Botulinum toxin therapy for osteoarticular pain: an evidence-based review

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***Abstract*:** Botulinum (BoNT) toxin has been used for its muscle-paralyzing action in conditions such as treatment of wrinkles, cervical dystonia and blephrospasm. There is preclinical and emerging clinical evidence of another mechanism of action of BoNT, namely, an antinociceptive action. In this review, we provide an evidence-based review of clinical studies of BoNT in osteoarticular conditions, such as osteoarthritis, tennis elbow, low back pain, and hand pain. Many randomized controlled trials (RCTs) found evidence of short-term efficacy of an injection of BoNT in relief of pain, and in some cases, improvement of function and quality of life. However, more clinical trials are needed to better define the clinical use of BoNT for treatment of refractory osteoarticular pain.

***Keywords*:** arthritis, Botulinum toxin, pain, therapy

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Introduction

Recent population surveys have reported that 22–28% of adults in the US reported physician-diagnosed arthritis [Huijnen *et al.* 2006; Layeeque *et al.* 2004]. Arthritis and rheumatism are the leading causes of disability in adults aged 18 years and over in the US [Centers for Disease Control and Prevention, 2009]. In a European survey of prevalence of pain in the general population, moderate to severe pain lasting 6 months or longer was reported by 19% of respondents, of whom 40% (~8% of all respondents) had joint pain due to osteoarthritis and rheumatoid arthritis [Breivik *et al.* 2006], the two most common types of arthritic conditions in the population [Lawrence *et al.* 1998]. Both osteoarthritis and rheumatoid arthritis are associated with significant joint pain and functional limitations [Hunter *et al.* 2009; Bjork *et al.* 2007] and deficits in health-related quality of life [Slatkowsky-Christensen *et al.* 2007; Salaffi *et al.* 2005; Kvien and Uhlig, 2005]. Thus, arthritis constitutes a significant public health burden.

While significant therapeutic advances have been made in targeting inflammation in patients with rheumatoid arthritis [Feldmann and Maini, 2008; Siddiqui, 2007], few therapies are available to treat refractory pain and functional limitation in patients with osteoarthritis. Use of common therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioid medications and analgesics is associated with significant adverse events in some patients [Zhang *et al.* 2008, 2007; Ge *et al.* 2006]. Intra-articular corticosteroids, intra-articular hyaluronic acid and topical preparations have limited efficacy in patients with osteoarthritis [Bellamy *et al.* 2006a, 2006b; Van Der Windt *et al.* 2003; Green *et al.* 2003; Rains and Bryson, 1995]. Physical therapy is effective [Jamtvedt *et al.* 2008]; however, compliance with therapy has not been assessed and many patients are unable to pursue the therapy due to personal preference, comorbidities and/or distance from the therapy site. Thus, limited effective and safe therapeutic options are available for the treatment of refractory joint pain in patients with arthritis. There is a need therefore for new therapeutic options for treatment of refractory osteoarticular pain.

Botulinum toxin (BoNT) is one of the most potent neurotoxins. It exists in seven serotypes, A through G. It consists of a 50 KDa light chain and a 100 KDa heavy chain linked with a disulfide bond. Most clinical applications of BoNT are based on its ability to block neuromuscular transmission by blocking the release of acetylcholine [Arnon *et al.* 2001], which leads to reversible muscle paralysis. However, in several clinical studies, including those of treatment of painful

muscle contractions in patients with cervical dystonia [Sycha *et al.* 2004; Jankovic and Schwartz, 1990] and migraine/tension headaches [Gobel *et al.* 2001], an independent antinociceptive action was noted [Freund and Schwartz, 2003; Aoki, 2003]. The onset of muscle pain relief after muscular injection of BoNT occurred sooner than relief of muscle spasm; it outweighed and often lasted longer than the relief of muscle spasm, thereby suggesting a different antinociceptive action [Sycha *et al.* 2004; Freund and Schwarz, 2003]. This led to investigation of BoNT as a treatment for headaches, with many randomized controlled trials (RCTs) underway.

In this evidence-based review, the evidence from nonhuman studies and the clinical observations from nonmusculoskeletal application in human studies supporting an antinociceptive action of BoNT are summarized. A systematic review of published nonrandomized (prospective and retrospective cohort studies and case series) and randomized studies of BoNT for osteoarticular pain was then undertaken by performing Pubmed searches for various musculoskeletal pain conditions and BoNT. Case reports were not included in this review. Myofascial pain syndromes were not included in this review, since they have been the focus of previous reviews [Ho and Tan, 2007; Cuevas-Trisan and Cruz-Jimenez, 2006].

