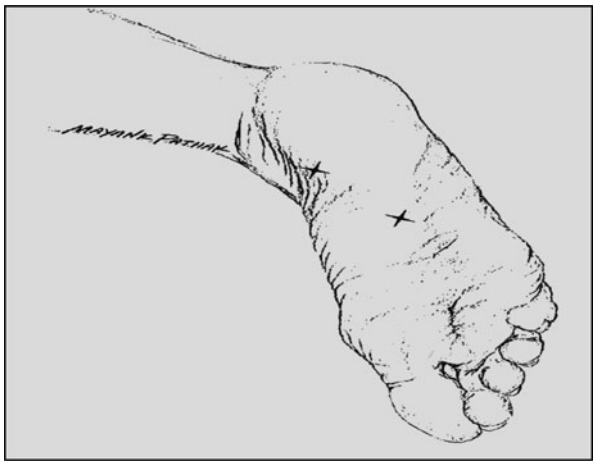

Fig. 6.3 Sites of BoNT-A injections for plantar faciitis (30 and 40 units). [99]

the placebo group ($p < 0.001$). The toxin-treated group also showed improved gait at 3 months as measured by increased center of pressure velocity ($p < 0.05$).

6.3.3.3 Piriformis Syndrome (Two Class II Studies)

The piriformis muscle originates from the anterior part of the sacrum and sacroiliac capsule and after exiting from the pelvis attaches to the greater trocanter. Spasms of the piriformis muscle cause pain deep in the buttock referred to as piriformis syndrome (PS). Childers et al. [57] conducted a double-blind, crossover study in ten patients with PS. OnabotulinumtoxinA, 100 units, was injected into the piriformis muscle under electromyographic and fluoroscopic guidance. The pain relief (measured by VAS scores) was significant in the onabotulinumtoxinA arm of the study compared to the placebo arm ($p < 0.05$). Fishman et al. [58] compared the results of 200 units of onabotulinumtoxinA with lidocaine and steroid injection and with placebo injection into the piriformis muscle in 72 patients with PS; 50 % or better improvement in VAS score was considered significant. Onabotulinumtoxin A was superior to the placebo ($p = 0.001$) and to steroids + lidocaine ($p < 0.005$) in relieving pain.

6.3.3.4 Refractory Painful Total Knee Arthroplasty (One Class I Study)

Refractory pain after total knee arthroplasty (TKA) is common and affects 8–13 % of the patients after surgery [59]. Singh et al. [60] assessed the efficacy of an intra-articular injection of 100 units of onabotulinumtoxinA in 54 patients with TKA. The primary end point was a two grade or more reduction of pain in VAS 2 months after treatment, and secondary end points included Physician's Global Assessment of Change (PGAC), 36-Item Short Form Health Survey (SF-36) and several other scales.

At 2 months, a significant response in VAS was noted in 71 % of the patients in BoNT versus 36 % in the placebo group ($p = 0.025$). Both PGAC and SF-36 (pain subscale) showed significant change in favor of the onabotulinumtoxinA group ($p = 0.003$ and $p = 0.049$, respectively).

Clinical Comment Larger class I studies are necessary to establish the efficacy of BoNT treatment in these painful disorders. Refinement of the technique and dose optimization could potentially lead to better results.

6.3.4 Pain Disorders with Level C Evidence (One Class II Study)

Recommendation: Possibly effective. May be used at the discretion of the clinician.

