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# REVIEW ARTICLE

# Treatment of Refractory Pain with Botulinum Toxins—An Evidence-Based Review

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## Abstract

**Objectives. To provide updated information on the role of botulinum toxins in the treatment of refractory pain based on prospective, randomized, double-blind, placebo-controlled studies.**

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

**Results. Level A evidence (two or more class I studies—established efficacy): pain of cervical dystonia, chronic migraine, and chronic lateral epicondylitis. Level B evidence (one class I or two class II studies—probably effective and recommended): post-herpetic neuralgia, post-traumatic neuralgia, pain of plantar fasciitis, piriformis syndrome, and pain in total knee arthroplasty. Level C evidence (one class II study—possibly effective, may be used at discretion of clinician): allodynia of diabetic neuropathy, chronic low back pain, painful knee osteoarthritis, anterior knee pain with vastus lateralis imbalance, pelvic pain, post-operative pain in children with cerebral palsy after adductor hip release surgery, post-operative pain after mastectomy, and sphincter spasms and pain after hemorrhoidectomy. Level U evidence (efficacy not proven due to diverse class I and II results): myofascial pain syndrome and chronic daily headaches. Studies in episodic migraine and tension headaches have shown treatment failure (level A—negative).**

**Conclusion. Evidence-based data indicate that administration of botulinum toxin in several human conditions can alleviate refractory pain. The problems with some study designs and toxin dosage are critically reviewed.**

**Key Words. Chronic Pain; Botulinum Toxin A; Botulinum Toxin B; Pain Medicine; Pain Management; Pain Disorder; Botulinum Toxin**

## Introduction

Over the past two decades, the use of botulinum neurotoxin (BoNT) in clinical medicine significantly improved management of many movement disorders, spasticity, and syndromes of autonomic overactivity [1]. More recently, animal data suggest an analgesic effect for BoNT, and human investigations demonstrate promising results in this area.

BoNT works by inhibiting the release of a number of neurotransmitters from presynaptic vesicles via deactivation of specific proteins located at, or in proximity of, the vesicular membrane. Of the seven distinct serotypes of BoNT (A to G), types A and B are currently used in clinical practice. In the case of type A toxin, the endopeptidase light chain of the toxin in the presence of zinc deactivates the synaptosomal-associated protein with the molecular mass of 25kDn (SNAP 25) located within the cell membrane [2]. The type B toxin deactivates the vesicle associated membrane protein, which is located on the vesicular membrane itself. In the case of motor neurons, these mechanisms lead to improvement of overactive movement disorders via blocking acetylcholine release. Recent identification of SNAP 25 on sensory neurons led to development of retargeted neurons with antinociceptive potentials [3]. Four types of BoNT type A are commercially available and are widely used. These include onabotulinumtoxinA (Botox, Allergan, Irvine, CA), abobotulinumtoxinA (Dysport, Ipsen, Cherry Valley, IL), and incobotulinumtoxinA (Xeomin, Merz, Frankfurt, Germany) available in the United States, and a Chinese toxin Prosigne (Lanzhou Institute, Lanzhou, China). BoNT type B is rimabotulinumtoxinB (marketed as Myobloc in the United States and Neurobloc in Europe; Solstice). These toxins have different units and as emphasized by Food and Drug Administration (FDA), the units are not comparable among the toxins.

This review includes only the evidence derived from high quality, prospective, double-blind, placebo-controlled investigations (class I and class II). The classification of the study type (class I–IV) and the method for evidence-based recommendations are adopted from the published guidelines of the American Academy of Neurology ([4]; Table 1).

**Table 1** American Academy of Neurology classification of evidence for therapeutic trials

**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*
  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.

* 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.
From Reference [4].

For this review, a search was conducted in PubMed (1966 to the end of January 2011) and OvidSP including online early release publications. The search terms comprised of "botulinum toxin," "botulinum neurotoxin," "botulinum toxin and pain," "botulinum toxin A," "botulinum toxin B," "pain," "refractory pain," and "chronic pain."

