Review

Botulinum Toxin for Shoulder Pain: A Cochrane Systematic Review

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ABSTRACT. ***Objective***. To perform a Cochrane Systematic Review of benefits and harms of botulinum toxin for shoulder pain.

Methods. We included clinical trials of adults with shoulder pain (population), comparing botulinum toxin (intervention) to placebo or other therapies (comparison), and reporting benefits or harms (outcomes). We calculated relative risk (RR) for categorical outcomes and mean differences (MD) for continuous outcomes.

Results. Six randomized controlled trials (RCT) with 164 patients all comparing single botulinum toxin type A injections to placebo were included. Five RCT in patients with post-stroke shoulder pain found that an intramuscular injection of botulinum toxin type A significantly reduced pain at 3–6 months (MD –1.2 points on 0–10 scale, 95% CI –2.4 to –0.07) and improved shoulder external rotation at 1 month (MD 9.8˚, 95% CI 0.2˚ to 19.4˚). Number of adverse events did not differ between groups (RR 1.46, 95% CI 0.6 to 24.3). One RCT in arthritis-related shoulder pain showed that single intraarticular botulinum toxin type A injection reduced pain (MD –2.0 on 0–10 scale, 95% CI –3.7 to –0.3) and shoulder disability (MD –13.4 on 0–100 scale, 95% CI –24.9 to –1.9) and improved shoulder abduction (MD 13.8˚, 95% CI 3.2˚ to 44.0˚) at 1 month, compared with placebo. Serious adverse events did not differ between groups (RR 0.35, 95% CI 0.11, 1.12).

Conclusion. With evidence from few studies with small sample sizes and medium to high risk of bias, botulinum toxin type A injections decreased pain and improved shoulder function in patients with chronic shoulder pain due to spastic hemiplegia or arthritis. (J Rheumatol First Release Feb 1 2011; doi:10.3899/jrheum.101081)

Key Indexing Terms:
BOTULINUM TOXIN SHOULDER PAIN BENEFIT
SAFETY COCHRANE SYSTEMATIC REVIEW

Shoulder pain is one of the most common musculoskeletal disorders affecting the adult population, with an estimated prevalence of 7% to 25% in Western general populations[1,2,3,4,5]. Persistent shoulder pain lasting longer than 1 month affects over 5% of adult Americans each year[2]. Shoulder pain limits the ability to enjoy an optimal quality of life and perform key functions in daily living[5,6,7], leading to disability[8], and higher healthcare utilization[9]. The common causes of shoulder pain include rotator cuff tendinitis, adhesive capsulitis, osteoarthritis (OA) of the shoulder, and acromio-clavicular joint disease. In the elderly, shoulder pain is a common complication after stroke[10] that is associated with reduction in quality of life[11]. Post-stroke shoulder pain may be due to spasticity, adhesive capsulitis, shoulder subluxation, or rotator cuff injury.

Conservative treatment options for shoulder pain include

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analgesics and antiinflammatory medications, oral steroids[12], local steroid injections[13], arthrographic distension[14], physiotherapy[15,16], acupuncture[17], and, more recently, novel interventions such as topical glyceryl trinitrate[18]. However, a significant proportion of patients are intolerant or refractory to these therapies, and therefore new treatment options are needed.

Botulinum toxin is one of the neurotoxins produced by *Clostridium botulinum* bacteria. Botulinum neurotoxins are zinc-dependent enzymes that reversibly block neurotransmission by inhibiting release of neurotransmitters (the chemical signals) and disrupting neuronal communication[19,20]. There are 7 botulinum serotypes (A to G), all of which inhibit acetylcholine release at the neuromuscular junction to prevent the muscle from contracting. This mechanism of action is thought to underlie its efficacy in treating spasticity associated with stroke, multiple sclerosis, Parkinson's disease, and cerebral palsy and for the treatment of facial wrinkles. There is also emerging evidence on the use of botulinum toxin for pain relief in neuropathic pain[21] and arthritis-related pain[22].

Laboratory observations suggest that botulinum neurotoxin A can directly inhibit peripheral nerve nociceptor activation and sensitization by local neurotransmitter release, and may indirectly reduce central sensitization in spinal cord neurons — mechanisms important in chronic pain. In a rat model of induced acute inflammatory pain, prior injection of botulinum neurotoxin A just below the paw skin reduced spinal cord activity and paw inflammation[23]. Botulinum neurotoxin A inhibited release of substance P in *in vitro* studies of embryonic rat dorsal neurons[24]; substance P acts as a neurotransmitter and is associated with inflammatory processes and pain. The clinical evidence for inhibition of pain sensation by botulinum neurotoxin is mounting: (1) improvement of neck pain has been noted before reduction in muscle spasm following botulinum toxin type A injection for cervical dystonia[25]; (2) pain relief typically outweighed the degree of spasm reduction in the treatment of painful spasticity in the extremities[26]; (3) botulinum toxin type A injections reduced severity/frequency of migraine and tension headaches[27]; and (4) observation of pain relief in patients with myofascial pain[28,29,30] and chronic tennis elbow[31,32,33]. These observations suggest an antinociceptive action for botulinum toxin that may be independent of its well described muscle paralyzing action.