Role of neuropeptides in chronic joint pain and effect of botulinum toxin on neuropeptides

Recent reviews summarize our current understanding of joint pain and various mechanisms contributing to it [Schaible *et al.* 2009, 2006]. The joints are innervated with articular nerves that contain A-delta, A-beta and C-fibers. All joint structures except articular cartilage have these nerve endings. In normal healthy individuals, these nociceptors have a high threshold for excitation in response to mechanical and thermal stimuli, such that normal activities of walking, stair climbing, sports, and palpation of the joint are not associated with pain/unpleasant sensation. However, in the presence of joint injury or inflammation, the excitation threshold of many of these nerve fibers is decreased. This leads to enhanced responses to both innocuous and noxious mechanical, chemical and thermal stimuli. This phenomenon is called peripheral sensitization [Schaible *et al.* 2009]. Chronic joint inflammation is also associated with hyperexcitability of spinal nociceptive neurons, ie central sensitization [Neugebauer *et al.* 1993; Schaible *et al.* 1987]. A variety of mediators can sensitize joint nerves and nociceptors to mechanical stimuli including bradykinin, prostaglandin E2, prostaglandin I2, serotonin, substance P (SP) and neuropeptide Y [Schaible *et al.* 2006]. Another contributor to joint pain and inflammation is neurogenic inflammation. Articular nerves stimulated due to inflammation in arthritis release neuropeptides from nerve terminals as a result of axon reflexes. Postganglionic sympathetic nerves release neuropeptides due to sympathetic reflexes, and local inflammatory cells release neuropeptides due to cytokine or neuropeptide-stimulation [Schaible *et al.* 2005]. It is likely that these processes underlie the clinical observed signs and symptoms of pain and mechanical hyperalgesia in inflamed joints.

Activation of glial cells, other immune cells, cytokines and neuropeptides contributes to the generation of pain [Watkins *et al.* 2003; Watkins and Maier, 2003, 2002; Woolf *et al.* 1997, 1994; Woolf and Weisfeld-Hallin, 1986]. Pain pathways, pain receptors and various contributors to both inflammatory and neuropathic pain have been summarized in recent studies and reviews [Woolf, 2004; Woolf and Mannion, 1999; Woolf and Decosterd, 1999; Woolf and Costigan, 1999; Willis and Westlund, 1997; Jones, 1991].

BoNT has been shown to interfere with expression of various neuropeptides such as SP and calcitonin gene-related protein (CGRP), which are key mediators of neurogenic inflammation [Birklein and Schmelz, 2008]. In an animal model of botulinum toxin A (BoNT/A), injections into rat paws reduced formalin-induced paw edema, tissue glutamate release and spinal cord electrical excitations [Cui *et al.* 2004]. BoNT/A inhibited stimulated SP release [Lucioni *et al.* 2008; Purkiss *et al.* 2000] and CGRP release [Lucioni *et al.* 2008; Rapp *et al.* 2006; Durham *et al.* 2004] in models of acute and chronic inflammation. *In vitro* studies showed that BoNT/A inhibited stimulated CGRP release from rat trigeminal ganglia [Meng *et al.* 2007] and capsaicin-stimulated SP release from embryonic rat dorsal root ganglia neurons [Purkiss *et al.* 2000]. In particular, BoNT have been shown to inhibit cytokines, neuropeptides and other inflammatory mediators that play an important role in pathophysiology of both rheumatoid arthritis and rat adjuvant arthritis

(animal model similar to human rheumatoid arthritis) [Ahmed *et al.* 1995; Larsson *et al.* 1991; Kar *et al.* 1991; Devillier *et al.* 1986]. Thus, there is preclinical evidence suggesting an antinociceptive mechanism of action of BoNT.

Clinical observations suggesting antinociceptive action of botulinum toxin

Various clinical studies support the antinociceptive action of BoNT [Yuan *et al.* 2009; Patti *et al.* 2008; Kramer *et al.* 2003], while some studies found no such evidence [Sycha *et al.* 2006; Voller *et al.* 2003; Blersch *et al.* 2002].

