Review

Botulinum Toxin Intramuscular Injections for Neck Pain: A Systematic Review and Metaanalysis

PIERRE LANGEVIN, JANET LOWCOCK, JEFFREY WEBER, MAY NOLAN, ANITA R. GROSS, PAUL M. PELOSO, JOHN ROBERTS, NADINE GRAHAM, CHARLES H. GOLDSMITH, STEPHEN J. BURNIE, and TED HAINES; for the Cervical Overview Group

ABSTRACT. ***Objective.*** To assess the effect of intramuscular botulinum toxin type A (BoNT-A) injections on pain, function/disability, global perceived effect, and quality of life (QOL) in adults with neck pain (NP).

Methods. We searched Central, Medline, and Embase databases up to June 2010. A minimum of 2 authors independently selected articles, abstracted data, and assessed risk of bias and clinical applicability. We estimated standard mean differences (SMD) with 95% CI, relative risks (RR), and performed metaanalyses (SMD_p) using a random-effects model for nonheterogeneous data. The approach of the Grading of Recommendations Assessment, Development, and Evaluation working group summarizes the quality of evidence.

Results. We selected 14 trials. High-quality evidence suggested BoNT-A was no better than saline at 4 weeks [4 trials/183 participants; SMD_p –0.21 (95% CI –0.50 to 0.07)] and 6 months for chronic NP. Moderate-quality evidence showed a similar effect for subacute/chronic whiplash-associated disorder (WAD) on pain [4 trials/122 participants; SMD_p –0.21 (95% CI –0.57 to 0.15)], disability, and QOL. Very low-quality evidence indicated BoNT-A combined with exercise and analgesics was not significant for chronic NP reduction at 4 weeks [3 trials/114 participants; SMD_p –0.08 (95% CI –0.45 to 0.29)] but was at 6 months [2 trials/43 participants; SMD_p –0.66 (95% CI –1.29 to –0.04)].

Conclusion. Current evidence does not confirm a clinically or statistically significant benefit of BoNT-A used alone on chronic NP in the short term or on subacute/chronic WAD pain, disability, and QOL. Larger trials, subgroups, and predictors of responses defined *a priori* (to facilitate selection of patients most likely to benefit) and factorial designs to explore BoNT as an adjunct treatment to physiotherapeutic exercise and analgesics are needed. (J Rheumatol First Release Dec 1 2010; doi:10.3899/jrheum.100739)

Key Indexing Terms:
BOTULINUM TOXIN NECK PAIN WHIPLASH-ASSOCIATED DISORDER

Neck disorders are common, disabling, and costly[1,2]. The 12-month prevalence of neck pain (NP) in adults varies from 30% to 50%[2]. Among Saskatchewan adults, 66% reported NP during their lifetime and 5% reported significant disability from NP in the previous 6 months[1]. Conceptually, botulinum toxin (BoNT) should decrease neck pain by reducing excessive muscle spindle activity, inhibiting retrograde neuronal flow to the central nervous system, inhibiting release of neuropeptides by nociceptors[3], and blocking release of acetylcholine by nerve endings, without interfering with neural conduction[4]. A single course of treatment could be expected to last for 3 to 4 months[5].

From the MClSc program, University of Western Ontario, School of Physical Therapy, Faculty of Health Sciences, London; Department of Clinical Epidemiology and Biostatistics, McMaster University; Biostatistics Unit, St. Joseph's Healthcare Hamilton; School of Rehabilitation Science, McMaster University; Department of Clinical Epidemiology and Biostatistics, McMaster University for the Cervical Overview Group (COG), Hamilton; Canadian Memorial Chiropractic College (CMCC), Toronto, Ontario; Departement de Réadaptation, Faculté de Médecine, Université Laval, Québec City, Québec; Department of Physical Therapy, University of Alberta, Edmonton, Alberta; School of Physical Therapy, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada; and Clinical Development Analgesia and Immunology, Merck, Rahway, New Jersey, USA.

Supported by Lifemark Health.