6.3.4.1 Refractory Low Back Pain

Low back pain (LBP) is the most common form of pain in adults producing some form of disability in 60 % of the patients. Foster et al. [61] studied 31 patients mostly with chronic spine disease (stenosis, disc degeneration) and LBP of more than 6 months duration (class II). They used a fixed paradigm of five lumbar-level injections (L1–L5) with onabotulinumtoxinA, each level receiving 40 units into erector spinae. Primary and secondary outcomes of pain intensity (VAS) and activities of daily living (ADLs) were met and were significantly different from placebo at both 3 weeks and 2 months. At 2 months, 60 % of the patients reported 50 % or more decrease in pain intensity with improvement of at least two ADLs. The same group of investigators conducted a prospective study of 14 months' duration in chronic LBP using the same technique and rating scales (plus a pain frequency scale) [62]. At 2 months, 52 % of the patients showed a significant improvement in all scales compared to placebo. Doses ranged from 250 to 400 units per session. Of early responders, 91 % continued to demonstrate the favorable response with repeat injections. Three patients experienced mild, transient, flu-like reactions.

Clinical Comment LBP has a number of causes which may respond differently to BoNT treatment. The class II study cited above included a heterogeneous group with predominantly unilateral LBP. Selective studies are needed with focus on different causes of LBP and in patients with bilateral LBP.

6.3.4.2 Diabetic Neuropathy

In a double-blind crossover study, Yuan et al. [63] studied the effect of onabotulinumtoxinA versus normal saline subcutaneous administration in 18 patients with diabetic neuropathy. Allodynia and pain sensitivity were assessed by VAS at 1, 4, 8 and 12 weeks. At all time points, onabotulinumtoxin A was superior to saline in reducing pain ($p < 0.05$).

Clinical Comment Study limitation includes the small number of patients. A double-blind study with larger numbers is needed to support the result of this crossover designed study.

6.3.4.3 Painful Knee Osteoarthritis (One Class II Study)

Intra-articular injection of low-dose BoNT type A (100 units), high-dose BoNT type A (200 units), and corticosteroids was investigated in 60 patients, randomly divided into three groups [64]. The primary outcome, significant improvement of VAS at 2 months, was met only for the low-dose BoNT group ($p = 0.01$). All three groups showed a statistically significant response to the secondary outcome, in McMaster Arthritis Index scores for pain, stiffness and function.

Comment One limitation of the study is the large number of dropouts (48 %). It is also hard to explain why the-low dose group fared better than the higher dose group.

6.3.4.4 Anterior Knee Pain Associated with Vastus Lateralis Imbalance

Investigators of this study injected abobotulinumtoxinA (500 units) or saline (1 cc) randomly into the vastus lateralis muscle of 24 patients with anterior knee pain [65]. The primary outcomes, improvement in knee pain-related disability and activity-related knee pain (in VAS) at 3 months, were both met ($p < 0.04$ for disability and < 0.003, < 0.02 and < 0.04 for pain in kneeling, squatting and walking, respectively).

6.3.4.5 Pelvic Pain

Chronic pelvic pain affects 3.8 % of women and imposes an annual burden of approximately US$ 2 billion (direct and indirect costs) to the US economy. In a double-blind, placebo-controlled study, Abbott et al. [66] investigated the effect of 80 units of onabotulinumtoxin A injected into pelvic floor muscles in 60 women with chronic (> 2 years) pelvic pain and pelvic floor spasms. Pelvic pain was assessed by VAS and pelvic floor pressure was gauged by vaginal manometry monthly for 6 months. Those patients who were injected with onabotulinumtoxinA reported significant relief from nonmenstrual pain compared to the placebo group ($p = 0.009$). The onabotulinumtoxinA group also demonstrated a significant decrease in the pelvic floor pressure ($p < 001$).

Comment Future studies should provide clearer definitions of primary and secondary outcomes.

6.3.4.6 Postoperative Pain in Children with Cerebral Palsy After Adductor Hip Release Surgery

Barwood et al. [67], in a randomized, double-blinded study, reported significant alleviation of postoperative pain in 16 children with cerebral palsy who received BoNT type A injections into thigh adductors before adductor hip release surgery for prevention of hip dislocation ($p < 0.003$). There was also a significant reduction in mean analgesic requirement ($p < 0.05$) and mean length of hospitalization ($p < 0.003$).