This review starts with a brief account of translational data from animal studies and their suggesting mechanisms for the analgesic effect(s) of BoNT. Then, clinical pain syndromes are critically reviewed and assigned to the appropriate level of evidence.

## Animal Studies

Emerging animal data over the past three decades indicate that BoNT can influence pain, peripheral sensitization, and central sensitization through a number of different mechanisms. BoNT type A inhibits the release of pain peptides, substance P, bradykinin, calcitonin gene-related peptide (CGRP), and glutamate in vivo from the dorsal root and trigeminal ganglia and from rat bladder tissue after injury [5–7]. Also in the rat bladder, BoNT type A, in addition to acetylcholine, inhibits adenosine triphosphate and purinergic receptors (mediator of sensory excitation) leading to reduction of painful bladder spasms [8]. In the formalin model of pain, injection of BoNT type A into rat paw a week prior to formalin injection reduces the post-formalin inflammatory peak of pain in a dose-related manner. Tissue examination of the injected site reveals decreased inflammation and decreased local glutamate accumulation compared with controls [9]. 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 [10]. Intra-prostatic injection of BoNT type A inhibits cyclooxygenase-2 expression and suppresses capsaicin-induced prostatitis in the animal model [11]. BoNT type A impairs sympathetic transmission [12] and thus can interfere with maintenance of pain via decreasing sympathetic overactivity. Injection of BoNT type A into rat jaw muscles decreases the discharge of muscle spindles, a major sensory input which can enhance central sensitization in chronic pain [13]. Femtomolar concentrations of BoNT type A inhibit membrane Na channels in rat central and peripheral neurons [14]. Over activity of sodium channels plays a pivotal role in erythromyalgia, a human model of chronic neurogenic pain [15]. Clostridial endopeptidases, which are specifically retargeted to nociceptive afferents, exert antinociceptive activity in the in vivo animal models of pain [16]. In diabetic rats with bilateral allodynia, unilateral subcutaneous injection of BoNT type A in the allodynic

region of one affected limb improves allodynia in both limbs, indicating a central analgesic effect of the toxin [17].

## Clinical Evidence in Human Subjects

The clinical evidence in this review as summarized in Table 2 is defined according to the guidelines of the Therapeutics and Assessment subcommittee of the American Academy of Neurology [18]. In these guidelines, level A = two or more class I studies, B = at least one class I or two class II, and C = one class II or two consistent class III studies. Level U is defined as unproven evidence.

### Pain Disorders with Level A Evidence: Efficacy Established and Recommended (Two or More Class I Studies)

#### *Neck Pain Associated with Cervical Dystonia (Eight Class I Studies)*

Cervical dystonia (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 and is seen in majority of the patients (68–75%) [19].

**Table 2** Summary of levels of evidence for use of botulinum toxins in various painful clinical conditions

| Level of Evidence | Clinical Condition |
|---|---|
| A | Cervical dystonia |
| | Chronic migraine |
| | Chronic lateral epicondylitis |
| B | Post-herpetic neuralgia |
| | Post-traumatic neuralgia |
| | Plantar fasciitis |
| | Piriformis syndrome |
| | Total knee arthroplasty |
| C | Allodynia of diabetic neuropathy |
| | Chronic low back pain |
| | Knee osteoarthritis |
| | Anterior knee pain with vastus lateralis imbalance |
| | Pelvic pain |
| | Post-operative pain in children with cerebral palsy after adductor hip release surgery |
| | Post-operative pain after mastectomy |
| | Sphincter spasms and pain after hemorrhoidectomy |
| U | Myofascial pain syndrome |
| | Chronic daily headaches |

Eight class I studies evaluated the issue of pain in CD in relation to BoNT treatment. Four studies investigated type A [20–23] and four investigated type B [24–27]. One other study compared efficacy and safety of abobotulinumtoxinA with trihexyphenidyl [28]. 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. The results uniformly show that treatment of CD with type A (Botox, Dysport, Xeomin) or type B (Myobloc) results in significant reduction of neck pain ($P < 0.05$). For example, in the study of Troung et al. [24] 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 vs 1.9 mm for the placebo ($P < 0.002$). AbobotulinumtoxinA is also superior to triheyphenidyl in terms of efficacy and better tolerance [28].

