

## The efficacy of botulinum toxin type A in managing chronic musculoskeletal pain: a systematic review and meta analysis

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### Abstract

**Background** Botulinum toxin type A (BoNTA) is a neurotoxin that acts by inhibiting the release of neurotransmitters acetylcholine at neuromuscular junctions, thus reducing muscular contractions. Recent evidence suggests that BoNTA can reduce nociceptive activities of sensory neurons in animal models by inhibiting release of certain neuropeptides. Despite the therapeutic benefit of BoNTA in alleviating painful muscle spasms, its efficacy in other musculoskeletal pain conditions is less clear.

**Objective** We aim to examine the efficacy of BoNTA in reducing chronic musculoskeletal pain.

**Methods** Studies for inclusion in our report were identified using MEDLINE, EMBASE, PUBMED, Cochrane Central Register of Controlled Trials, CINAHL, and reference lists of relevant articles. Studies were considered

eligible for inclusion if they were randomized controlled trials (RCTs), evaluating the efficacy of BoNTA injections in pain reduction. All studies were assessed and data were abstracted independently by paired reviewers. The outcome measures were baseline and final pain scores as assessed by the patients. The internal validity of trials was assessed with the Jadad scale. Disagreements were resolved through discussions.

**Main results** Twenty-one studies were included in the systematic review and 15 of them were included in the final meta-analysis. There was a total of 706 patients in the meta-analysis, represented from trials of plantar fasciitis ( $n = 1$ ), tennis elbow ( $n = 2$ ), shoulder pain ( $n = 1$ ), whiplash ( $n = 3$ ), and myofascial pain ( $n = 8$ ). Overall, there was a small to moderate pain reduction among BoNTA patients when compared to control (SMD =  $-0.27$ , 95% CI:  $-0.44$  to  $-0.11$ ). When the results were analyzed in subgroups, only tennis elbow (SMD =  $-0.44$ , 95% CI:  $-0.86$  to  $-0.01$ ) and plantar fasciitis (SMD =  $-1.04$ , 95% CI:  $-1.68$  to  $-0.40$ ) demonstrated significant pain relief. Although not in the meta-analysis, one back pain study also demonstrated positive results for BoNTA. Lastly, BoNTA was effective when used at  $\geq 25$  units per anatomical site or after a period  $\geq 5$  weeks.

**Conclusion** In our meta-analysis, BoNTA had a small to moderate analgesic effect in chronic musculoskeletal pain conditions. It was particularly effective in plantar fasciitis, tennis elbow, and back pain, but not in whiplash or shoulder pain patients. However, more evidence is required before definitive conclusions can be drawn. On the other hand, there is convincing evidence that BoNTA lacks strong analgesic effects in patients with myofascial pain syndrome. A general dose-dependent and temporal response with BoNTA injections was also observed.

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**Keywords** Botox · Botulinum toxin type A (BoNTA) · Musculoskeletal diseases · Pain · Plantar fasciitis · Tennis elbow · Shoulder pain · Whiplash · Myofascial pain · RCT · Systematic review · Meta-analysis

## Background

Musculoskeletal disorders are the most common cause of long-term chronic pain, affecting people worldwide in the range of hundreds of millions (Woolf and Pfleger 2003). In the United States alone, it has been estimated that more than 50 million Americans are suffering from chronic pain conditions with almost half due to ailments in the musculoskeletal system (Lang 2003). Without proper treatments, chronic pain can have a strong disruptive impact on an individual's physical, psychological and social well-being. For example, decreased physical activity (Tuzun 2007), depression (Magni et al. 1990; Herr et al. 1993), and impaired cognitive function (Eccleston et al. 1997) have all been found to associate with chronic pain. At the societal level, pain creates a tremendous economic and workplace burden. The annual cost of chronic pain in the United States, including health care expenditures, lost productivity, and absenteeism, is estimated to total \$100 billion (National Institute of Health 1998). As the prevalence of musculoskeletal pain is projected to rise with a greayer and longer living worldwide population (Woolf and Pfleger 2003), it calls for greater effort in development and evaluation of new ways of managing these patients.

Currently, pharmacotherapy plays an important role in alleviating pain for these patients. Non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and opioid analgesics are some of the most common classes of drugs provided. Unfortunately, these drugs may not be effective in many patients (Charles 2004) and can also lead to serious and occasionally fatal complications (Singh and Triadafilopoulos 1999). In light of these problems, the search for complementary or alternative therapies has received much attention. The emergence of botulinum toxin type A (BoNTA) is one such example of a potential new therapy aimed at musculoskeletal pain management.

Botulinum toxin type A is a neurotoxin that acts by inhibiting the release of the neurotransmitter, acetylcholine, at neuromuscular junctions, thus reducing muscular contractions (Borodic et al. 2001). Because of this muscle relaxing property, BoNTA was first used in humans to treat strabismus and blepharospasm (Flanders et al. 1987). Its clinical implications have since expanded as a treatment for focal dystonia and various types of muscle spasms (Hallett 1999). Additionally, pain caused by the muscle overactivity in these disorders can also be alleviated. Recently, Cui (2004) proposed another mechanism of action for BoNTA

based on their work with the rat formalin model. Their observations suggest that BoNTA may reduce nociceptive activities of sensory neurons by inhibiting release of certain neuropeptides, thus decreasing perception of pain. The exact mechanisms are yet to be clarified.

Despite the promising therapeutic potential of BoNTA in alleviating painful muscle spasms, its efficacy in other musculoskeletal pain conditions are not well established, including its use in myofascial pain (Lew 2002). With this meta-analysis, we set out to examine the evidence regarding the usefulness of BoNTA in treating musculoskeletal pain conditions.

## Objectives

The primary objective of this review is to examine the efficacy of BoNTA versus non-active injection or other treatments in reducing chronic musculoskeletal pain as assessed by a series of pain scales. We hypothesized a priori that BoNTA would be more effective, reflected by an improvement in patients' pain scores. Subgroup analyses were then proposed to explore whether the analgesic effects of BoNTA varies across different musculoskeletal disorders, doses, and time periods.

## Criteria for considering studies for this review

### Types of studies

We only considered randomized controlled trials (RCTs), investigating BoNTA as a single or complementary therapy.

### Types of participants

Patients of all ages, genders, and degrees of severity were included in the review, provided that they were experiencing chronic musculoskeletal pain.

### Types of interventions

Intramuscular or subcutaneous BoNTA injections (from any commercially available preparations) were compared to placebos or other non-active therapies, including exercise. We allowed all techniques and schema of administration.