Kramer and colleagues studied the effect of intradermal injection of 5–20 mouse units of BoNT/A or placebo in a RCT in 15 healthy volunteers, followed up for 14 days [Kramer *et al.* 2003]. Transcutaneous electrical stimulation was used to produce pain, hyperalgesia and neurogenic flare. BoNT/A caused an anhidrotic skin area in all cases, and had a significantly smaller axon reflex flare, lower pain rating, but similar amount of hyperalgesia to pinprick and allodynia after electrical stimulation, as compared to placebo. This study suggested that BoNT/A reduces peripheral neuropeptide release, but the evidence for a direct analgesic effect was limited.

Yuan and colleagues performed a double-blind crossover trial of intradermal BoNT/A for diabetic neuropathic pain in 18 patients [Yuan *et al.* 2009]. There was a significant reduction in visual analog scale (VAS) pain by 0.83 at 1 week, 2.22 at 4 weeks, 2.33 at 8 weeks, and 2.53 at 12 weeks after injection in the BoNT/A group, as compared to the respective changes of 0.39, −0.11, 0.42, and 0.53 for the placebo group at the same time points ($p < 0.05$). Within the BoNT/A group, 44.4% of the participants experienced a reduction in VAS of 3 or more within 3 months of injection, whereas there was no similar response in the placebo group.

Patti and colleagues studied 30 patients with thrombosed external hemorrhoids who did not desire surgery [Patti *et al.* 2008]. Patients were randomized to a single intrasphincteric injection of 30 units of BoNT or saline. After 5 days of treatment, the maximum resting pressure on anal manometry fell more significantly in the BoNT group ($p = 0.004$). The reduction in pain intensity with BoNT was noted within 1 day of injection ($p < 0.001$).

Ranoux and colleagues performed a RCT of single intradermal injection of 20–190 units of BoNT/A into the painful area in 29 patients with focal painful neuropathies and mechanical allodynia [Ranoux *et al.* 2008]. Patients were followed for 24 weeks. BoNT/A injections were associated with persistent sustained effects on spontaneous pain intensity, neuropathic symptoms, and general activity from 2 weeks after the injection to 14 weeks, compared to placebo.

In a randomized, double-blind study, Sycha *et al.* compared a single intracutaneous injection of BoNT/A 100 units to placebo in six healthy volunteers using a human acute inflammatory skin model with ultraviolet B radiation induced sunburn [Sycha *et al.* 2006]. No significant differences were noted between the groups in heat or cold pain perception threshold, skin blood flow, mechanical pain threshold or mechanical allodynia. BoNT/A produced changes in sudomotor function. The sample size in this study was very small, leading to a possibility of type II error, ie failure to notice a difference when one truly exists. Blersch and colleagues compared the heat and cold thresholds in 50 healthy volunteers who were each injected with BoNT/A 100 units or placebo in the two forearms in a double-blind fashion [Blersch *et al.* 2002]. Using quantitative sensory testing, no differences were found between the groups with regards to heat and cold pain thresholds at 4 and 8 weeks. In addition, no differences were found in electric stimulation pain thresholds between the groups. This study suggested that there was no evidence of direct antinociceptive effect of BoNT/A in this skin model of nociception, and that antinociceptive action may be secondary to other effects of BoNT/A such as chemodenervation or anti-inflammatory effects.

Voller and colleagues studied 16 healthy volunteers after injection of either 30 units of BoNT/A or placebo intracutaneously and responses were studied up to 28 days after the injection and after capsaicin application at 28 days [Voller *et al.* 2003]. The groups did not differ significantly in any of the following outcomes at day 28: heat pain perception and tolerance thresholds; electric pain perception and tolerance thresholds; area of secondary hyperalgesia

after capsaicin application; and for the capsaicin-induced flare.

Open-label studies of botulinum toxin in osteoarticular pain

Refractory joint pain

In a retrospective study, we reported the results of intra-articular injection of 25–100 units of BoNT/A in 15 refractory painful shoulder and lower extremity joints in 11 patients [Mahowald *et al.* 2006]. There were nine women and two men with age ranging from 42 to 82 years. A clinically and statistically significant decrease in pain severity and improvement in function was noted from baseline: lower extremity and shoulder pain decreased from 7 to 2.7 and 8.2 to 2.4, respectively; shoulder flexion and abduction improved from 68 to 113 degrees and 50 to 74 degrees, respectively; and timed stands test (time to stand up 10 times from a sitting position) improved from 36 to 23 seconds. The duration of relief/improvement lasted 3–10 months, and relief began by 2 weeks in most patients. None of the patients experienced any adverse event.