6.3.4.7 Postoperative Pain After Mastectomy

In a randomized and placebo-controlled study [68] of 48 patients, injection of 100 units of BoNT type A into the pectoralis major, serratus anterior and rectus abdominis muscles before mastectomy reduced postoperative pain significantly ($p < 0.0001$) and facilitated reconstruction with a tissue expander. The placebo group used more narcotics to alleviate pain postoperatively compared to the BoNT type A group ($p < 0.0001$).

6.3.4.8 Sphincter Spasms and Pain After Hemorrhoidectomy

In a double-blind study [69] of 50 patients, injection of 20 units of BoNT type A into the internal rectal sphincter prior to hemorrhoidectomy resulted in significant reduction of postoperative sphincter spasms ($p < 0.05$).

6.3.5 Pain Disorders with Level-U Evidence: The Evidence to Support or Refute Efficacy Is Insufficient Due to Contradictory Results

6.3.5.1 Myofascial Pain Syndrome

Myofascial pain syndrome (MFPS) is characterized by the presence of focal regions of muscle tenderness and trigger points (tPts) which, upon pressure, provoke radiating pain. The tPts probably represent erratic or dysfunctional motor end plates with excessive acetylcholine content. Table 6.3 summarizes the results of class I and II studies with BoNT treatment in MPS [70]–[78]. As can be seen in this table, each one of the nine studies used different doses per tPt, and responses were evaluated at different time points and with different scales. All studies used BoNT type A toxin, seven onabotulinumtoxinA and one abobotulinumtoxinA. Four studies (including one class I) reported significant pain relief at some point after treatment (two at primary outcome time point), whereas five did not.

Table 6.3 Randomized, controlled trials of botulinum toxins in MFPS

Author	No	Study	Location	Outcome measures	Dose	Result
Freund and Schwartz 2000 [70]	26	Class II	Neck	PO, VAS, ROM, at 4 weeks	B: 20 U/tp	$p = 0.001$
Wheeler et al. 2000 [71]	50	Class II	Cervico-thoracic	PO, NPAD, GAI, SF-36	B: $231 \pm 50\,\mu$	ns
Ferrante et al. 2005 [72]	142	Class II	Neck and shoulder	PO, VAS, PPT, SF-36	B: 10, 25, 50 U/tp	ns
Ojala et al. 2006 [73]	31	Class II	Neck and shoulder	PO, VAS, VRS, PPT at 4 weeks	B: 15–35 U 5 U/tp	ns
Gobel et al. 2006 [74]	144	Class I	Upper back	PO: mild or no pain at 5 weeks	D: 400 U 40 U/tp	$p = 0.002$
Qerma et al. 2006 [75]	30	Class II	Infra-spinatus	PO: pain intensity 0–10 scale (3 and 28 weeks)	B: 50 U/tp 12.5 U/tp	ns
Lew et al. 2007 [76]	29	Class II	Cervico-thoracic	PO: VAS, NDI, SF-36 at 2 months	B: 100–200 U 50 U/tp	ns
Miller et al. 2009 [77]	47	Class II	Cervico-thoracic	PO: VAS, PF at 2 months	B: 150–300 μ	$p = 0.001$ (VAS)
Benecke et al. 2011 [78]	153	Class II	Cervico-thoracic	PO: percent of pts with mild or no pain at 5 weeks	D: 400 U	5 weeks = ns 9 and 10 weeks, $p = 0.04$

B onabotulinumtoxinA, *D* dysport, *GAI* global assessment of improvement, *NDI* neck disability index, *NPAD* neck pain and disability scale, *NS* not significant, *PF* pain frequency, *PO* primary outcome measure, *PPT* pain pressure threshold, *ROM* range of motion, *SF-36* 36-item short form health survey, *tp* trigger point, *VAS* pain intensity in visual analog scale, *VSR* verbal reporting score