The objective of this Cochrane systematic review was to assess the benefit and harms of botulinum toxin for shoulder pain, as compared to placebo or other treatment options[34].

MATERIALS AND METHODS

Selection criteria and search methodology. We considered all published clinical trials including adults (age > 18 years) with shoulder pain treated with botulinum toxin injections by any route (including but not limited to intramuscular, subcutaneous, intradermal, or intraarticular) compared to placebo/comparator, reporting benefits and/or harms. Shoulder pain could be due to any type of arthritis in the glenohumeral or acromio-clavicular joint [OA, rheumatoid arthritis (RA), and other inflammatory arthritides], rotator cuff tendinitis, adhesive capsulitis, or post-stroke shoulder pain.

With the search strategy shown in Appendix 1, we searched the following databases in September 2009: Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library 2009, Issue 3) on Wiley InterScience (www.thecochranelibrary.com); Ovid MEDLINE (1966 to August Week 4, 2009); CINAHL (via EBSCOhost; 1982 to September 2009); Dissertation abstracts; EMBASE (1980 to Week 36, 2009); Science Citation Index (Web of Science; 1945 to August 2009); and Current Controlled Trials. The search was updated January 22, 2010.

We also searched the US Food and Drug Administration (FDA) (www.fda.gov/) and European Medicines Agency (EMEA) websites (www.ema.europa.eu/) for labels and warnings to summarize warnings related to botulinum toxin injections.

Data collection and analysis. Two authors (JAS, PMF) independently reviewed trials identified for potential inclusion, based on predetermined criteria (see "Criteria for selecting studies") and extracted data independently including source of funding, study population, number of centers, intervention, route and dose, comparator, and outcomes. A third individual (K. McMaken) checked data accuracy by comparing original data from included articles to the abstracted data. When possible, we extracted numbers based on intention-to-treat analysis.

Primary and secondary outcomes. Primary outcomes were (1) Pain, on visual analog scale (VAS), numeric rating scale (NRS), or semiquantitative descriptive scales such as the short-form McGill Pain Questionnaire (range 0–45; higher score denotes worse pain)[35] or other instruments; and (2) Harms, as assessed by total and serious adverse events, number of withdrawals due to adverse events, and deaths.

Secondary outcomes were (1) Disability/function measured using instruments such as the American Shoulder and Elbow Surgeons Shoulder Score (ASES)[36]; (2) Joint range of motion in flexion and extension, and abduction and adduction; (3) Quality of life, assessed by validated instruments such as the Medical Outcomes Study Short-form 36 (SF-36); (4) Patient or physician evaluated success of treatment; (5) Radiographic progression for patients with shoulder arthritis; (6) Stroke patient disability instruments, including the Barthel Index[37], motor component of the Functional Independence Measure (M-FIM), and/or the Modified Ranking Scale[38].

Assessment of risk of bias in studies. For each included study, 2 authors (JAS, PMF) independently assessed risk of bias against key criteria[39]: random sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by The Cochrane Collaboration[39]. These criteria were labeled as: Yes (low risk of bias); No (high risk of bias); or Unclear (either lack of information or uncertainty over the potential for bias). Different assessments by the 2 authors for risk of bias were resolved by consensus.

Data analyses. We calculated mean differences for continuous outcomes and risk ratios (RR) with corresponding 95% confidence interval (CI) for dichotomous outcomes. Number needed to treat to benefit or harm (NNT) was calculated using the Visual Rx NNT calculator for categorical outcomes[40] and the Wells calculator software for continuous outcomes (available from the Cochrane Musculoskeletal Group). Based on an *a priori* decision, we analyzed arthritis studies separately from the post-stroke studies.

We assessed studies for clinical homogeneity. Outcomes of clinically homogeneous studies were pooled for metaanalysis using the random-effects model to be conservative. We used the I^2 statistic to test statistical heterogeneity[41], as follows: 0–40%, not important heterogeneity; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity.

We present the main results of the review in the summary of findings (see Table 3), with *a priori* chosen outcomes (pain; disability/function; total adverse events; number of withdrawals due to adverse events; serious

adverse events; revision rate), as recommended by The Cochrane Collaboration[42]. The summary of findings includes an overall grading of the evidence related to each of the main outcomes, using the GRADE approach[43].