P. Langevin, BSc Physio, MClSc, Professeur de Clinique, Departement de Réadaptation, Faculté de Médecine, Université Laval; J.E. Lowcock, BSc PT, MClSc, Department of Physical Therapy, University of Alberta; J. Weber, BSc PT, MClSc, Clinical Lecturer, Department of Physical Therapy, University of Alberta; M.M. Nolan, BSc Physio, MClSc, Clinical Assistant Professor, School of Physical Therapy, Faculty of Medicine, University of British Columbia; A.R. Gross, MSc, Associate Clinical Professor, School of Rehabilitation Science, McMaster University; P.M. Peloso, MD, MSc, Clinical Development Analgesia and Immunology, Merck; J.P. Roberts, BSc PT, MClSc; N. Graham, MSc, Assistant Clinical Professor, School of Rehabilitation Science, McMaster University; C.H. Goldsmith, PhD, Emeritus Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Senior Biostatistician, Biostatistics Unit, St. Joseph's Healthcare; S.J. Burnie, DC, MSc, Lecturer, CMCC; T. Haines, MD, MSc, Associate Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University for the COG.

Address correspondence to P. Langevin, Cliniques Physio Interactive, 3520 rue de l'Hêtrière, Local 202, St-Augustin-de-Desmaures, Québec G3A 0B4, Canada. E-mail: plangevin@physiointeractive.com

Accepted for publication September 20, 2010.

Our objective was to assess the effect of BoNT intramuscular injections, used alone or with an adjunctive treatment (e.g., physiotherapy, exercise, or additional medication), on pain, function, patient global perceived effect (GPE), and quality of life (QOL) in subacute and chronic NP, including NP accompanied by cervicogenic headache (CGH) and whiplash-associated disorders (WAD), over about 4 weeks (short term) to 6 months (intermediate term).

MATERIALS AND METHODS

Characteristics of included studies. Included studies were randomized controlled trials (RCT) or quasi-RCT of BoNT injections for adults age > 18 years, with NP of any duration (acute, < 30 days; subacute, 30–90 days; chronic, > 90 days) including NP associated with myofascial pain, degenerative changes[6], headache (CGH)[7], WAD grades I–III[8,9], and with[10] or without radiculopathy (lower motor neuron signs)[9,11,12].

Excluded were studies of NP with long tract (upper motor neuron) signs, infection, or inflammation[6], WAD grade IV[9], NP grade IV[8], and noncervical or "mixed" headache types. BoNT could be compared to placebo or another treatment (e.g., ultrasound), or combined with an additional treatment and compared to placebo plus the additional treatment. Outcomes of interest included pain, function/disability, GPE, and QOL measured by patient self-report or performance tests[13,14]. Given the expectation that BoNT efficacy would last 3 to 4 months, the analysis was limited to periods of < 6 months.

Search methods. Search databases included Central (The Cochrane Library 2010, issue 6), Medline, and Embase, from beginning to June 2010, without language restriction. Subject headings (MeSH) and key words included anatomical, disorder or syndrome, treatment, and methodological terms. Additional searches included review of article references, personal files, contacts with identified experts, and meeting abstract searches. Authors were contacted for additional unpublished data.

Data collection. At least 2 authors with differing clinical backgrounds independently selected studies, abstracted data, assessed study quality, and evaluated clinical applicability. Agreement was assessed using the quadratic weighted κ statistic, Cicchetti weights[15]. A third author was consulted in cases of persisting disagreement for all components of data collection. Prepiloted forms were used for all elements of data abstraction, except for the clinical applicability criteria, which were developed for this review based on Cochrane standards[16,17].

Data analysis. Descriptive statistics summarized treatment groups, interventions, outcomes, adverse effects, and costs, and used intention-to-treat (ITT) principles. Standard mean differences (SMD) with 95% CI were calculated for continuous data, to accommodate the different outcome measures used. Effect sizes were calculated for continuous outcomes reporting medians[18]. The minimum clinically important difference (MCID) was assumed to be 10 on a 100-point pain intensity scale[19], and 7/50 neck disability index units[20]. For dichotomous outcomes, relative risks (RR) were calculated, where RR < 1 represents treatment benefit. When data were not extractable and contacted authors did not respond, we used the statistical significance reported in the original study. Data imputation may have been performed. The number needed to treat and the treatment advantage were calculated to indicate the magnitude of treatment effect[21] (Table 1).