Clinical Comment It is not possible at this time to make a firm statement regarding the role of BoNT treatment in MFPS due to the diverse nature of the studies. In positive studies of Gobel et al. [74] and Miller et al. [77], the investigators injected a larger number of tPts (> 5). The negative results of Ferrante et al. [72] might have been be confounded by exclusion of patients with more than five tPts; the cohort probably had a milder form of MFPS. In the study of Bencke et al. [78], pain relief was achieved at 9 and 10 weeks but not at 5 weeks. The fixed pattern of injection might have contributed to earlier pain relief. In the study of Ojala et al. [73], the dose per tPt (5 units) might have been too small to be effective. Future studies of MFPS should use methodologies which have proved effective in the past, perhaps with larger doses and with customized rather than fixed designs.

6.3.5.2 Chronic Daily Headaches

Four class I and II studies addressed the issue of CDH directly. All four class I studies [79]–[82] used a mean change in headache-free days/month as the primary outcome. Three used a flexible injection paradigm [79]–[81]. In one study [79], BoNT type A (200 units) increased the number of headache-free days/month significantly (11 days versus 8 days of placebo) ($p < 0.05$). In another study [80] of 355 patients, the response to BXT type A was compared to placebo over a 9-month period during which the patients received three treatment cycles (105–260 units). The study did not meet the primary outcome. The third study [81] looked at a subset of this cohort, 228 patients with no prophylactic medications. When compared with placebo, the between-group difference was statistically significant at successive time points (for the first 3 months, $p = 0.004$, $p = 0.032$ and $p = 0.023$, respectively). In the fourth study [82], 702 patients were stratified into four groups, one placebo group and three treatment groups (75, 150 and 225 units) with a fixed injection paradigm. The primary outcome measure (an increase in pain-free days) was not met.

Clinical Comment Inconsistent results of the aforementioned studies led to depiction of U evidence for BoNT treatment of CDH by the AAN subcommittee in 2008 [83]. It is fitting to consider each major category of CDH separately, namely CM and chronic tension headaches (CTHs). As mentioned above, the new data illustrated a positive response to BoNT treatment for CM (level-A evidence).

6.3.6 Major Pain Disorders with Predominantly Negative Results: Episodic Migraine and CTHs

6.3.6.1 Episodic Migraine (Four Class I and Four Class II Studies)

The first class I study [84] compared BoNT type A to placebo in 232 patients, each with four to eight episodes of migraine per month. Up to 25 units BoNT type A was injected into the frontal and temporal muscles. Both groups showed a reduction in

frequency, intensity, and duration of migraine headaches but the difference between two groups was not statistically significant (at 1 and 3 months). Another class I study [85], investigated the efficacy and safety of BoNT type A in 418 patients with the same migraine frequency using doses of 7.5–50 units. Both BoNT type A and placebo decreased the migraine frequency from baseline at each time point between 1 and 4 months after injection. Again, the difference between the two treatments was not significant. A third class I study [86] enrolled 369 patients, each with 4 to 15 episodes of migraine/month. The patients were stratified into three treatment groups. The total dose of BoNT type A ranged from 110 to 260 units (mean 190 units). The primary outcome was a decrease in frequency of migraine episodes from baseline between days 30 and 180 post treatment. The primary outcome was not met but patients who had the highest pain frequency (12–15 per month) responded considerably better to BoNT type A than to the placebo ($p = 0.041$). The fourth class I study [87] evaluated the efficacy and safety of BoNT type A in 495 patients after a 30-day placebo run-in. Patients were studied in four groups, three on BoNT type A (225 units, 150 units, 75 units) and one on placebo. The primary outcome, frequency of migraine episodes on day 180, was not met for any of the three groups.