RESULTS

Description of studies and risk of bias. The search strategy is provided in Appendix 1. The original search (September 2009) identified 160 titles and abstracts (Figure 1). Of the 21 articles that qualified for full-text review, 6 studies met the inclusion criteria; 15 were excluded (Figure 1). An updated search on January 22, 2010, identified another 7 potential studies, but none qualified for full-article review. Therefore, 6 studies were included in this systematic review[44,45,46,47,48,49]. Table 1 describes the key characteristics of the included studies. All were double-blind randomized controlled trials (RCT).

The sample size ranged from 17 patients[45] to 43 patients[49]. All studies used botulinum toxin type A, a one-time injection (at single or multiple sites), and it was compared to placebo in all studies but one[46], where it was compared to triamcinolone. Botulinum toxin was injected intramuscularly in patients with spasticity after stroke or hemiplegia in 5 studies[44,45,46,47,48], and intraarticularly in patients with refractory pain due to OA or RA in one study[49]. The preparation was 500 units of Dysport® (Ipsen Inc., Slough, UK) in 3 studies[45,47,48] and 100 units of Botox® (Allergan Pharmaceuticals Inc.) in 3 studies[44,46,49].

The results were described separately based on the underlying condition, that is, shoulder spasticity due to hemiplegia or shoulder arthritis, and by the comparator (placebo vs triamcinolone).

In general, there was medium to high risk of bias across all the included studies due to small sample size and lack of blinding (Table 2). Four studies were partially funded by the makers of botulinum toxin[45,46,48,49].

Summary of findings for spasticity studies: Botulinum toxin compared to placebo. Three of the 5 prespecified outcomes for the summary of findings were not presented in any spasticity study — serious adverse events and withdrawals due to adverse events (Table 3). For most outcomes, data were available from only one study. No heterogeneity was noted between study estimates for the few outcomes where 2 studies provided data.

Pain severity was reduced more significantly in the botulinum toxin group compared to placebo at 12–24 weeks, with 1.2-unit greater reduction in pain severity on a 0–10 scale ($p = 0.02$; Table 3). No difference in number of adverse events was noted between botulinum toxin and placebo groups.

Shoulder spasticity due to hemiplegia: Effect of intramuscular botulinum toxin compared with intramuscular placebo or with intraarticular triamcinolone. In addition to presenting pain and adverse event outcomes in the summary of findings, we analyzed additional outcomes as follows. Four

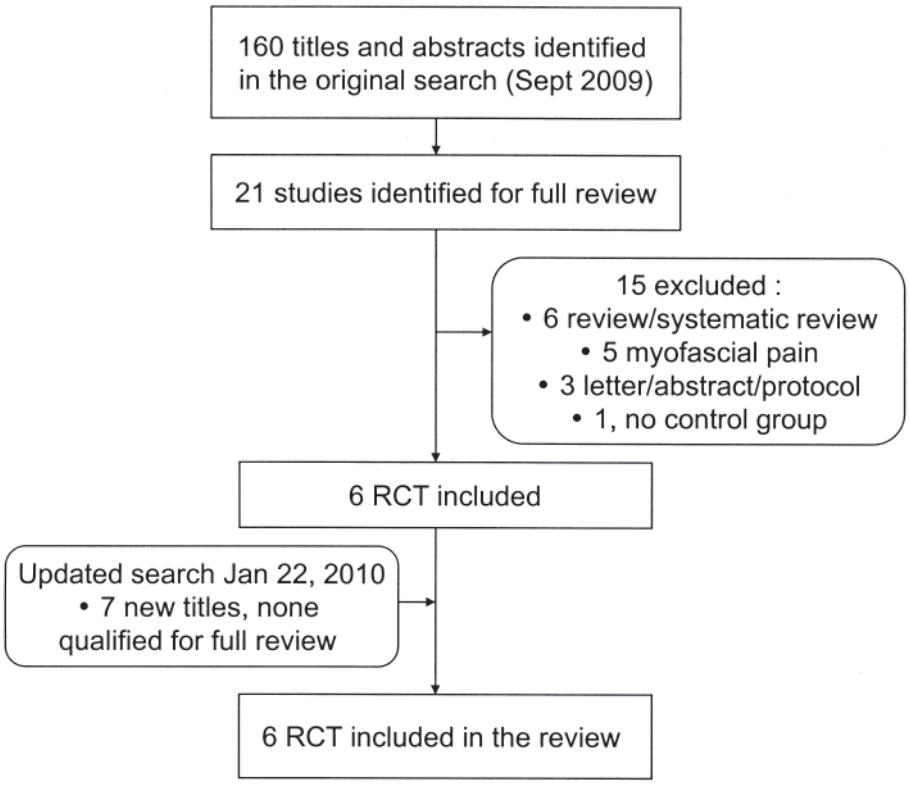

Figure 1. The process of study selection.