### Types of outcomes

The primary outcome for our study is the reduction in pain severity through the period of follow-up. Only self-assessments of pain from patients were included because it

is commonly reported. Other forms of pain assessment, such as those used by the health care providers, were known to be not readily available in every study. Patient characteristics, such as the disease of interest, dosing regimen, and length of follow-up were also recorded.

#### Exclusion criteria

Observational studies, case reports, and other non-randomized studies were not included. Studies comparing BoNTA with other active medical injections or studies without measures of pain were excluded. Additionally, because of the mixed pathogenesis for conditions of localised head pain, referred pain to the head, and intrinsic headache, we did not consider these types of conditions in our study.

#### Search methods for identification of studies

We identified relevant trials from the following sources:

1. MEDLINE (1950–November week 3 2008).
2. EMBASE (1980–2008 week 50).
3. PUBMED (date of search: December 18, 2008).
4. Cochrane Central Register of Controlled Trials (4th quarter 2008).
5. CINAHL (1982–December 2008).
6. Reference lists of relevant articles.

The following search terms and their MESH equivalents were used: BoNTA, BTX, BoNT, musculoskeletal diseases, arthritis, whiplash, shoulder pain, neck pain, back pain, limb pain, and joint pain. Another search was conducted on August 25, 2009. An additional article was retrieved (Singh et al. 2009).

#### Methods of review

Four reviewers (AA, MM, WZ, and AV), paired into two groups, independently reviewed all studies identified by our search strategy. Using the criteria described above, they first assessed titles and abstracts to determine relevant studies using standardized forms. Full-texts of these articles were then retrieved to ascertain if all inclusion criteria have been met. Upon inclusion of a study, our reviewers (TZ and AA) then performed data extraction in an independent duplicate manner using pilot-tested forms. Any disagreements were resolved through discussions. Authors were contacted through email to retrieve or clarify data when necessary. The qualities of included trials were independently graded by two reviewers (AA and WZ) using the Jadad scale (Jadad et al. 1996), which takes into

account the method of randomization, blinding, and loss to follow-up. Each study received a grade of 0–5. Higher grades indicate higher methodological quality.

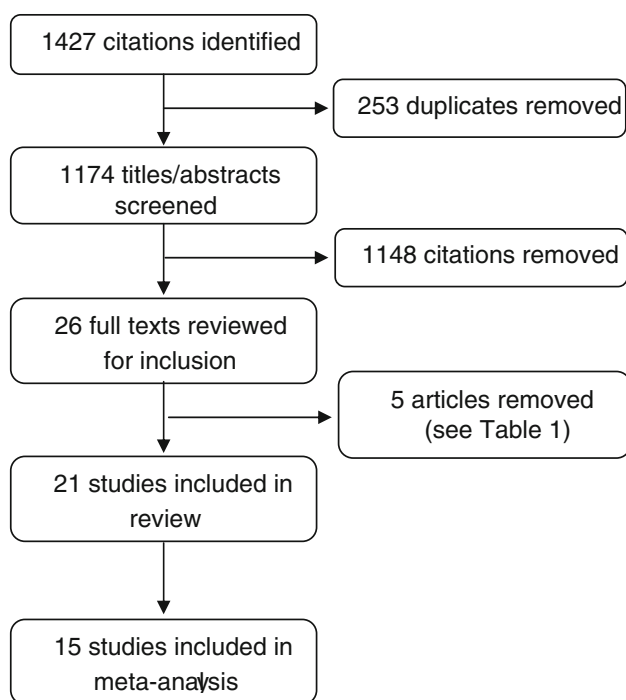
#### Statistical analysis

We used kappa statistics to evaluate agreement between reviewers on study selection. We used the standardized mean difference (SMD) with two-sided 95% confidence interval to assess the effect sizes of BoNTA because of the different pain scales employed in the selected studies. The included scales are both 10 and 100 points pain visual analog scales, 50 points neck pain and disability scale, as well as a Biobehavioural Questionnaire. When multiple BoNTA groups with varying dosages were evaluated in a single study, we employed the inverse variance weighting method to estimate the overall analgesic effect of BoNTA before comparing to the placebo. For cross-over trials, only data from the first period was incorporated. Where it was not reported, we calculated the standard deviation (SD) for the change score using estimated SDs of pre- and post-treatment pain scores and zero correlation (Wiebe et al. 2006).

We employed a random-effects model suggested by DerSimonian and Laird (1986) to pool data across studies, accounting for both within- and between-study variability. We used Cochran's chi-square test to examine heterogeneity with statistical significance at  $\alpha = 0.10$ . We calculated the  $I^2$  statistic to quantify the degree of inconsistency between studies due to heterogeneity rather than sampling error. We performed subgroup analyses primarily to generate hypotheses regarding three factors: patient's presenting disease, dosage per injection site, and treatment period. Studies examining multiple BoNTA groups with varying dosages were not included in the dosage subgroup analysis. However, sensitivity analysis was performed to evaluate the effect of incorporating the low dose or high dose group. We applied a conversion ratio of 3:1 Units to equate Dysport<sup>®</sup> potency with that of Botox<sup>®</sup> (Odergren et al. 1998; Wohlfarth et al. 2009). We generated funnel plot to investigate the extent of publication bias. We performed all meta-analyses in RevMan 5.0 (Review Manager 2008).

#### Description of studies

With a broad based search strategy, we identified a total of 1,427 articles (Fig. 1). 253 citations were duplicates. Upon an initial screening of the titles and abstracts alone, all articles were found to be unsuitable except for 26 of them. These articles were retrieved and a total of 21 studies were eventually included.



**Fig. 1** Attrition diagram for literature search

**Table 1** Characteristics of excluded studies

Author	Reason for exclusion
Jabbari (2007)	Review article
Porta (1999)	Control was active medical therapy
Kamanli et al. (2005)	Controls were active medical therapies
Szczepanska-Szerej et al. (2003)	Unable to locate the article/abstract; published in Polish
Sohling (2002)	Unable to locate the article/abstract; published in German

Assessment of study selection agreement between the reviewers resulted in a  $\kappa = 0.70$  (95% CI: 0.51–0.90) and 0.72 (95% CI: 0.56–0.88) between the two groups of reviewers.