In long-term follow-up of these 15 joints in 11 patients, 10 joints were reinjected with 30–150 units of BoNT/A intra-articularly (Botox, Allergan, Irvine, California, USA) [Singh *et al.* 2009a]. Nine of the 10 reinjections were associated with pain reduction, as seen with the first injection. Reduction in pain severity from 6.6 (SD, 1.2) to 3.3 (SD, 2.7) lasting 3–17 months was noted, which was statistically significant ($p = 0.003$). None of the patients experienced any systemic adverse event related to BoNT. One patient had increased joint swelling with no increase in joint pain 3 weeks after BoNT injection. Another patient had continued increase in joint pain after BoNT injection, which was relieved with a subsequent BoNT injection.

In another case series, 11 adults with refractory pain underwent injection of BoNT type A (25–100 units; Botox, Allergan) or type B (5000 units; Myobloc, Solstice Neurosciences, San Francisco, California, USA) into sacroiliac, cervical/lumbar facet or sternoclavicular joint joints and C-2 roots and lumbar disc [Dykstra *et al.* 2007]. There were nine women and two men with mean age of 48 years (SD, 10 years; range, 32–68 years). Median pain scores decreased significantly after botulinum toxin injections, with median decrease of 3 on 0–10 pain scale (range, 0–5; $p = 0.008$). Pain decrease began within 3–5 days for patients who responded. Three patients had no change in pain severity after BoNT injections, while eight had a decrease. Five patients received repeat injections with no evidence of decreasing efficacy of pain relief with BoNT injections; in fact, the duration of pain relief increased with each successive treatment for four of the five patients having multiple treatments. Median duration of pain relief with BoNT injections was 1.6 months longer than that seen with corticosteroid injections. No adverse events were reported by the patients.

Tennis elbow

In an open-label case series of 14 patients with 'treatment-resistant' tennis elbow, 20–40 units of BoNT/A were injected into the extensor digitorum communis, Moore and colleagues found >50% pain relief in nine of 14 patients, and complete pain relief in four of 14 patients during the 6–8 month follow-up [Morre *et al.* 1997]. Pain relief began by 2 weeks in 10 patients, 3 weeks in one and after 1 month in two patients.

Temporomandibular joint pain

In an open-label study of 41 patients with painful hyperactivity of the masticatory muscles, 200 units of BoNT/A (Dysport, Ipsen, Slough, UK) was injected on either side under electromyographic guidance and patients observed for up to 12 months [Von Lindern, 2001]. 80% patients had improvement in pain; pain severity decreased from a mean of 6.4 to 3.5 and 13 patients had a 'major improvement' as evident by disappearance of pain. Relief lasted 3–12 months during the observation period for most; only seven patients requested reinjection. One patient had temporary speech impairment and swallowing difficulty postinjection. In an open-label study, 46 patients with TMD for a median duration of 96 months were injected with 150 units of BoNT A in both massager and temporal is muscles and followed up to 8 weeks [Freund *et al.* 2000]. A significant improvement was noted in pain VAS, functional index, tenderness to palpation and interincisal oral opening.

Anterior knee pain

Singer and colleagues injected 300–500 units of BoNT/A (Dysport) into vastus lateralis muscles followed by a 12 week home exercise program to strengthen vastus medialis in eight female patients with chronic anterior knee pain of

Table 1. Summary of studies of botulinum toxin in osteoarticular pain-efficacy outcomes.