Additionally, six prospective, blinded, multicenter studies compared two serotypes of BoNTs with each other in terms of safety and efficacy and response to pain [27,29–33]. The comparison studies of onabotulinumtoxinA with rimabotulinumtoxinB [27,29,30] and incobotulinumtoxinA [31] showed that both serotypes effectively reduced pain, and there was no significant difference between the two except the study of Lew et al. [27], which demonstrated a significantly higher response rate of pain relief for type B (59% vs 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, and the abobotulinumtoxinA group demonstrated more side effects [32]. A recent double-blind class II study compared pain efficacy of onabotulinumtoxinA with Prosigne (Lanzhou Institute) (using 300 u of each) in patients with CD. Pain efficacy was the same for both toxins at 4 and 16 weeks [33].

Three prospective long-term studies of abobotulinumtoxinA with six or more injections (performed every 3 months) demonstrated a sustained responses following repeated treatments with mild side effects (local pain, subtle weakness, dysphagia) [23,34,35]. Approximately 20% of the patients choose not to continue the treatment due to high cost, dislike of injections, and loss of efficacy [34,35].

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.

#### *Chronic Migraine (Three Class I Studies)*

Chronic migraine is defined as a headache with a frequency of 15 or more headache days per month (at least eight migraine types), for more than 3 months, lasting

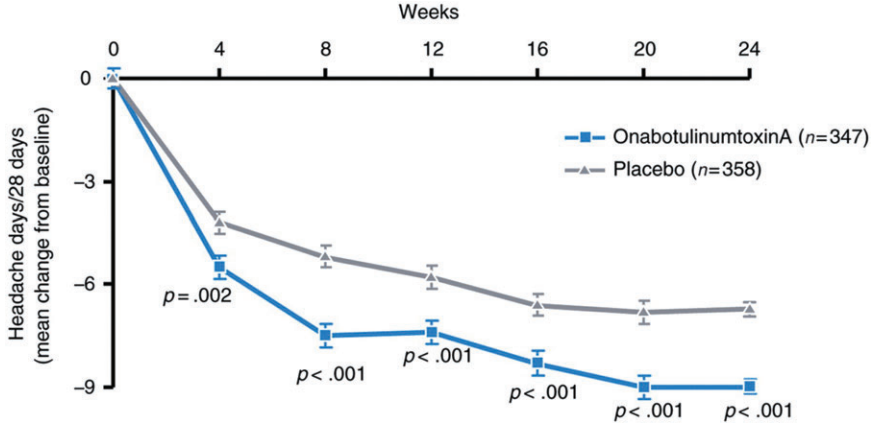


**Figure 1** PREEMPT 2: showing significant improvement of pain days from botulinum toxin group compared with placebo group over all time points of 24-month blinded arm of the study. From Cephalalgia July 2010 with permission.

more than 4 hours per day [36]. Freitag et al. [37], in a double-blind, placebo-controlled study, compared the effect of 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 overuse were excluded. The primary outcome was the number of migraine episodes on 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 PREEMPT 1 and PREEMPT 2 [38,39], two large class I, multicenter studies assessing efficacy of onabotulinumtoxinA in chronic migraine, were published. Each study included approximately 700 patients, with comparable and close number in toxin and placebo groups, in a 24-week blinded arm followed by a 32-week open arm. Both studies included patients with medication overuse. The primary outcome for PREEMPT 1 was the number of headache episodes, and for PREEMPT 2, the number of headache days, which were 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 (Figure 1 and Table 3). For the primary outcome, the change in headache days was 9 for onabotulinumtoxinA vs 6.7 for the placebo ($P < 0.001$). The pooled data [40] of the two studies also showed significant change from the baseline in favor of onabotulinumtoxinA regarding the primary and secondary parameters (Table 3). Although PREEMPT 1 did not meet the primary outcome, it met its secondary outcomes (Table 3). The FDA considered headache days a better outcome measure than headache episodes for the study of chronic migraine (PREEMPT 2). OnabotulinumtoxinA was approved for treatment of chronic migraine in the UK and Canada in the summer of 2010 and in the United States in October 2010. Inclusion of patients with medication overuse is considered a weakness of the PREEMPT studies.