#### Excluded studies

Five of the 26 articles were excluded (Jabbari 2007; Porta 1999; Kamanli et al. 2005; Szczepanska-Szerej et al. 2003; Sohling 2002). For detailed characteristics, please see Table 1. One study was a review article (Jabbari 2007) and thus was excluded. Two trials (Porta 1999; Kamanli et al. 2005) were RCTs but active medical therapies were used as controls, which did not meet our inclusion criteria. The last two studies (Szczepanska-Szerej et al. 2003; Sohling 2002) were excluded as the abstract/full text could not be located and attempts to contact the authors were unsuccessful.

#### Included studies

Twenty-one studies have been included in this review. 15 of them were selected for the meta-analysis. They are summarized below with details provided in Tables 2, 3.

#### Participants

##### *Plantar fasciitis*

There was only one trial retrieved examining plantar fasciitis (Babcock et al. 2005). Patients were recruited with bilateral symptoms consistent with plantar fasciitis. Patients were excluded if they had other pain or neurological conditions, including fibromyalgia.

##### *Tennis elbow*

Two of the three trials included patients who were previously diagnosed with tennis elbow and who already tried some conservative therapies (Placzek et al. 2007; Hayton et al. 2005). The other trial recruited similar patients (Wong et al. 2005). However, subjects were excluded if they had any previous local injection treatments.

##### *Shoulder pain*

The included trial studied patients with osteoarthritis or rheumatoid arthritis induced shoulder pain and who were not responsive to corticosteroid injections (Singh et al. 2009).

##### *Chronic low back pain*

The single study in this category had participants with lateral pain between L1 and S1 that lasted more than 6 months (Foster et al. 2001).

##### *Whiplash associated disorder*

The three studies all recruited patients with a history of a whiplash injury and subsequent localized neck pain (Braker et al. 2008; Carroll et al. 2008; Padberg et al. 2007). However, the duration of symptoms prior to trial enrolment was not consistent among the studies, ranging from 2 weeks to a year.

##### *Myofascial pain syndrome*

There are 12 studies in this category (Ferrante et al. 2005; Guarda-Nardini et al. 2008; Lew et al. 2008; Kurtoglu et al. 2008; Nixdorf et al. 2002; Ojala et al. 2006; Qerama et al. 2006; Wheeler et al. 2001b; Cheshire et al. 1994; Esenyel

**Table 2** Characteristics of studies

Clinical condition	References	Jadad score (0–5)	Method	Participants	Anatomic site of pain	Duration of pain prior to enrolment	Intervention	Adjunctive therapy	Outcomes	Follow-up (weeks)
Plantar fasciitis	Babcock et al. (2005)	5	Prospective RCT parallel, double-blind	$n = 27$ , Female 67%, median age 44, country USA	Localized to the medial process of the calcaneal tuberosity	6 months	70 U for 2 sites (Botox <sup>®</sup> ) or placebo (saline)	Home stretching program; no changes to existing medications	Pain VAS (0–10)	8
Shoulder pain	Singh et al. (2009)	5	RCT parallel, double-blind	$n = 43$ (36 patients 43 joints), female 2%, mean age 71, country USA	Glenohumeral joint	≥6 months	100 U (Botox <sup>®</sup> ) or placebo (2 mL, 1% lidocaine and 1 mL sterile normal saline)	None	Pain VAS (0–10)	4
Tennis elbow	Placzek et al. (2007)	4	RCT parallel, multicentre Study	$n = 132$ , female 52%, Mean age 47, country Germany	Radial epicondyle	4 months	60 U for 2 sites (Dysport <sup>®</sup> ) or placebo (saline)	Diclofenac; physical therapy withheld for 6 weeks	Pain VAS (0–10)	18
	Wong et al. (2005)	5	RCT parallel	$n = 60$ , Female 82%, mean age 45, country Hong Kong, China	Lateral side of the elbow and lateral epicondyle	3 months	60 U (Dysport <sup>®</sup> ) or placebo (saline)	None; all medications/treatments for treatment of tennis elbow stopped (including physical therapy)	Pain VAS (0–10)	12
Whiplash associated disorder	Braker et al. (2008)	5	RCT parallel	$n = 20$ , Female 60%, mean age 47, country Israel	Neck	2–48 weeks	200 U for 4r sites (Botox <sup>®</sup> ) or placebo (saline)	None	Pain VAS (0–10)	24
	Carroll et al. (2008)	4	RCT parallel	$n = 37$ , Female 57%, mean age 39, country Ireland	Neck	N/A	250 U for 5 sites (Dysport <sup>®</sup> ) or placebo (saline)	None, interventions aside from simple analgesia and short-term anti-inflammatory drugs were not recommended	Pain VAS (0–10)	12
Myofascial pain syndrome	Padberg et al. (2007)	4	RCT parallel	$n = 40$ , Female 68%, mean age 36, country Netherlands	Neck	>6 months	100 U (Botox <sup>®</sup> ) or placebo (saline)	None	Pain VAS (0–10)	16
	Ferrante et al. (2005)	4	RCT parallel	$n = 132$ , Female 61%, mean age 45, country USA	Surface muscles of the neck and shoulder area	6 months	10 U, 25 or 50 U (Botox <sup>®</sup> ) up to 5 sites or placebo (saline)	Pharmacotherapeutic regimen and physical therapy	Pain VAS (0–100)	12
	Guarda-Nardini et al. (2008)	2	RCT parallel	$n = 20$ , Female 50%, mean age 25–45, country Italy	Muscles of mastication (masseter and anterior temporalis)	6 months	100 U (Botox <sup>®</sup> ) for 5 sites or placebo (saline)	None	Pain VAS (0–10)	24
	Lew et al. (2008)	5	RCT parallel	$n = 29$ , Female 31%, mean age 48, country USA	Neck and upper back	2–6 months	Maximum 100 U (Botox <sup>®</sup> ) or placebo (saline)	Concomitant pain medication and physical therapy allowed.	Pain VAS (0–10)	24
	Kurtoglu et al. (2008)	5	RCT parallel	$n = 24$ , Female 83%, mean age 26, country Turkey	Temporomandibular muscles	N/A	100 U (Botox <sup>®</sup> ) for 10 sites or placebo (saline)	None; analgesics, anti-inflammatory, or muscle relaxants were not given	Behavioural questionnaire	4
	Nixdorf et al. (2002)	4	Crossover study	$n = 15$ , Female 100%, mean age 35, country Canada	Temporomandibular region	>6 months	75 U (Botox <sup>®</sup> ) or placebo (saline)	Breakthrough analgesic was provided; no other analgesics allowed	Pain VAS (0–10)	24