Table 1. Characteristics of included studies.

Study	Followup, mo	Intervention/ Comparison	Population	Route	Mean Age, yrs; M/F	Primary Outcome	Secondary Outcomes
De Boer 2008[44]	3	100 units Botox® vs placebo	Post-stroke shoulder spasticity	IM	59; 12/9	Pain VAS, external rotation	—
Kong 2007[45]	3	500 units Dysport™ vs placebo	Post-stroke shoulder spasticity	IM	52; n = 17	Pain VAS	Muscle tone, shoulder abduction
Lim 2008[46]	3	100 units Botox® vs triamcinolone acetonide	Post-stroke shoulder spasticity	IM	61; 15/14	Pain NRS, physician global, shoulder ROM	Spasticity, adverse events, arm function
Marco 2007[47]	6	TENS + 500 units Dysport™ vs TENS + placebo	Post-stroke shoulder spasticity	IM	66; 21/8	Pain VAS	Spasticity, shoulder ROM
Yelnik 2007[48]	1	500 units Dysport™ vs placebo	Post-stroke shoulder spasticity	IM	54 15/5	Pain VAS, spasticity, use of analgesics, ROM, spasticity	—
Singh 2009[49]	1	100 units Botox® vs placebo	OA, RA	IA	71; 35/1	Pain VAS	Dropout, shoulder disability, global scale, quality of life, adverse events

VAS: visual analog scale; NRS: numeric rating scale; IM: intramuscular; IA: intraarticular; OA: osteoarthritis; RA: rheumatoid arthritis. ROM: range of motion.

Table 2. Risk of bias of studies.

Study	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Reporting	Free of Other Bias
De Boer 2008[44]	Unclear	Unclear	Unclear	Unclear	Unclear	Yes
Kong 2007[45]	Yes	No	Unclear	Yes	Unclear	No
Lim 2008[46]	Yes	Yes	Yes	Yes	Unclear	No
Marco 2007[47]	Yes	Yes	Yes	Yes	Unclear	Yes
Yelnik 2007[48]	Yes	Unclear	Unclear	Yes	Unclear	No
Singh 2009[49]	Yes	Yes	Yes	Yes	Yes	No

"Unclear": enough information was not available to make a determination regarding that criterion.

studies provided data comparing botulinum toxin to placebo[44,45,47,48] (Table 4) and one study comparison to triamcinolone injection[46]. The details of each outcome at 4–6 weeks and at 6–12 weeks (as applicable) are provided.

Compared to placebo, pain reduction at 4–6 weeks was not statistically different in the botulinum toxin group (p = 0.22). As noted above, pain reduction at 12–24 weeks was statistically significantly greater in the botulinum toxin group compared to placebo (p = 0.02). The I^2 statistic (measure of heterogeneity) was 76% at 4 to 6 weeks, the timepoint when the difference was not significant; and 0% at the 12 to 24-week endpoint, when the difference was significant. The heterogeneity at 4 to 6 weeks was due to a single study[45] in which the magnitude of change favored placebo; removal of this study reduced the heterogeneity to 0% and the difference between botulinum toxin was statistically significantly in favor of botulinum toxin (mean difference 2.0, 95% CI 1.0–3.5, p = 0.0002). Sensitivity analyses assuming a fixed-effect instead of a random-effects model had no effect on the 6 to 12 week estimate, but made the 4 to 6 week estimate significant, with a mean difference of –0.9 favoring botulinum toxin over placebo (95% CI –1.8 to –0.1, p = 0.03).

Compared to placebo, shoulder external rotation was significantly better in patients who received botulinum toxin, with a difference of 9.8 degrees (95% CI 0.20, 19.5). There were no significant differences in shoulder flexion, abduction, spasticity, or number of adverse events [for botulinum toxin, 9/31 (29%) vs placebo groups, 8/34 (24%)] between groups. Sensitivity analyses using a fixed-effect model did not change estimates or significance for any outcome except shoulder abduction at 4 to 6 weeks, which changed from being insignificant in the random-effects model to being significant in the fixed-effect model (mean difference 9.6, 95% CI 1.6 to 17.5, p = 0.02). The I^2 statistic was 36% at 4 to 6 weeks and 67% at 6 to 12 weeks for shoulder abduction.

One study (25 participants) comparing intramuscular

Table 3. Summary of findings comparing intramuscular botulinum toxin to placebo in patients with shoulder spasticity.