### Clinical Comment

Chronic migraine is a huge 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 with either total number of pain days or headache episodes. This measure

**Table 3** Results (*P* values) of PREEMPT studies and pooled data comparing botulinum toxin and placebo with baseline

| Parameters | PREEMPT 1 | PREEMPT 2 | |
|---|---|---|---|
| Number of headache days | 0.006 | <0.001 (primary outcome) | <0.001 |
| Number of headache 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 |

HIT-6 = Headache Impact Test (six questions); HD = headache days.

was significant for the toxin group in all three studies (the two PREEMPTs and the pooled data) (Table 3).

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

Wong et al. [41] 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 the 4 and 12 weeks 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. [42] found no significant change in VAS or quality of life (measured by short form 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 [43] of 130 patients 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 18 weeks at different time points ($P = 0.003$ and 0.001, respectively). Weakness of the third finger developed in the number of patients but 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 [44]. The site of injection was one-third down the length of the forearm from the tip of the lateral epicondyle along the course of 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 fourth finger, which lasted for 2 months.

Clinical Comment

The three class I studies with larger number of patients depicted significance for BoNT treatment in CLE. There are two issues with the study of Hayton et al. that disclosed negative results: 1) the assessment was done at 3 months. This may be too late as most patients who receive BoNT treatment show fading of improvement by 3 months; and 2) small sample size of the study could have led to type II error in statistical assessment. Weakness of fingers and wrist extension limits the practical value of BoNT therapy in CLE. Future studies may consider smaller doses and more refined techniques to avoid this side effect.

**Pain Disorders with Level B Evidence (One Class I or Two Class II Studies)**

*Recommendation: Probably Effective, Should Be Considered for Treatment*

Post-Herpetic and Post-Traumatic 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 may result from nociceptive injury [45]. The pain often has a burning quality and may be associated with dermal hypersensitivity and allodynia. Xiao et al. [46] assessed pain relief by VAS at 1, 7, and 90 days in a class I study in 60 patients with post-herpetic neuralgia after administering BoNT type A, lidocaine, and placebo (20 in each group). Pain relief and improvement of sleep from BoNT was superior to lidocaine and placebo groups ($P < 0.05$). Patients in the BoNT group also used significantly less opioids (22% vs 52% and 66%). Ranoux et al. [47] conducted a double-blind, placebo-controlled study on 29 patients with refractory neuropathic pain, 25 with post-traumatic neuralgia (PTN)/allodynia, and four with post-herpetic neuralgia. OnabotulinumtoxinA (20 to 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 brushing, and quality of life. Patients who received BoNT type A had diminished pain intensity, neuropathic symptoms, allodynic brush sensitivity and reduced number of pain paroxysms, along with improvement of certain quality of life markers (general activity, mood) compared with the placebo group ($P < 0.05$).

Plantar Faciitis (Two Class II Studies)

Pantar faciitis (PF) is the most common cause of heel pain caused by microtears and inflammation as the 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 treatment failures are not uncommon. Babcock et al. [48] investigated the efficacy of onabotulinumtoxinA in 27 patients (43 heels) with chronic PF (class II). Injection of 40 and 30 units of onabotulinum toxin A, one medial to the heel and the other about 1 to 3 in. anterior to the heel (tender area in PF), resulted in significant improvement of the pain in the onabotulinumtoxinA group. Two months post-injection, the study met all three primary outcomes (pain intensity measured by pressure algometry, pain frequency, and the Maryland foot score) ($P < 0.05$).

Huang et al. [49] conducted a prospective, double-blind study in 50 patients with PF and refractory pain. In the toxin group, 50 units of onabotulinumtoxinA was 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 with 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 ($P < 0.05$).