Table 2 continued

Clinical condition	References	Jadad score (0–5)	Method	Participants	Anatomic site of pain	Duration of pain prior to enrolment	Intervention	Adjunctive therapy	Outcomes	Follow-up (weeks)
	Ojala et al. (2006)	4	RCT crossover, double-blind	$n = 31$ , Female 90%, mean age 44, country Finland	Neck-shoulder area (trapezius, levator scapulae, and Infraspinatus)	2 months	15–35 U (Botox®) for 3–7 sites or placebo (saline)	None	Severity of neck-shoulder pain (0–10)	8
	Qerama et al. (2006)	5	RCT parallel	$n = 30$ , female 60%, mean age 50.6, country Denmark	Shoulder and arm (infraspinatus muscle)	>6 months	50 U (Botox®) or Placebo (saline)	None	Pain VAS (0–10)	4
	Wheeler et al. 2001b	4	RCT parallel, double-blind	$n = 50$ , Female 76%, mean age 44, country USA	Neck	3 months	Mean of 230 U (Botox®) or placebo (saline)	None	Pain NPAD (0–50)	16

VAS Visual analogue scale NPAD neck pain and disability scale

et al. 2007; Gobel et al. 2006; Wheeler et al. 1998). A broad spectrum of patients were therefore represented in those trials with differences in affected anatomical sites, trigger points, previous exposure to conservative therapies, and presenting pain.

#### Types of interventions

BoNTA used in our studies were one time injections. They were either Botox® from Allergan Inc., USA or Dysport®, from Ipsen Limited, UK.

#### Types of outcomes

The outcomes documented in included trials range from pain scores using visual analog scale, global assessment scores, physician rating scores to regional pain scales (Maryland foot score, neck pain and disability scale). We decided a priori to use only patient's self rating scores.

#### Methodological quality

The Jadad scores of included studies ranged from 1 to 5 but the mean Jadad score assigned was 4.1, indicating the general high quality of studies included. In addressing our particular clinical question, double blinding is especially important since our outcome of interest (pain as measured on various scales) is patient-determined and thus subjective. All of the studies were conducted in a double-blind manner. However, in Esenyel's study (2007), reporting of blinding was not found. For the most part, concealment of the allocation sequences was also described and carried out adequately in the studies. All studies were examined for the possibility of selective outcome reporting, and none was noted.

#### Results

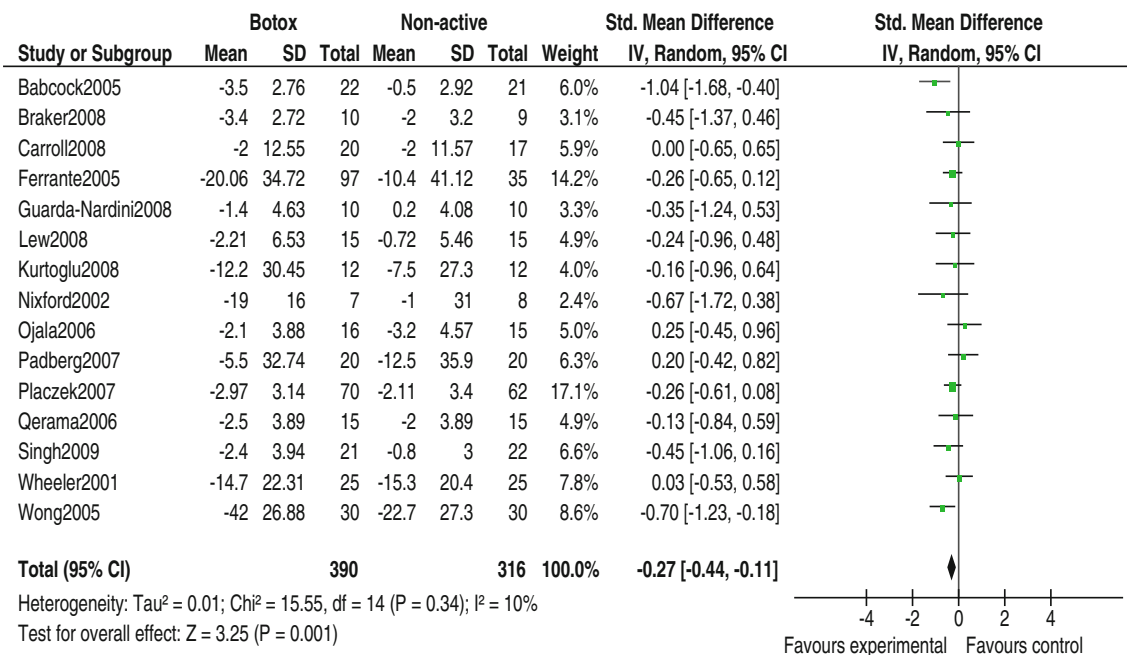
A total of 15 studies with 706 patients were included in the meta-analysis—390 in BoNTA group and 316 in non-active group.

A total of 21 studies (Foster et al. 2001; Hayton et al. 2005; Cheshire et al. 1994; Esenyel et al. 2007; Gobel et al. 2006; Wheeler et al. 1998) were not included in the statistical analysis because of inadequate data reporting. Among the 15 trials included, the musculoskeletal conditions studied were plantar fasciitis ( $n = 1$ ), tennis elbow ( $n = 2$ ), shoulder pain ( $n = 1$ ), whiplash ( $n = 3$ ), and myofascial pain ( $n = 8$ ). The mean age of patients ranged from 25 to 71. The percentage of females across the studies was wide-ranging from 2 to 100%. Most of these patients had experienced pain for at least 3 months with little or no