Study: author; number of patients	RCT *versus* open-label	Intervention and comparison	Mean age in years (SD)/male/female	Mean pain duration in months (SD)	Primary outcome	Main result—efficacy
Tennis elbow						
Wong *et al.* 2005 60 patients	RCT, double-blind, 3 months	Single injection of 60 units of BoNT/A (Dysport) *versus* saline placebo in SQ tissue and muscle	BoNT: 46 (9) PL: 44 (6)/ 49 M/11 F	BoNT: 12 (9) PL: 19 (21)	Pain on VAS 0–100 mm at 4 and 12 weeks	BoNT: 25.3 mm at 4 weeks; 23.5 mm at 12 weeks PL: 50.5 mm at 4 weeks; 43.5 mm at 12 weeks Differences significant at both 4 ($p < 0.0001$) and 12 weeks ($p = 0.0006$)
Keizer *et al.* 2002 40 patients	Randomized, not blinded, 24 months	Surgical release *versus* one or two injections of 30–40 units BoNT	All pts: 43 years (range, 25–72 years) 19 M/21 F	All pts: 11 (range, 6–48 months)	Pain on VAS, range of motion, sick leave, modified scoring system of pain, function, tenderness, and satisfaction	No difference in pain between groups Range of motion significantly better in BoNT compared to surgery group at 3 and 6 months; no difference at 12 or 24 months Sick leave lower in surgery group *versus* BoNT group at 3 months ($p = 0.01$), but no difference at 6, 12 and 24 months Overall score was similar in the two groups at 3, 6, 12 and 24 months
Hayton *et al.* 2005 40 patients	RCT, double-blind, 3 months	Single injection of 50 units of BoNT/A *versus* saline placebo intramuscular 5 cm distal to area of maximum tenderness	All pts: 47 years (range, 35–71 years) 21 M/19 F	All pts: 11 (range, 6–48 months)	Pain on VAS, grip strength, Short Form 12	Differences in pain scores were not significant at 3 months No significant differences in grip strength or SF-12 scores between groups at 3 months
Facial pain and temporomandibular disorder						
Von Lindern, 2001 90 patients	RCT, double-blind, 1–3 months	BoNT/A 35 MU (MU - mouse units) *versus* placebo injected on each side of masticatory muscle	No information provided	Failed conservative treatment for 3–34 months	Pain on VAS	Reduction in VAS pain at 1–3 months postinjection significantly more in BoNT *versus* placebo ($p < 0.01$) Greater proportion with ≥2-point reduction in VAS pain in BoNT/A *versus* placebo: ~76% *versus* 10% (no statistical comparisons)
Low back pain						
Foster, 2001 [Foster *et al.* 2001] 31 patients	RCT, double-blind, 2 months	200 units BoNT/A *versus* placebo injected into five lumbar or lumbosacral sites on more painful side	BoNT: 47 years (range, 20–73) PL: 46 years (range, 21–65)/ 15 M/16 F	BoNT: 72 (range, 6–120) PL: 96 (range, 12–360)	Pain on VAS; Oswestry Back Pain Inventory	73% (11/15) patients in BoNT/A group had ≥50% reduction in VAS pain compared to 25% (4/16) in placebo group at 3 weeks ($p = 0.012$) 60% in BoNT *versus* 13% in placebo had ≥50% reduction in VAS pain at 8-weeks ($p = 0.009$) Improvement in Oswestry scores were seen in 67% of BoNT and 19% of placebo-treated patients at 8 weeks ($p = 0.011$)

(*continued*)

Table 1. Continued.

Study: author; number of patients	RCT *versus* open-label	Intervention and comparison	Mean age in years (SD)/male/female	Mean pain duration in months (SD)	Primary outcome	Main result—efficacy
Shoulder joint pain						
Singh *et al.* 2009b 36 patients; 43 shoulders	RCT, double-blind, 1 month	100 units of BoNT/A *versus* placebo into glenohumeral joint	BoNT: 72 (SE, 2) PL: 70 (SE, 3)/ 35 M/1 F	BoNT: 8 (SE, 2) PL: 11 (SE, 3)	Pain on VAS; drop-out due to treatment failure; shoulder pain and disability index (SPADI) Short Form 36 Short form McGill Pain	Significantly greater reduction in VAS pain in BoNT/A (2.4) *versus* placebo (0.8) group ($p = 0.02$) Higher proportion dropped out at 1 month from placebo (45%) than BoNT/A (19%) ($p = 0.13$) SF-36 scores improved significantly more in BoNT/A *versus* placebo in 5/8 subscales (p ranging 0.04–0.001) McGill affective dimension scores were significantly greater in BoNT/A *versus* placebo group ($p = 0.047$) Trend towards significance in SPADI disability scores ($p = 0.083$) No significant differences in active flexion, active abduction, SPADI pain and total and McGill sensory and total scores
Hand pain and carpal tunnel syndrome						
Breuer *et al.* 2006 20 patients	RCT, double-blind, 3 months	2500 units BoNT/B *versus* placebo injected into three hypothenar muscles in carpal tunnel	No information provided	No information provided	Pain on Numeric Rating Scale (NRS) West Haven-Yale Multidimensional Pain Inventory (WHYMPI)	Pain scores, pain-related sleep disturbances, WHYMPI scores improved in both groups at follow-up, but didn't significantly differ between groups At 6 weeks, 8/10 (80%) BoNT patients *versus* 6/9 (67%) had clinically meaningful reduction of pain VAS (30% or 2 point reduction). Similar reductions at 13 weeks were 2/7 (29%) BoNT *versus* 4/9 (44%) of placebo.
Plantar fasciitis						
Babcock *et al.* 2005 27 patients; 43 feet	RCT, double-blind, 2 months	70 units BoNT/A (40 units on medial aspect of the heel and 30 units in the foot arch) *versus* placebo	All: median age, 44 (range, 21–65) 9M/18F	No information provided	Pain VAS, 0–10 cm Pressure algometry response Maryland Foot Score (0–100 points) Pain relief VAS, 0–10 cm	At 3 weeks, improvements were significantly higher for BoNT *versus* placebo: Pain VAS, 2.7 (39% decrease) *versus* 4.7 ($p < 0.004$); Maryland Foot score, 72 (34%) *versus* 49 ($p = 0.001$); pressure algometry, 2.7 (40% increase) *versus* 1.8 ($p = 0.003$); and pain improvement scale, 4.8 *versus* 0.6 ($p < 0.005$) At 8 weeks, improvements were significantly higher for BoNT *versus* placebo: Pain VAS, 1.6 (56% decrease) *versus* 4.4 ($p < 0.005$); Maryland Foot score, 81 (47%) *versus* 54 ($p = 0.001$); pressure algometry, 2.8 (56% increase) *versus* 1.8 ($p = 0.003$); and pain improvement scale, 5.0 *versus* 1.2 ($p < 0.005$)