### 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. [50] conducted a double-blind, crossover study in 10 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 with the placebo arm ($P < 0.05$). Fishman et al. [51] compared the results of 200 units of onabotulinumtoxinA with lidocaine and steroid and with placebo injection into the piriformis muscle in 72 patients with PS. A 50% or better improvement in VAS score was considered significant. OnabotulinumtoxinA was superior to the placebo ($P = 0.001$) and to steroids + lidocaine ($P < 0.005$) in relieving pain.

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

Refractory pain after total knee arthroplasty (TKA) is common and affects 8–13% the patients after surgery [52]. Singh et al. [53] assessed the efficacy of an intra-articular injection of 100 units of onabotulinumtoxinA in 54 patients with TKA. The primary endpoint was a two grade or more reduction of pain in VAS 2 months after treatment, and secondary endpoints included physicians' global assessment of change (PGAC), SF-36, and several other scales. At 2 months, a significant response in VAS was noted in 71% of the patients in BoNT vs 36% in the placebo group ($P = 0.025$). Both PGAC and SF-36 (pain subscale) showed significant change in favor of 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.

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

*Recommendation: Possibly Effective—May Be Used at the Discretion of the Clinician*

### Refractory Low Back Pain

Low back pain is the most common form of pain in adults, producing some form of disability in 60% of the patients. Foster et al. [54] studied 31 patients mostly with chronic spine disease (e.g., stenosis, disc degeneration) and low back pain of more than 6 months duration (class II). They used a fixed paradigm of five lumbar level injections (L1 to 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 14-month study in chronic LBP using the same technique and rating scales (plus a pain frequency scale) [55]. At 2 months, 52% of the patients showed a significant improvement in all scales compared with placebo. Doses ranged from 250 to 400 units per session. Of early responders, 91% continued the favorable response with repeat injections. Three patients experienced mild, transient flu-like reactions.

*Clinical Comment.* Low back pain has a number of causes that may respond differently to BoNT treatment. The class II study cited earlier mainly dealt with younger patients with predominantly unilateral low back pain (i.e., military personnel).

### Diabetic Neuropathy

In a double-blind crossover study, Yuan et al. [56] studied the effect of onabotulinumtoxinA vs 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, onabotulinumtoxinA was superior to saline in reducing pain ($P < 0.05$).

*Clinical Comment.* Study limitation includes small number of patients and crossover design of the study.

### Painful Knee Ostheoarthritis (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 [57]. The primary response, 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 in McMaster Arthritis Index scores (secondary outcome) for pain, stiffness, and function.

*Comment.* Study limitation comprises a large number of dropouts (48%) and hard to explain better response seen with the low dose.

### 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 [58]. 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, <0.04 for pain in kneeling, squatting, and walking, respectively).

### Pelvic Pain

Chronic pelvic pain affects 3.8% of the women and imposes an annual burden of approximately 2 billion dollars (direct and indirect costs) to the U.S. economy. In a double-blind, placebo-controlled study, Abbott et al. [59] investigated the effect of 80 units of onabotulinumtoxinA 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 with the placebo group ($P = 0.009$). The onabotulinumtoxinA group also demonstrated a significant decrease in the pelvic floor pressure ($P < 001$).

*Comment.* The primary and secondary outcomes were not well defined.

### Post-Operative Pain in Children with Cerebral Palsy after Adductor Hip Release Surgery

Barwood et al. [60], in a randomized, double-blinded study, reported significant alleviation of post-operative 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 ($P < 0.003$).

### Post-Operative Pain After Mastectomy

In a randomized and placebo-controlled study [61] of 48 patients, injection of 100 units of BoNT type A into the pectoralis major, serratus anterior, and rectus abdominis muscles before mastectomy reduced post-operative pain significantly ($P < 0.0001$) and facilitated reconstruction with tissue expander. The placebo group used more narcotics post-operatively compared with the BoNT type A group ($P < 0.0001$).

### Sphincter Spasms and Pain after Hemorroidectomy

In a double-blind study [62] of 50 patients, injection of 20 units of BoNT type A into the internal rectal sphincter prior to hemorroidectomy resulted in significant reduction of post-operative sphincter spasms ($P < 0.05$).