Assessment of heterogeneity and subgroup analysis. Studies were assessed for heterogeneity prior to combination in metaanalysis, first by consideration of clinical features (symptom duration, NP subtype, intervention and treatment application, and outcome measures) and then by statistical methods (chi-squared test for trend, $p > 0.10$, $I^2 < 40\%$). Results were calculated as pooled SMD (SMD_p) or RR using a random-effects model.

Methodological quality assessment. The inherent trial validity was assessed through risk of bias (ROB) evaluations using the updated Cochrane criteria[22], and an interprofessional team. The results reported in Table 2 represent group consensus. Studies scoring ≥ 6/12 were deemed to have high validity as assessed by a low ROB. The influences of ROB, duration of pain, and subtypes of NP (WAD, non-WAD, headache, myofascial pain) were assessed by subgroup analysis.

The overall quality of the summarized evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation working group approach, as recommended by Cochrane[16,22] (Table 1).

RESULTS

Description of studies. Table 3 represents the 14 trials selected of 147 eligible trials (estimated $\kappa = 0.84$, 95% CI 0.75 to 0.94). Only botulinum toxin type A (BoNT-A) was used in the included studies. No trial included neck pain subjects with radicular findings. Of the 8 trials for chronic myofascial NP[23,24,25,26,27,28,29,30], 1 did not have extractable data[30]. There was 1 study of chronic CGH[31], 3 studies of subacute and chronic WAD grade I or II[32,33,34], 1 study of WAD and chronic CGH[35], and 1 study combining chronic WAD and non-WAD[36].

The following comparisons were made to BoNT-A: saline in 11 trials[23,25,26,28,29,31,32,33,34,35,36], dry needling and lidocaine in 1 trial[27], lidocaine in 2 trials[24,27], and ultrasound, stretching and lidocaine in 1 trial[24].

Cointerventions included exercise[24,27], physiotherapy and medications[25,28,32], hot packs and massage[31], and additional prescription medications[25].

Two studies used a crossover design with BoNT-A/saline[23,29].

The timeframe of interest meant that data were abstracted from the first period in the Ojala (2006)[29] trial and from both periods in Cheshire (1994)[23].

Methodological quality. The ROB assessments showed variation in reviewer agreement for study quality (estimated $\kappa = 0.23$ to 1.00) with disagreement usually secondary to poor trial reporting. Ten high-quality studies scored ≥ 6[23,25,26,28,30,32,33,34,35,36], with 4 studies having a high ROB[24,27,29,31] (Table 2). Methodological weaknesses in multiple trials included failure to describe or use appropriate randomization (64%, 9/14), improper allocation concealment (57%, 8/14), and ineffective blinding procedures for patients (29%, 4/14), care providers (36% 5/14) and outcome assessors (36% 5/14). Other concerns included dropout rates, inadequate ITT analyses, unexplained baseline differences, and a lack of cointervention standardization across treatment arms. Table 1 summarizes the findings by population, quality of the evidence, and comparison type.

Subacute/chronic NP; BoNT-A vs placebo. High-quality evidence from 4 trials, 183 participants[23,26,28,29], showed no short-term statistically significant difference [SMD_p –0.21 (95% CI –0.50 to 0.07)] for chronic NP (Figure 1).

Low-quality evidence from 1 trial, 24 participants[28], showed no difference up to 6 months for chronic NP.

Very low-quality evidence from 1 trial, 31 participants[29], showed a short-term difference in GPE favoring BoNT-A in chronic NP [SMD –1.12 (95% CI –1.89 to –0.36)].

Table 1. Summary of findings across all outcomes for botulinum toxin type A against a placebo control group or various comparisons. Quality refers to Cochrane Grading of Recommendations Assessment, Development, and Evaluation working group levels of high, moderate, low, or very low.