BoNT, botulinum toxin; BoNT/A, Botulinum toxin type A; BoNT/B, Botulinum toxin type B; NRS, Numeric Rating Scale; PL, placebo; pts, patients; RCT, randomized controlled trial; SE, standard error; SF-12, Short Form 12; SPADI, shoulder pain and disability index; SQ, subcutaneous; VAS, Visual Analog Scale; WHYMPI, West Haven-Yale Multidimensional Pain Inventory.

Table 2. Safety outcomes from randomized studies of botulinum toxin use in osteoarticular pain.

Study: Reference, number of patients	RCT versus open label	Intervention and comparison	All adverse events	Serious adverse events	Weakness	Systematic adverse events	Others: pain, redness etc.
Tennis Elbow							
Wong *et al.* 2005 60 patients	RCT, double-blind	60 units of BoNT/A *versus* saline placebo in SQ tissue and muscle	BoNT: 19/30 PL: 9/30		Weakness in finger extension: BoNT = 10/30, PL = 6/30 at 4 weeks; BoNT = 2/30, PL = 1/30 at 12 weeks Paresis of digits: BoNT = 4/30, PL = 0/30 at 4 weeks; BoNT = 1/30, PL = 0/30 at 12 weeks	Nausea: BoNT = 0/30, PL = 1/30	Pain: BoNT = 2/30, PL = 1/30
Keizer *et al.* 2002 40 patients	Randomized, not blinded	Surgery *versus* single injection of BoNT/A			No data provided on adverse events		
Hayton *et al.* 2005 40 patients	RCT, double-blind	50 units of BoNT/A *versus* saline placebo intramuscular				Extensor lag of long finger BoNT: 12/18 PL: 0/19	
Facial pain and temporomandibular disorder							
Von Lindern, 2001 90 patients	RCT, single-blind	70 units of BoNT/A *versus* saline placebo intramuscular				Swallowing difficulty or temporary paralysis of facial expression muscle: BoNT: 1/60 PL: 0//30	

(*continued*)

Table 2. Continued.

Study: Reference, number of patients	RCT *versus* open label	Intervention and comparison	All adverse events	Serious adverse events	Weakness	Systematic adverse events	Others: pain, redness etc.
Low back pain							
Foster *et al.* 2001 31 patients	RCT, double-blind	200 units BoNT/A *versus* placebo injected into five lumbar or lumbosacral sites on more painful side					Worsening of pain: BoNT: 0/15 PL: 2/16
Shoulder joint pain							
Singh *et al.* 2009b 36 patients; 43 shoulders	RCT, double-blind, 1 month	100 units of BoNT/A *versus* placebo into glenohumeral joint	BoNT: 50 AEs PL: 46 AEs	BoNT: 3 SAEs PL: 9 SAEs	BoNT: 1 PL: 1	Dry mouth BoNT:5 PL: 3 Cough BoNT: 4 PL: 3 Dizziness BoNT:3 PL: 4	Pain in study joint BoNT:1 PL: 2
Hand pain and carpal tunnel syndrome							
Breuer *et al.* 2006 20 patients	RCT, double-blind, 3 months	2500 units BoNT/B *versus* placebo injected into three hypothenar muscles in carpal tunnel					First two patients with weakness of finger muscles
Plantar fasciitis							
Babcock *et al.* 2005 [27 patients; 43 feet	RCT, double-blind, 2 months	70 units BoNT/A *versus* placebo (40 units on medial aspect of the heel and 30 units in the foot arch	No complications in patients who followed up				