## Pain Disorders with Level U Evidence

*Recommendation: The Evidence to Support or Refute Efficacy is Insufficient Due to Contradictory Results*

### Myofascial Pain Syndrome

Myofascial pain syndrome (MPS) is characterized by the presence of focal regions of muscle tenderness and trigger points (tPts) which, upon pressure, provoke radiating pain. The trigger points probably represent erratic or dysfunctional motor end plates with excessive acetylcholine content. Table 4 summarizes the results of class I and II studies with BoNT treatment in MPS [63–70]. As

**Table 4** Randomized, controlled trials of botulinum toxin treatment of MPS

| Author | No. | Study | Location | Outcome Measures | Dose | Result |
|---|---|---|---|---|---|---|
| Freund & Schwartz 2000 [63] | 26 | Class II | Neck | PO, VAS, ROM, at 4 weeks | B: 20 u/tp | $P < 0.001$ |
| Wheeler et al. 2001 [64] | 50 | Class II | Cervico-thoracic | PO, NPAD, GAI, SF-36 | B: 231 ± 50 | ns |
| Ferrante et al. 2005 [65] | 142 | Class II | Neck and shoulder | PO, VAS, PPT, SF-36 | B: 10, 25, 50 u/tp | ns |
| Ojala et al. 2006 [66] | 31 | Class II | Neck and shoulder | PO, VAS, VRS, PPT at 4 weeks | B: 15–35 U<br>5 u/tp | ns<br>ns |
| Gobel et al. 2006 [67] | 144 | Class I | Upper back | PO: mild or no pain at 5 weeks | D: 400 unit<br>40 u/tp | $P = 0.002$ |
| Qerma et al. 2006 [68] | 30 | Class II | Infra-spinatus | PO: pain intensity 0–10 scale (3 & 28 weeks) | B: 50 unit/tp<br>12.5/tp | ns |
| Lew et al. 2007 [69] | 29 | Class II | Cervico-thoracic | PO: VAS, NDI, SF-36 at 2 months | B: 100–200 U<br>50 u/tp | ns<br>ns |
| Miller et al. 2009 [70] | 47 | Class II | Cervico-thoracic | PO: VAS, PF | B: 150–300 | $P = 0.001$(VAS) at 2 months |

PO = primary outcome measure; VAS = pain intensity in visual analog scale; ROM = range of motion; B = onabotulinum toxin A; D = Dysport; NPAD = neck pain and disability scale; GAI = global assessment of improvement; PPT = pain pressure threshold; VRS = verbal reporting score; tp = trigger point; NDI = neck disability index; PF = pain frequency; ns = not significant.

can be seen in this table, each one of the eight studies used different doses per trigger point, and responses were evaluated at different time points and with different scales. All studies were conducted using BoNT type A toxin, seven with onabotulinumtoxinA and one with abobotulinumtoxinA. Three studies (including one class I) reported significant pain relief, whereas five did not.

*Clinical Comment.* It is not possible at this time to make a firm statement regarding the role of BoNT treatment in MPS due to the diverse nature of the studies. In positive studies of Gobel et al. [67] and Miller et al. [70], these authors injected a larger number of trigger points (>5). The negative results of Ferrante et al. [65] may be confounded by exclusion of patients with more than five trigger points; the cohort probably had a milder form of MPS. In the study of Ojala et al. [66], the dose per trigger point (5 units) might have been too small to be effective. Future studies of MPS should use methodologies that succeeded to relieve pain in previous studies.