**Table 3** Characteristics of additional studies in the systematic review (but not in the meta-analysis)

Clinical condition	References	Jadad score (0–5)	Method	Participants	Anatomic site of pain	Duration of pain prior to enrolment	Intervention	Adjunctive therapy	Outcomes	Follow-up (weeks)
Chronic low back pain	Foster et al. (2001)	4	RCT parallel, double-blind	n = 31, Female 52%, mean age 47, country USA	Low back pain (between L1 and S1)	6 months	200 U for 5 sites (Botox®) or placebo (saline)	None; no changes were made to analgesic and antispasmodic medications	Pain VAS (0–10)	8
Tennis elbow	Hayton et al. (2005)	5	RCT parallel	n = 40, Country UK	Localized over the lateral epicondyle	>6 months	50 U (Botox®) or placebo (saline)	None	Pain VAS (0–10)	12
Myofascial pain	Cheshire et al. (1994)	3	RCT cross-over	n = 6, Female 67%, mean age 44, country USA	Localized to paraspinal or shoulder girdle muscles	3 years	50 U (Botox®) or Placebo (saline)	None	Pain VAS (0–100)	8
	Esenyel et al. (2007)	1	RCT parallel, multiple interventions	n = 90, Female 73%, mean age 25–40, country Turkey	One side of upper trapezius muscle	6 months	10 U (Dysport®) or lidocaine or conventional US or Static US placebo (exercise programme)	Therapy session	Pain VAS (0–10)	4
	Gobel et al. (2006)	5	Prospective RCT parallel, multicentre, double-blind	n = 145, Female 79%, mean age 44, country Germany and Austria	Cervical and/or shoulder muscles	6–24 months	400 U (Dysport®) over 10 sites or placebo (saline)	None	Ordinal self-rating pain scale (1–4)	12
	Wheeler et al. (1998)	3	RCT parallel, double-blind	n = 33, Mean age 41, country USA	Neck	3 months	50 or 100 U (Botox®) or placebo (saline)	None	Pain NPAD (0–50)	16

VAS Visual analogue scale NPAD neck pain and disability scale



**Fig. 2** Effects of BoNTA on pain reduction among patients of musculoskeletal pain

response to traditional pain-modulating therapies (e.g., NSAIDs, steroids).

Based on Cohen's (1988) difference index, there was a significant small to moderate pain reduction among BoNTA patients comparing to controls (SMD =  $-0.27$ , 95% CI:  $-0.44$  to  $-0.11$ ) (Fig. 2). No significant heterogeneity was present in the overall analysis ( $p = 0.34$ ,  $I^2 = 10\%$ ).

The results of disease subgroup analysis are presented in Fig. 3. In the myofascial pain group, BoNTA resulted in small pain relief which was not statistically significant (SMD =  $-0.16$ , 95% CI:  $-0.39$  to  $0.06$ ). Among patients with tennis elbow, two studies demonstrated significant pain relief (SMD =  $-0.44$ , 95% CI:  $-0.86$  to  $-0.01$ ). Three other trials recruited patients with prior whiplash injuries. The usage of BoNTA did not seem to lead to greater pain relief for patients (SMD =  $0.00$ , 95% CI:  $-0.41$  to  $0.40$ ). Lastly, plantar fasciitis and shoulder pain were each examined by a study. BoNTA was shown to be effective in plantar fasciitis (SMD =  $-1.04$ , 95% CI:  $-1.68$  to  $-0.40$ ) but not in shoulder pain (SMD =  $-0.45$ , 95% CI:  $-1.06$  to  $0.16$ ).

When patients were stratified on the basis of dosage (Fig. 4), only those who received an injection of 25 units or more per anatomical site benefited (SMD =  $-0.57$ , 95% CI:  $-0.92$  to  $-0.22$ ). Moreover, the study done by Ferrante et al. 2005 was not included in the subgroup analysis since it had multiple intervention arms with varying BoNTA dosages. However, including the results from either the 50 U/site ( $n = 31$ ) or 10 U/site ( $n = 32$ ) group as part of a sensitivity analysis did not significantly change our

outcome. By incorporating the low dose arm, the 1–10 U/site subgroup analysis showed a comparable result as before (SMD =  $-0.08$ , 95% CI:  $-0.29$  to  $0.14$ , heterogeneity  $p = 0.75$ ,  $I^2 = 0\%$ ). Similarly, including the high dose arm results did not lead to any deviation in original outcomes (SMD =  $-0.45$ , 95% CI:  $-0.76$  to  $-0.13$ , heterogeneity  $p = 0.31$ ,  $I^2 = 17\%$ ).

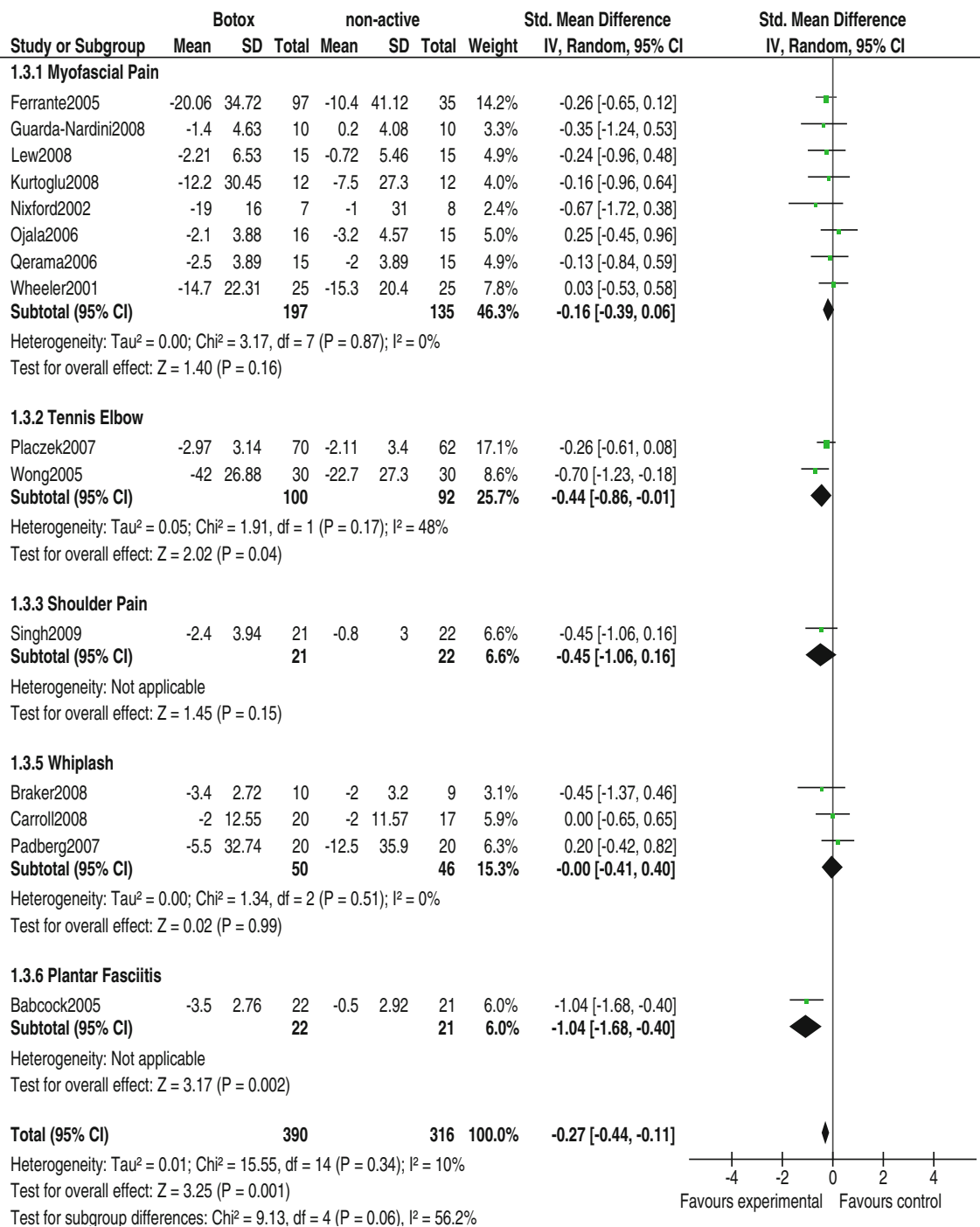
As shown in Fig. 5 studies with short-term follow-up showed no significant pain relief effect with BoNTA (SMD =  $-0.15$ , 95% CI:  $-0.50$  to  $0.2$ ). For the 5–8 weeks group, BoNTA group experienced significantly greater pain reduction (SMD =  $-0.94$ , 95% CI:  $-1.49$  to  $-0.39$ ). A similar analgesic effect was also observed for long-term follow-up group although to a lesser degree (SMD =  $-0.24$ , 95% CI:  $-0.41$  to  $-0.06$ ).