Outcomes	Illustrative Comparative Risks* (95% CI) Assumed Risk Control	Corresponding Risk Intramuscular Botulinum toxin	Relative Effect (95% CI)	No. Participants (studies)	Quality of Evidence (GRADE)	Comments
Pain (0–10 cm VAS or 0–10 VRS at 12–24 wks	Mean pain (0–10 cm VAS): pain at 6–12 wks in control groups was 4.8	Mean pain (0–10 cm VAS): pain at 6–12 wks in intervention groups was 1.22 lower (0.07 to 2.37 lower)	NA	76 (3)	+ + – – Low[1,2]	Absolute risk difference 12% (95% CI 1% to 24%); relative percentage change 25% (95% CI 1% to 49%); NNT benefit = 4 (95% CI 2 to 102)
No. adverse events (followup 4-24 wks)	235 per 1000	343 per 1000 (150 to 790)	RR 1.46 (0.64 to 3.36)	65 (3)	+ + – – Low[1,2]	Absolute risk difference 9% (95% CI –22% to 39%); relative percentage change 46% (95% CI –36% to 226%); NNT harm = not estimable[3]
Disability/function	Not reported in any study	Not reported in any study	Not estimable	—	NA	NA
Withdrawals due to adverse events	Not reported in any study	Not reported in any study	Not estimable	—	NA	NA
Serious adverse events	Not reported in any study	Not reported in any study	Not estimable	—	NA	NA

* The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (95% is based on the assumed risk in the comparison group and the relative effect of the intervention (95% CI). [1] Allocation sequence generation and allocation concealment was not described in some studies. [2] Sample sizes were small for all studies, making estimates liable to error. [3] 95% CI includes both positive and negative numbers, therefore NNT harm is not estimable.

GRADE Working Group grades of evidence: High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important influence on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important influence on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate. RR: risk ratio; NA: not applicable; VAS: visual analog scale; VRS: verbal rating scale; NNT: number needed to treat.

botulinum toxin to intraarticular triamcinolone found no significant differences in pain severity, physician global rating, shoulder range of motion, or muscle spasticity between botulinum toxin and placebo groups[46].

Shoulder arthritis due to OA or RA: Effect of intraarticular botulinum toxin compared to placebo. One study provided data[49]. The efficacy data were presented by joints, and safety data by patient as the unit of analysis. At 1 month, there were significantly greater improvements in VAS pain, patient-reported shoulder disability, active shoulder abduction, Short-Form McGill Pain Questionnaire total, sensory, and affective pain scores in the botulinum toxin group compared with the placebo group (Table 5). There were no significant between-group differences in shoulder flexion, serious events, number of patients with one or more adverse events, or deaths (Table 5).

None of the planned subgroup analyses (route, dose, type of toxin, and underlying diagnosis) could be carried out due to lack of studies.

Summary of warnings from the FDA and other regulatory websites and other outcomes are provided in the published Cochrane review[34].

DISCUSSION

In this study we reviewed 6 small RCT of botulinum toxin in patients with shoulder pain due to hemiplegia (5 RCT) and endstage arthritis (one RCT). In patients with shoulder pain and spasticity after hemiplegia, a single intramuscular injection of botulinum toxin A was associated with statistically significantly greater reduction in pain severity at 3 to 6 months compared to placebo. Significantly greater improvements in shoulder external rotation were noted at 1 month but not at 3 to 6 months. No significant differences were noted in muscle spasticity, shoulder flexion, or shoulder abduction. Adverse events were reported by only 3 studies and were not significantly different between placebo and botulinum toxin.

In patients with endstage arthritis, significant improvements were noted in pain severity, shoulder-related disability, and shoulder abduction in participants receiving a single intraarticular injection of botulinum toxin compared with placebo at 1-month followup. Quality of life improvements were also reported to be significantly greater in the botulinum toxin group. Again, the outcomes were at 1-month followup and the sample size was small.

The improvements in pain severity with botulinum toxin A were not only statistically significant in both patient populations (hemiplegia and arthritis) but also exceeded the threshold for clinically important changes in pain severity of 2 points or a 33% reduction[50]. This is an important observation, since the findings of significant pain relief were replicated by multiple studies, with a similar magnitude of pain

Table 4. Additional outcomes for comparison of intramuscular botulinum toxin to placebo or to triamcinolone in patients with shoulder spasticity.