The first class II study [88] investigated the effect BoNT type A administration (25 and 75 units) into glabellar and frontal muscles. The primary outcome was the proportion of the patients with 50 % or more reduction of headaches frequency as compared to baseline. This outcome was not met but the BoNT type A group showed a significant decrease in frequency of moderate and severe headaches at 2 months and of any migraine at 3 months ($p < 0.05$). The second class II study [89] compared the effect of two doses of 16 and 100 units of BoNT type A with placebo. The primary outcome, a change in frequency of moderate or severe headaches per month, was not met. The study, however, showed a significant decrease in the proportion of the patients experiencing a reduction of two or more headaches per month. The third class II study [90] also did not find a significant difference in the frequency and severity of episodic migraine (EM) between BoNT type A and placebo after the first of a series of treatments. From the second treatment on, however, the migraine index (frequency $\times$ intensity) was significantly lower for the BoNT type A group at all measured time points. The fourth class II study [91] compared the effect of BoNT type A and divalproex sodium with saline and divalproex sodium in 59 patients with EM and CM. Several primary outcomes, including a decrease in frequency, intensity and disability assessment score, were met for both groups at multiple time points (1, 3, and 6 months). There was, however, no statistically significant difference between the responses of the two groups at any time point.

6.3.6.2 Chronic Tension Headaches

Four class I studies [92]–[95] (two using onabotulinumtoxinA and two using abobotulinumtoxinA) and three class II studies [96]–[98] (one using onabotulinumtoxinA and two using abotulinumtoxinA), investigated the efficacy of BoNT treatment in patients with CTHs. The dose of onabotulinumtoxinA varied from 20 to 150 units and

that of abobotulinumtoxinA from 30 to 500 units. Although some secondary outcomes were met, all four class I and two of three class II [96]–[97] studies did not meet their primary outcome which, for most, was the number of pain-free days.

Clinical Comments All class I studies of EM (less than 15 episodes per month) and CTH have shown no improvement with BoNT-A treatment hence denoting a probably ineffective, level A evidence. However, there are important technical issues that need to be discussed and clarified:

1. EM studies have taken frequency of migraine episodes as a primary outcome. This is probably an unrealistic measure since what is most disturbing to the patient is the episodes of moderately severe and severe headaches. Most patients are not much bothered by subtle and mild headache episodes which do not change their quality of life. As discussed above, some studies of EM have shown significance for BoNT treatment in reducing frequency of moderately severe to severe migraine episodes [88] and others have emphasized the importance of migraine severity by showing significant reduction of migraine index (frequency $\times$ severity) in the second treatment [90]. We recommend that future studies of EM take the frequency of moderately severe to severe episodes as the primary outcome measure.

2. The studies of CTH have several limitations:

a. Considering the number of headache-free days (half of the studies) or local skull tenderness (half of the studies) as a primary outcome is probably also unrealistic. The study of Silberstein et al. [94] shows that the BoNT group had a 50 % or more reduction in headaches days ($p = 0.024$) but demonstrated no significant change in headache-free days. A better measure again seems to be number of days with moderate to severe headaches.

b. The majority of CTH studies used a small total dose of the toxin (less than 100 units for onabotulinumtoxinA and less than 500 units for abobotulinumtoxinA), small dose per site, and small number of injected sites. These limitations have been mentioned by the investigators themselves. Recent successful studies of CM (PREEMPT II) used a larger number of injection sites, coverage of more muscles and doses larger than 150 units/session (155–195 units). Future studies of CTH with BoNTs may use a technical approach similar to the one which proved effective for CM.

6.4 Conclusion

Over the past decade, BoNT treatment has shown efficacy in a large spectrum of human pain disorders. Animal data have provided evidence for a variety of mechanisms to explain BoNTs' analgesic effects. To date, with the exception of pain in CD, the majority of human pain data comes from investigations conducted with botulinum toxin A and in particular with onabotulinumtoxinA. There is a need for more extensive investigations with other forms of botulinum toxin A and with botulinum toxin B in treatment of pain disorders. Selection of the appropriate primary outcome and

proper dosage are crucial for obtaining favorable results in clinical trials with BoNTs in pain disorders.

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