There was no major publication bias as assessed by the funnel plot (Fig. 6).

#### Studies not in the statistical analysis

Among the 6 studies that were not included in the statistical analysis, four followed patients with myofascial pain syndrome (Cheshire et al. 1994; Esenyel et al. 2007; Gobel et al. 2006; Wheeler et al. 1998). In a study of 33 patients with refractory cervicothoracic paraspinal myofascial pain syndrome, Wheeler et al. (1998) reported no statistically significant benefit of 50/100 U BoNTA over placebo after a follow-up of 16 weeks. The trial by (Gobel et al. 2006) included 145 patients with moderate to severe myofascial pain syndrome. Seventy-five patients received

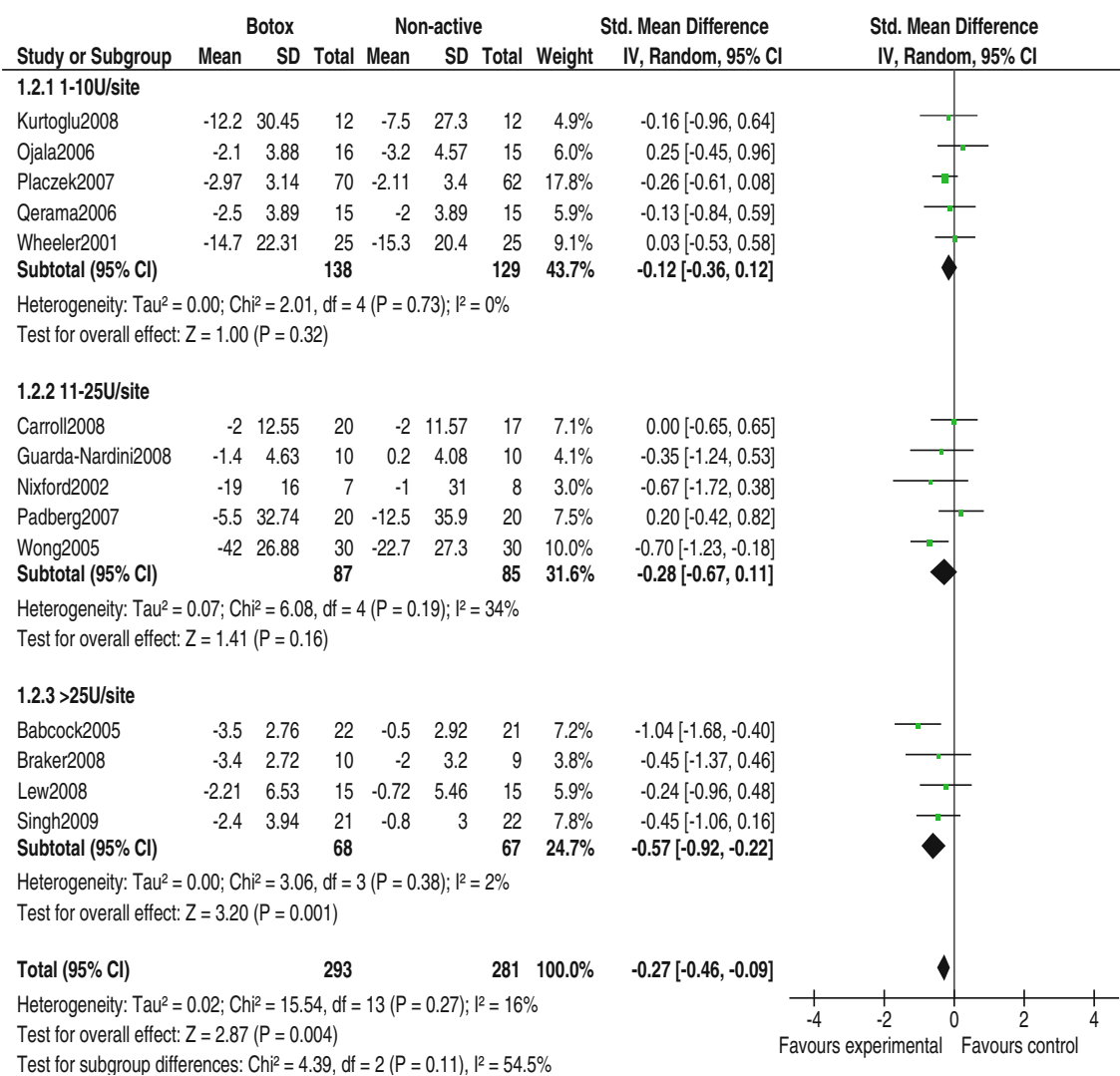




**Fig. 3** Subgroup analysis of RCTs based on clinical conditions

Dysport<sup>®</sup> treatments with an average of 40 U/site. At week 5, significantly more people in the Dysport<sup>®</sup> group experienced mild or no pain. Another trial (Hayton et al. 2005) studied six patients with chronic myofascial pain syndrome. Botox<sup>®</sup> was used in four patients with a total of 50 U divided between two and three sites while the rest received saline solution. At follow-up, all Botox<sup>®</sup> patients

reported at least 30% pain reduction comparing to no pain relief in placebo group. In the last study, Esenyel et al. (2007) compared BoNTA group to a number of interventions, including stretching exercise and lidocaine. There were a total of 90 subjects—18 in BoNTA group and 18 with stretching exercise. Each of the BoNTA subjects received a 10 U injection per trigger point. After



**Fig. 4** Subgroup analysis of RCTs based on dosage of injection per anatomical site

4 weeks, BoNTA and lidocaine were found to be statistically more effective in relieving pain than other modalities.