Outcome	No. Studies	No. Patients	Mean difference or Risk Ratio* (95% CI)
Intramuscular botulinum toxin compared to placebo: outcomes at 4–6 and 12-24 weeks			
Pain (0–10 cm VAS or verbal rating scale)			
At 4–6 wks	4	86	–1.12 (–2.89, 0.66)
At 12–24 wks	3	66	–1.22 (–2.37, –0.07)**
Spasticity on modified Ashworth Scale (0–5; higher = worse)			
At 4–6 wks	2	45	–0.62 (–1.40, 0.17)
At 12–24 wks	2	45	–0.13 (–0.65, 0.38)
Passive shoulder flexion (0–180; higher = better function)	1		
At 4–6 wks	1	29	3.00 (–15.54, 21.54)
At 12–24 wks	1	29	1.00 (–17.87, 19.87)
Passive shoulder abduction (0–180; higher = better function)			
At 4–6 wks	3	65	8.49 (–2.40, 19.39)
At 12–24 wks	2	45	17.72 (–9.61, 45.04)
Shoulder external rotation (0–180; higher = better function)			
At 4–6 wks	3	70	9.84 (0.20, 19.49)**
At 12–24 wks	2	50	11.86 (–0.61, 24.33)
No. adverse events	3	65	1.46 (0.64, 3.36)
At 4–6 wks	1	20	3.00 (0.37, 24.17)
At 12–24 wks	2	45	0.84 (0.10, 7.10)
Intramuscular botulinum toxin compared to triamcinolone: outcomes at 12 weeks			
Change in pain on 0–10 numeric rating scale (higher = more pain)	1	29	1.70 (–0.08, 3.48)
Change in physician global rating scale (0–4; 4 = maximum improvement)	1	29	0.00 (–0.72, 0.72)
Change in passive shoulder flexion (0–180; higher = better function)	1	29	8.30 (–4.06, 20.66)
Change in passive shoulder abduction (0–180; higher = better function)	1	29	5.60 (–6.05, 17.25)
Change in passive shoulder external rotation (0–90; higher = better)	1	29	7.90 (–5.30, 21.10)
Change in passive shoulder internal rotation (0–90; higher = better)	1	29	9.30 (–0.36, 18.96)
Change in spasticity on modified Ashworth Scale (0–5; higher = worse)	1	29	–0.20 (–1.00, 0.60)

* All numbers are mean differences except number of adverse events for which risk ratio is presented. ** Significant with $p < 0.03$ for all. VAS: visual analog scale.

Table 5. Intraarticular botulinum toxin compared to placebo in patients with arthritis: outcomes at 4 weeks.

Outcome	No. Studies	No. Patients	Mean difference or Risk Ratio* (95% CI)
Pain on visual analog scale (0–10 cm; higher = worse pain)	1	36	–2.00 (–3.71, –0.29)**
SPADI disability subscale score (0–100; higher = worse function)	1	36	–13.40 (–24.93, –1.87)**
SPADI pain subscale score (0–100; higher = worse pain)	1	36	–9.10 (–20.33, 2.13)
Active shoulder flexion (0–180; higher = better function)	1	36	13.80 (–9.21, 36.81)
Active shoulder abduction (0–180; higher = better function)	1	36	23.60 (3.25, 43.95)**
McGill total pain score (0–45; higher = worse pain)	1	36	–7.20 (–13.06, –1.34)
McGill sensory dimension pain (0–33; higher = worse)	1	36	–4.50 (–8.96, – 0.04)
McGill affective dimension pain (0–12; higher = worse pain)	1	36	–2.70 (–4.39, –1.01)
Serious adverse events	1	36	0.35 (0.11, 1.12)
No. patients with 1 or more serious adverse events	1	36	0.79 (0.20, 3.10)
Death	1	36	Not estimable†

* All numbers are mean differences except number of adverse events for which risk ratio is presented. ** Significant with $p \leq 0.02$ for all. Differences are significant when 95% confidence interval for the mean difference does not include 0 and 95% confidence interval for the relative risk does not include 1. No patient in either group died. SPADI: Shoulder Pain and Disability Index.

reduction, and findings were consistent across 2 disease conditions (hemiplegia and arthritis). The route of administration differed between the 2 conditions, intramuscular for hemiplegia and intraarticular for arthritis. The pain reduction at 1 month in the hemiplegia group did not achieve statistical significance, primarily due to one study that reported an effect in the opposite direction favoring placebo[45], which led to high heterogeneity; effects became statistically

significant when this study was excluded. The magnitude of effect (mean difference of –1.1 points from placebo on a 0 to 10 pain scale) was similar to the –1.3-point difference noted at 3 to 6 months. There was greater heterogeneity (I^2 = 68%) at 1 month compared to that noted at 3 to 6 months in the hemiplegia group (I^2 = 0%); when the single study leading to heterogeneity was removed, I^2 was reduced to 0% at 4–6 weeks and the difference in pain severity became statistically significant. In conjunction with the absence of a statistically significant improvement in spasticity in these studies, this observation supports the notion that the antinociceptive action of botulinum toxin type A is likely to be independent of its muscle spasmolytic action, as discussed in detail in the introduction section of this report.