BoNT, botulinum toxin; BoNT/A, botulinum toxin type A; PL, placebo; pts, patients; RCT, randomized controlled trial; AEs, adverse events; SAEs, serious adverse events; SQ, subcutaneous.

longer than 6 months that had failed conservative management [Singer *et al.* 2006]. Patients reported decreased knee pain, increased function and had an improvement in the time taken to ascend and descend a flight of 11 stairs from 12 to 10 seconds; improvements that were maintained at 24 weeks.

Low back pain

Ney and colleagues reported the results of injection of 200–500 units of BoNT/A intramuscularly from L2 to S1 in 60 patients with chronic low back pain of 9-year mean disease duration in an open-label prospective study [Ney *et al.* 2006]. Response as defined by the occurrence of two of three of the following criteria: ≥50% improvement in pain VAS, ≥2 grade improvement in pain and functional subsets of Oswestry Low Back Pain Questionnaire, and ≥30% improvement in number of pain days from baseline. At 2 months 58% patients responded, with 17% still showed improvement at 4 months of follow-up.

Plantar fasciitis

Placzek and colleagues reported 1 year follow-up of a case series of nine patients with chronic plantar fasciitis, who were injected with 200 units of BoNT/A (Dysport). Statistically significant pain relief began 2 weeks after the injection (pain scale, 0–10, 4.2–1.9, $p = 0.012$) and persisted until 52 weeks (pain scale, 0–10, 4.2–0.4, $p = 0.043$) [Placzek *et al.* 2005].

Randomized controlled trials of botulinum toxin in osteoarticular pain

Tennis elbow

In a study by Hayton and colleagues 40 patients with refractory painful tennis elbow with pain lasting more than 6 months, who had failed treatment with one or more corticosteroid injections and a full course of physiotherapy were randomized to 50 units of BoNT/A (Allergan) or normal saline placebo (2 ml) 5 cm distal to the area of maximal tenderness at the lateral epicondyle (Tables 1 and 2) [Hayton *et al.* 2005]. There were no statistically significant differences between BoNT and placebo groups at 3 months after the injection in pain, grip strength or quality of life measured by Short-Form 12 physical and mental component summary scores.

In another study by Wong and colleagues (Tables 1 and 2), 60 patients with painful tennis elbow for 3 months or longer were randomized to either a single injection of 60 units of BoNT/A (Dysport; Ipsen) or placebo and followed for 12 weeks in a double-blinded multicenter study [Wong *et al.* 2005]. Patients were treatment-naïve with no prior local acupuncture therapy for their tennis elbow. Pain on a VAS (0–100 mm) scale decreased significantly more in the active treatment group (65.5 at baseline to 25.3 at week 4 and 23.5 at week 12) than placebo (66.2 at baseline to 50.5 at week 4 and 43.5 at week 12). The differences between groups were statistically significant at both week 4 ($p < 0.001$) and week 12 ($p = 0.006$). Although four patients in the botulinum group had paresis of the fingers at 4 weeks (in one patient it persisted to week 12) compared to none in the placebo group, the grip strength was similar in both groups at the two time points. A small sample and short follow-up period are the limitations of the study. These two studies differed in patient population (all patients *versus* those with refractory disease), duration of disease (>3 months *versus* >6 months), site of injection (1 cm *versus* 5 cm from the lateral epicondyle) and the preparation used [60 units of Dysport (Ipsen Pharmaceuticals) *versus* 50 units of Botox (Allergan Pharmaceuticals)].

Another randomized study (Tables 1 and 2) compared one or two injections of 30–40 units of BoNT/A (Allergan) with the surgical release of the extensor origin of the extensor carpi radialis brevis tendon in 40 patients with refractory chronic painful tennis elbow (average duration of symptoms ~10 months) [Keizer *et al.* 2002]. They found no differences between the groups with regards to pain and grip strength up to 2 years of follow-up, while minor differences were noted at shorter follow-up periods. A limitation of the study was lack of description of outcomes, no a priori designation of outcomes as primary *versus* secondary and use of nonvalidated outcomes.