### Chronic Daily Headaches

Four class I and II studies addressed the issue of CDH directly. All four class I studies [70–73] used a mean change in headache-free days/month as the primary outcome. Three used a flexible injection paradigm [71–74]. In one study [71], BoNT type A (200 units) increased the number of headache-free days/month significantly (11 days vs 8 days of placebo; $P < 0.05$). In another study [72] of 355 patients, the response to BoNT type A was compared with placebo over a 9-month period during which the patients received three treatment cycles (105 to 260 units). The study did not meet the primary outcome. The third study [73] looked at a subset of this cohort, 228 patients with no prophylactic medications. When compared with placebo, between group difference was statistically significant at successive time points (for first 3 months, $P = 0.004$, $P = 0.032$, and $P = 0.023$, respectively). In the fourth study [74], 702 patients were stratified into four groups, one placebo 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.* The inconsistent results of the aforementioned studies qualified for level U evidence for BoNT treatment of CDH in a 2008 assessment [75]. It is, however, more logical to consider each major category of CDH separately, namely chronic migraine and chronic tension headaches (THs). As mentioned earlier, chronic migraine seems to respond to BoNT treatment (level A evidence). THs are not shown to respond to this treatment (see further discussion), but the studies were focused on episodic THs. Harden et al.'s [76] recent small class II study, which suggests efficacy of BoNT treatment in chronic TH, deserves further exploration.

## Major Pain Disorders with Predominantly Negative Results

### *Episodic Migraine and Tension Headaches*

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

The first class I study [77] compared BoNT type A with placebo in 232 patients, each with four to eight episodes of migraine per month. Up to 25 units of BoNT type A were injected into the frontal and temporal muscles. Both groups showed a reduction in frequency, intensity, and duration of migraine headaches, but the difference between the two groups was not statistically significant (at 1 and 3 months). Another class I study [78] investigated the efficacy and safety of BoNT type A in 418 patients with the same migraine frequency using doses of 7.5 to 50 units. Both BoNT type A and placebo decreased the migraine frequency from baseline at each time point between 1 to 4 months after injection. Again, the difference between the two was not significant. A third class I study [79] enrolled 369 patients, each with 4 to 15 episodes of migraine per 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 to 180 post-treatment. The primary outcome was not met, but patients who had the highest pain frequency (12 to 15 per month) responded considerably better on BoNT type A than placebo ($P = 0.041$). The fourth class I [80] study 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.

The first class II study [81] investigated the effect of BoNT type A administration (25 and 75 units) on glabellar and frontal muscles. The primary outcome was the proportion of the patients with 50% or more reduction of headache frequency as compared with 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 [82] 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 [83] 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 headache index was significantly lower for the BoNT type A group at all measured time points. The fourth class II study compared the effect of BoNT type A and divalproex sodium with saline

and divalproex sodium in 59 patients with EM and CM [84]. 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.

### Tension Headaches

Four class I studies ([85–88]; two using onabotulinumtoxinA and two using abobotulinumtoxinA) and three class II studies ([89,90,76]; one using onabotulinumtoxinA and two using abobotulinumtoxinA) investigated the efficacy of BoNT treatment in patients with THs. The dose of onabotulinumtoxinA varied from 20 to 150 units, and that of abobotulinumtoxinA from 200 to 500 units. Although some secondary outcomes were met, none of the studies met their primary outcome which for most was the number of pain-free days.

### Clinical Comments

The studies of EM and TH (less than 15 episodes per month) are overall negative and at this time denote a level A evidence as probably ineffective. 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 mild and subtle episodes, which do not change their quality of life. As discussed earlier, some studies of EM have shown significance for BoNT treatment in reducing frequency of moderately severe to severe migraine episodes [81] and others emphasized the importance of migraine severity by showing significant reduction of headache index in the second treatment [83]. We recommend that future studies of EM take the frequency of moderately severe to severe episodes as the primary outcome measure.
2. The study of THs have several limitations:
   - 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 unrealistic. Silberstein et al.'s study [87] 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.
   - The majority of TH studies used a small total dose (less than 100 units for onabotulinumtoxinA and 500 units for abobotulinumtoxinA), small dose per site, and small number of injected sites which is considered inadequate by today's standards for treatment of headaches with BoNTs. Future studies are needed to use more appropriate dosing and apply better primary outcomes.

## Conclusion

BoNTs have shown efficacy in a large spectrum of human pain disorders. Animal data provide evidence for a variety of mechanisms which can explain BoNTs' analgesic effects. To date, with the exception of pain in CD, the majority of data comes from investigations conducted with onabotulinumtoxinA. Selection of right primary outcome and right dosage is crucial for obtaining favorable results after BoNT treatment.

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