Out of the other two trials that could not be incorporated in the statistical analysis, one (Foster et al. 2001) studied the usefulness of Botox<sup>®</sup> injections (40 U/site) in patients with chronic low back pain. In this randomized, double-blind study, 15 patients in the Botox<sup>®</sup> group and 16 in the control group were evaluated. This trial revealed a significant increase in Botox<sup>®</sup> patients having at least 50% pain relief in comparison to control at 8 weeks (60 vs. 12.5%). The other study (Hayton et al. 2005) involved a total of 40 patients with diagnosed tennis elbow. No significant differences were observed between the two groups at 12 weeks.

It was not the purpose of this study to address the toxicity or adverse effects of BoNTA use. However, it is

important to state that the adverse reactions identified in the studies reported did not influence the outcome measures in any major way. Most studies report none or only transient side effects that resolved spontaneously. There were two studies where dropout occurred due to side effects. In the Gobel et al. (2006) study, there were no serious events. However, one patient from the BoNTA group ( $n = 75$ ) and one from the control group ( $n = 70$ ) dropped out due to sore muscles. In a cross-over trial by Nixdorf et al. (2002), there were a total of 15 patients and 5 dropped out before completion of the study. Three were receiving BoNTA, and their reasons for withdrawal were paralysis ( $n = 2$ ), and increased pain ( $n = 1$ ). The other two patients who dropped out were receiving placebo and their reasons for withdrawal were increased pain. A detailed review of BoNTA's toxicity is provided in the Compendium of Pharmaceuticals and Specialties (2010).