Facial pain and temporomandibular disorder

Temporomandibular disorder is a group of pathologic conditions affecting the temporomandibular joint, its associated structures and its functions. In a single-blinded, randomized study of 90 patients with chronic facial pain caused by hyperactivity of masticatory muscles, who had failed conservative treatment, received

intramuscular injections of 35 mouse units of BoNT/A (Allergan; $n = 60$) or placebo ($n = 30$) on each side of the masticatory muscle (Tables 1 and 2) [Von Lindern *et al.* 2003]. A significantly greater reduction of 0–10 VAS pain was noted in the botulinum toxin (3.2 units) *versus* placebo group (0.4 units) ($p < 0.01$; at follow-up between 1 and 3 months). A greater proportion of patients in BoNT/A compared to the placebo group had ≥2-point improvement in VAS pain during the follow-up (Table 1). This study has many limitations: blinding was not described (patient or physician blinded single-blind), the outcome measurement time-point was not described, and the study had a very short follow-up duration.

Low back pain

Foster and colleagues compared 200 units of BoNT/A (Allergan) injected intramuscular paravertebrally from L1-5/L2-S1 ($n = 15$) to placebo ($n = 16$) in 31 patients with chronic back pain of ≥6 month duration (Table 1) [Foster *et al.* 2001]. Pain relief exceeding 50% on VAS was significantly higher in Botox *versus* placebo group, respectively: 73% *versus* 25% at 3 weeks, and 60% *versus* 13% at 8 weeks (Table 1). The Oswestry Low Back Pain Questionnaire score improved in significantly more patients in Botox *versus* placebo group. A small sample size is a limitation of this study.

Refractory shoulder joint pain

Singh and colleagues injected 100 units of BoNT/A (Allergan Pharmaceuticals) into glenohumeral (shoulder) joints of patients with osteoarthritis or rheumatoid arthritis related refractory, chronic shoulder joint pain due to osteoarthritis or rheumatoid arthritis, who had all failed conservative management with intra-articular corticosteroids and oral medications (Tables 1 and 2) [Singh *et al.* 2009b].

Hand pain and carpal tunnel syndrome

Breuer and colleagues randomized 20 patients with carpal tunnel syndrome with hand pain to receive electromyographically-guided placebo or botulinum toxin type B injections in three hypothenar muscles anatomically attached to the carpal tunnel (Tables 1 and 2) [Breuer *et al.* 2006]. During the 13-week trial, significant decrease in pain outcomes and improvement in function were noted in both placebo and the BoNT/A groups compared to the baseline, but there were no significant differences between the two groups. A small sample size, unblinding of the first two patients and variation in the BoNT/A dose during the trial were the limitations of this study.

Heel pain and plantar fasciitis

Babcock and colleagues compared 70 units of BoNT/A injected into plantar fascia compared to a placebo injection in 27 patients (43 feet) with chronic refractory plantar fasciitis for ≥6 months, that had failed all conservative strategies except surgery or extracorporeal shock therapy (Tables 1 and 2) [Babcock *et al.* 2005]. Compared to the placebo group, botulinum group improved significantly more pain relief on a VAS (4.75 *versus* 0.6 at 3 weeks and 4.95 *versus* 1.2 at 8 weeks, $p < 0.005$ for both; 0–10 cm scale), significantly lower VAS pain, and significantly better foot function as assessed by the Maryland Foot Score and less muscle tenderness at plantar fascia insertion as assessed by pressure algometry response at both 3 and 8 weeks follow-up.

Summary and conclusions

In this paper, studies of use of BoNT for osteoarticular pain are reviewed. Preclinical laboratory evidence and clinical evidence emerging from use of BoNT for other applications suggests an independent antinociceptive mechanism of action. While there are several osteoarticular conditions for which BoNT had been studied in an RCT compared to placebo, for most conditions there was a single RCT. These studies had several limitations. Most studies were single center, had a small sample size, short follow-up and in some cases, nonstandardized injection techniques. Observation of larger effect size in uncontrolled studies (retrospective and prospective) as compared to controlled trials indicates bias and placebo effect, as reported previously for other conditions. The evidence for an antinociceptive action of BoNT in osteoarticular pain is growing. Larger multicenter studies of longer duration that test various doses, regimens and routes of administration of BoNT are needed to better define its role in management of osteoarticular pain.

Conflict of interest statement

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