The antinociceptive action of botulinum toxin A for shoulder pain noted in this review is very similar to the antinociceptive action of botulinum toxin A noted for neck pain in patients with torticollis (or "wry neck")[51]. Other studies of botulinum toxin have demonstrated a potential antinociceptive action in patients with migraine and tension headaches[27], myofascial and back pain[28,29,52], and chronic tennis elbow[29,52].

Our study has several limitations. Most studies were small and were performed at tertiary medical centers, raising issues of generalizability. The strength of evidence synthesis is limited by the quality of the included studies, some of which were not of the highest quality. More evidence is needed from large multicenter studies to confirm these findings. Our review is limited to published data and therefore we may have overlooked unpublished data showing absence of effect. In studies of patients with hemiplegia, patients had both spasticity and pain in the shoulder and the findings may be applicable only to hemiplegic patients with both spasticity and pain. Only a single injection of botulinum toxin A was tested in these studies; it is unknown if different dosing schedules may have had better efficacy. The duration of pain relief following a single injection is unknown with the current evidence. Three studies were partially supported by pharmaceutical company funding and the authors of one study had received grants from these companies in the past.

Our study has several strengths including a published protocol, use of standard methodology for performing systematic review, and duplicate abstraction of data up to January 2010.

Shoulder pain is a common medical problem in the general population, with very few effective treatment options. This review summarizes data from 5 RCT of shoulder pain associated with shoulder spasticity after stroke and one RCT of patients with endstage shoulder arthritis pain. The interpretation of these findings is limited because it is based on few studies with small sample sizes and moderate to high risks of bias. A single intramuscular or intraarticular injection of botulinum toxin A decreased shoulder pain severity in the short term postinjection, with no significant decrease in spasticity. However, studies included in this systematic review were of small sample size and of mediocre quality. Large-scale multicenter RCT are needed to confirm these findings and to assess safety. Botulinum toxin A is not approved by the FDA for use in post-stroke or arthritis shoulder pain. Future studies should confirm these findings in a larger sample and test different dosages and schedules to determine the schedule or dose that is most effective and safe.

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APPENDIX The search strategy.

Ovid MEDLINE® In-Process and Other Non-Indexed Citations and Ovid MEDLINE®
1. Shoulder Pain/
2. Shoulder Impingement Syndrome/
3. Rotator Cuff/
4. exp Bursitis/
5. Shoulder/
6. Shoulder Joint/
7. exp Pain/
8. (5 or 6) and 7
9. ((should$ or rotator cuff) adj5 (bursitis or frozen or impinge$ or tend?nitis or pain$)).tw.
10. or/1-4,8-9
11. exp Botulinum Toxins/
12. botulin$.tw.
13. botox.tw.
14. OnabotulinumtoxinA.tw.
15. RimabotulinumtoxinB.tw.
16. AbobotulinumtoxinA.tw.
17. BTXA.tw.
18. dyslor.tw.
19. dysport.tw.
20. lanzox.tw.
21. myobloc.tw.
22. neurobloc.tw.
23. oculinum.tw.
24. prosigne.tw.
25. vistabel.tw.
26. vistabex.tw.
27. xeomin.tw.
28. or/11-27
29. 10 and 28

EMBASE
1. Shoulder Pain/
2. Shoulder Impingement Syndrome/
3. rotator cuff/
4. Bursitis/
5. shoulder/
6. exp Pain/
7. 5 and 6
8. ((should$ or rotator cuff) adj5 (bursitis or frozen or impinge$ or tend?nitis or pain$)).tw.
9. or/1-4,7-8

10. exp botulinum toxin/
11. botulinum toxin E/ or botulinum toxin B/ or botulinum toxin A/ or botulinum toxin F/
12. botulin$.tw.
13. botox.tw.
14. OnabotulinumtoxinA.tw.
15. RimabotulinumtoxinB.tw.
16. AbobotulinumtoxinA.tw.
17. BTXA.tw.
18. dyslor.tw.
19. dysport.tw.
20. lanzox.tw.
21. myobloc.tw.
22. neurobloc.tw.
23. oculinum.tw.
24. prosigne.tw.
25. vistabel.tw.
26. vistabex.tw.
27. xeomin.tw.
28. or/10-27
29. 9 and 28