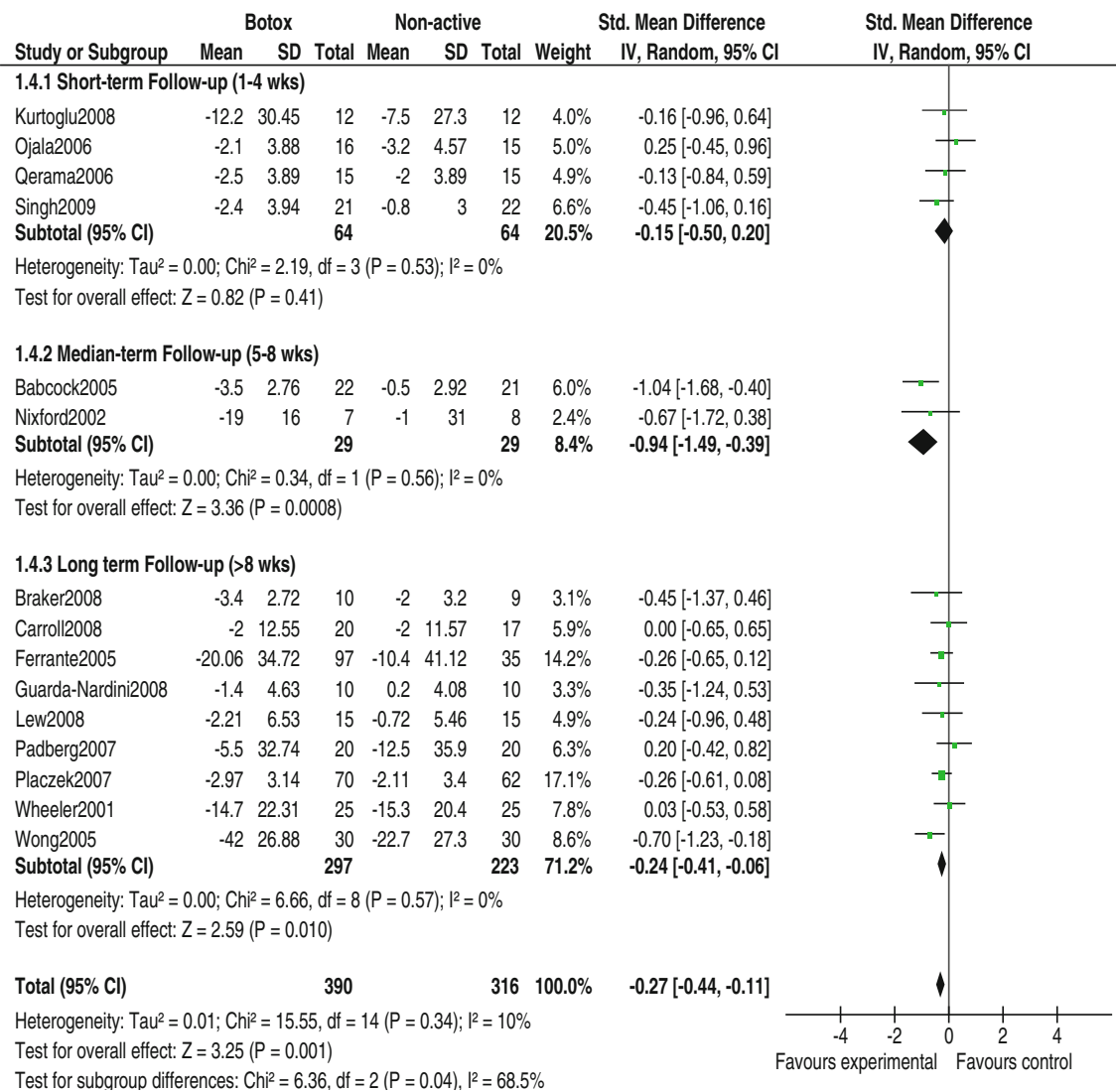


Fig. 5 Subgroup analysis of RCTs based on duration of follow-up

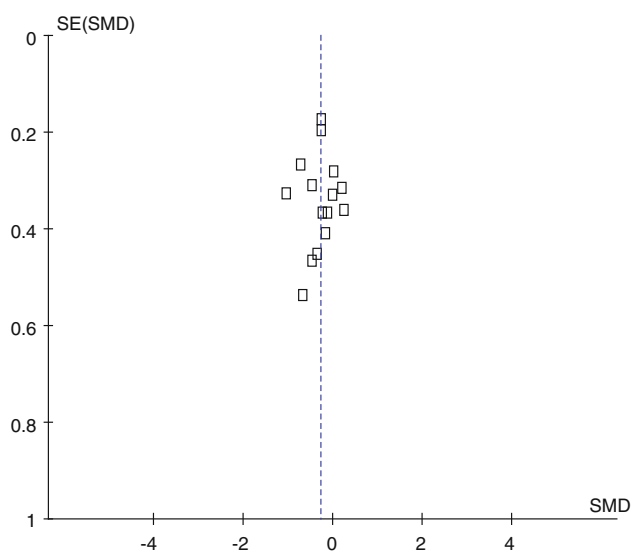
**Discussion**

The primary objective finding of this meta-analysis is that BoNTA treatments resulted in small to moderate pain relief. This beneficial effect was especially noted in patients with tennis elbow, plantar fasciitis, and low back pain. The effect was also noticeable when the injection was >25 U (Botox<sup>®</sup>) per anatomical site or when the post-injection period was equal to or greater than 5 weeks.

**MSK pain disorders**

Myofascial pain syndrome is a regional condition of muscle pain and stiffness. It is also characterized by trigger points that generate local twitch response and referred pain on palpation. Its etiology is still unclear but muscle hyperactivity and inflammatory processes have been associated with this

phenomenon (Simons et al. 1999; Borg-Stein and Simons 2002). A number of open label and retrospective studies have been done to assess the usefulness of BoNTA in treating this condition. The preliminary results were encouraging as Botox was shown to be effective in relieving pain (Lang 2000; De Andrés et al. 2003; Wheeler et al. 2001a; Royal et al. 2001). However, these findings have not been confirmed by RCTs. Out of the 12 myofascial pain trials included in our study, only 3 were positive with respect to alleviating pain intensity. Cheshire (1994) showed that Botox reduced experience of pain significantly at follow-up but the trial was rather small with 6 chronic myofascial pain patients. Similarly, Esenyel (2007) concluded with favourable results for Botox<sup>®</sup> in terms of pain alleviation when comparing to stretching exercises. Lastly, Gobel (2006) reported significantly greater pain reduction with Dysport<sup>®</sup> among patients of myofascial pain syndrome in the upper back. Despite these positive studies,



**Fig. 6** Funnel plot assessing publication bias of the meta-analysis. The graph plots effect estimates on the horizontal axis against standard error of intervention effect estimates. This places larger or most powerful studies towards the *top* and smaller studies scattering more widely at the *bottom*. There seems to be missing some small sized studies that strongly favour or disfavour BoNTA. Nevertheless, included studies are plotted symmetrically around the pooled estimate

the majority of trials have not demonstrated BoNTA's analgesic effects in treating myofascial pain syndrome.

Plantar fasciitis, tennis elbow, shoulder pain, whiplash injuries, and back pain were also studied although to a more limited extent. Given the inflammatory pathophysiology of these conditions, BoNTA was shown to have antinociceptive effects in the plantar fasciitis trial (Babcock et al. 2005) and the two tennis elbow studies (Porta 1999; Placzek et al. 2007). However, the other tennis elbow study by Hayton et al. (2005) did not demonstrate the usefulness of BoNTA in reducing pain. In addition, BoNTA did not significantly improve pain scores among the small number of shoulder pain and whiplash injury studies (Singh et al. 2009; Braker et al. 2008; Carroll et al. 2008; Padberg et al. 2007). Back pain was evaluated in one RCT in our systematic review (Foster et al. 2001). It demonstrated significant pain relief with BoNTA injections. On the basis of this result, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology concluded in its 2008 report that BoNTA is "possibly effective" for low back pain (Naumann et al. 2008). Nevertheless, more robust evidence is required for a more definitive understanding.

### Dosing

In this meta-analysis, there were two studies that specifically examined the dose–response relationship. In one trial, Ferrante used 10, 25, or 50 U Botox® injections per site in the

assigned patients (Ferrante et al. 2005). When compared to placebo group, no differences in pain scores were found. In the other study by Wheeler et al. (1998), a total of 50 or 100 U Botox® injections were used in each subject. Injection dosage per site, however, could not be determined. Again, no differences between saline and intervention groups were observed. This seemingly lack of dose–response relationship from these two studies needs to be considered in the context of the studies' population. Both trials involved patients with myofascial pain, which BoNTA has shown based on our results not to be consistently effective. In our subgroup analysis, however, studies with >25 U Botox® injections reported significant pain reduction with the treatment (Fig. 4). Furthermore, dose response relationships have been observed in other clinical applications of BoNTA, such as its usage in spastic hypertonia (Francisco 2004). Further research is certainly warranted to discern the painkilling effects of BoNTA in MSK pain disorders when used in various doses.

### Duration of effectiveness

It is well known that Botox can decrease muscular tone and associated symptoms of pain by inhibiting the release of acetylcholine at neuromuscular junctions (Borodic et al. 2001). The onset of action and duration of this mechanism can vary from days to weeks. However, little is known about the temporality of its anti-nociceptive effect. In rats, the effect was found to last about 12 days (Cui et al. 2004). Clinically, there have been observations that pain reduction precedes muscular improvements but no accurate scientific documentation has been established (Aoki 2003).

Based on our analysis, the period of significant analgesic effect took place during the median and long term post-injection timeframe. The greatest effect was noted during the median-term follow-up (5–8 weeks).

### Limitations

Our meta-analysis has a number of limitations. First, the study is limited in making reliable conclusions with regards to BoNTA's efficacy in treating non-myofascial related musculoskeletal pain due to limited number of patients included. More RCTs in those clinical areas would be valuable. Second, we did not explore other factors, such as variation in injection techniques or gender differences because of the existing clinical heterogeneity of the population.

### Conclusions

Overall, we show that BoNTA treatments can result in a small to moderate pain relief when injected in patients with

musculoskeletal pain. It was especially noted in the small number of plantar fasciitis, tennis elbow, and back pain studies but not in the whiplash or shoulder pain studies. More RCTs are required to further understand the role of BoNTA in these conditions. On the other hand, our results from a convincing number of RCTs suggested that BoNTA injections do not result in any significant pain relief for patients with myofascial pain syndrome. Finally, we noted an increased analgesic effect of BoNTA with increased dosage or longer follow-up period. These observations should warrant closer examination in future studies.

**Conflict of interest** None declared.

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