The Cochrane Library
#1 MeSH descriptor Shoulder Pain explode all trees
#2 MeSH descriptor Shoulder Impingement Syndrome explode all trees
#3 MeSH descriptor Rotator Cuff explode all trees
#4 MeSH descriptor Bursitis explode all trees
#5 MeSH descriptor Shoulder explode all trees
#6 MeSH descriptor Shoulder Joint explode all trees
#7 MeSH descriptor Pain explode all trees
#8 ((#5 OR #6) AND #7)
#9 ((should* or rotator cuff) Near/5 (bursitis or frozen or impinge* or tendinitis or pain*)):ti,ab
#10 (#1 OR #2 OR #3 OR #4 OR #8 OR #9)
#11 MeSH descriptor Botulinum Toxins explode all trees
#12 botulin*:ti,ab
#13 botox:ti,ab
#14 OnabotulinumtoxinA:ti,ab
#15 RimabotulinumtoxinB:ti,ab
#16 AbobotulinumtoxinA:ti,ab
#17 BTXA:ti,ab
#18 dyslor:ti,ab
#19 dysport:ti,ab
#20 lanzox:ti,ab
#21 myobloc:ti,ab
#22 neurobloc:ti,ab
#23 oculinum:ti,ab
#24 prosigne:ti,ab
#25 vistabel:ti,ab
#26 vistabex:ti,ab
#27 xeomin:ti,ab
#28 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27)
#29 (#10 AND #28)

CINAHL
S28 S12 and S27
S27 S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26
S26 ti vistabex or ab vistabex
S25 ti vistabel or ab vistabel
S24 ti prosigne or ab prosigne
S23 ti oculinum or ab oculinum
S22 ti neurobloc or ab neurobloc
S21 ti lanzox or ab lanzox
S20 ti myobloc or ab myobloc
S19 ti dyslor or ab dyslor
S18 ti dysport or ab dysport
S17 ti OnabotulinumtoxinA or ab OnabotulinumtoxinA or ti RimabotulinumtoxinB or ab RimabotulinumtoxinB or ti AbobotulinumtoxinA or ab AbobotulinumtoxinA
S16 ti BTXA or ab BTXA
S15 ti botox or ab botox
S14 ti botulin* or ab botulin*
S13 (MH "Botulinum Toxins") Search
S12 S1 or S2 or S3 or S4 or S9 or S10 or S11
S11 TI rotator cuff N5 bursitis or AB rotator cuff N5 bursitis or TI rotator cuff N5 frozen or AB rotator cuff N5 frozen or TI rotator cuff N5 impinge* or AB rotator cuff N5 impinge* or TI rotator cuff N5 tendonitis or AB rotator cuff N5 tendonitis or TI rotator cuff N5 tendinitis or AB rotator cuff N5 tendinitis or TI rotator cuff N5 pain* or AB rotator cuff N5 pain* Search modes
S10 TI should* N5 bursitis or AB should* N5 bursitis or TI should* N5 frozen or AB should* N5 frozen or TI should* N5 impinge* or AB should* N5 impinge* or TI should* N5 tendonitis or AB should* N5 tendonitis or TI should* N5 tendinitis or AB should* N5 tendinitis or TI should* N5 pain* or AB should* N5 pain*
S9 S7 and S8
S8 S5 or S6
S7 (MH "Pain+")
S6 (MH "Shoulder Joint+")
S5 (MH "Shoulder")
S4 (MH "Bursitis+")
S3 (MH "Rotator Cuff+")
S2 (MH "Shoulder Impingement Syndrome")
S1 (MH "Shoulder Pain")

Web of Science
#3 #2 AND #1
#2 Topic=(botulin* or botox or OnabotulinumtoxinA or RimabotulinumtoxinB or AbobotulinumtoxinA or BTXA or dyslor or dysport or lanzox or myobloc or neurobloc or oculinum or prosigne or vistabel or vistabex or xeomin)
#1 Topic=(shoulder* AND (pain* or frozen or impinge* or tendonitis or tendinitis or bursitis)) OR Topic=(rotator cuff)

Dissertation Abstracts
Shoulder* or rotator cuff in citation and abstract
AND (botulin* or botox or OnabotulinumtoxinA or RimabotulinumtoxinB or AbobotulinumtoxinA or BTXA or dyslor or dysport or lanzox or myobloc or neurobloc or oculinum or prosigne or vistabel or vistabex or xeomin) in in citation and abstract

Current Controlled Trials
Search 1 botox and shoulder*
Search 2 botox and rotator cuff
Search 3 botulin* and shoulder*
Search 3 BTXA
Search 4 dyslor
Search 5 dysport
Search 6 lanzox
Search 7 neurobloc
Search 8 oculinum
Search 9 prosigne
Search 10 vistabel
Search 11 vistabex

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