Study; Disorder Subtype	Quality Assessment: Design* Followup Period	Limitations (Risk of Bias)*	Inconsistency*	Indirectness (Generalizability; Group Size)*	Imprecision (Sparse Data; Group Size)*	Patients, n: Int	Cntl	Summary of Findings: Effect Size (95% CI) or Pooled Effect Size (95% CI)	Clinical Impact, Absolute Benefit, Treatment Advantage, NNT	Quality
1. BoNT-A vs placebo (saline)										
a. Chronic neck pain — short-term followup										
Pain										
Cheshire[23]; chronic MND (MPS)									AB: BoNT-A 13, Pbo –7 TA 30%, NNT 3	
Gobel[26]; chronic MND (MPS, moderate to severe)	RCT-ST	Low	A	A	A	96	93	SMDp –0.21 (95% CI random –0.50 to 0.07)	AB unknown TA 3%	High
Lew[28]; subacute/chronic MND (MPS)									AB: BoNT-A 2.0, Pbo 1.3 TA 6%, NNT 15	
Ojala[29]; chronic MND (MPS)									AB: BoNT-A 1, Pbo 1.2 TA 1%	
Patient global assessment of efficacy										
Ojala[29]; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	15	16	SMD –1.12 (95% CI random –1.89 to –0.36)	AB: NA TA 29%	Very low
b. Chronic neck pain — intermediate-term followup										
Pain										
Lew[28]; subacute/chronic MND (MPS)	RCT-IT	Low	NA	–1	–1	10	14	SMD –0.56 (95% CI random –1.39 to 0.27)	AB: BoNT-A 2.2, Pbo 0.8 TA 19%, NNT 5	Low
Disability										
Wheeler[36]; chronic MND (MPS)	RCT-IT	Low	NA	–1	–1	21	24	SMD 0.43 (95% CI random –0.17 to 1.02)	AB: BoNT-A 14.1, Pbo 15.3 TA –6%, NNT NA	Low
Patient global assessment of efficacy										
Wheeler[36]; chronic MND (MPS)	RCT-IT	Low	NA	–1	–1	21	24	SMD 0.14 (95% CI random –0.45 to 0.72)	AB, TA, and NNT: NA	Low
c. WAD — short-term followup										
Pain										
Braker[32]; WAD subacute									AB: BoNT-A 1.2, Pbo 0.8 TA 7%, NNT 6	
Carroll[33]; subacute WAD I and II	RCT-ST	Low	A	A	–1	64	58	SMDp –0.21 (95% CI random –0.57 to 0.15)	AB: BoNT-A 2, Pbo 2 TA 0%, NNT 115	Moderate
Freund[35]; chronic WAD with CGH									AB: BoNT-A 6.2, Pbo –0.8 TA 44%, NNT 3	
Padberg[34]; chronic WAD I and II									AB: BoNT-A 12.5, Pbo 5.4 TA 11%, NNT 6	
Disability										
Carroll[33]; subacute WAD I and II	RCT-ST	Low	A	–1	–1	34	29	SMDp 0.15 (95% CI random –0.37 to 0.68)	AB: BoNT-A 6, Pbo 9 TA –6%	Low
Freund[35]; chronic WAD with CGH									AB: BoNT-A 2.9, Pbo 1.7 TA 4%	
Patient global assessment of efficacy										
Padberg[34]; chronic WAD I and II	RCT-ST	Low	NA	–1	–1	19	20	Risk ratio 1.05 (95% CI random 0.64 to 1.73)	AB: NA TA – 3%	Low
d. WAD — intermediate-term followup										
Pain										
Braker[32]; WAD subacute	RCT-IT	Low	NA	–1	–1	10	9	SMD –0.79 (95% CI random –1.74 to 0.15)	AB: BoNT-A 3.5, Pbo 0.8 TA 45%, NNT 3	Low
Patient global assessment of efficacy										
Braker[32]; WAD subacute	RCT-IT	Low	NA	–1	–1	10	9	SMD –0.96 (95% CI random –1.91 to 0.01)	AB: NA TA 20%	Low

Low-quality evidence from 1 trial, 45 participants[36], showed no difference at 6 months in disability or GPE for chronic NP.

WAD; BoNT-A vs placebo. Moderate-quality evidence from 4 trials, 122 participants[32,33,34,35], showed no difference up to 4 weeks [SMD_p –0.21 (95% CI –0.57 to 0.15)] and low-

Table 1. Continued.

Study; Disorder Subtype	Quality Assessment: Design* Followup Period	Limitations (Risk of Bias)*	Inconsistency*	Indirectness (Generalizability; Group Size)*	Imprecision (Sparse Data; Group Size)*	Patients, n: Int	Cntl	Summary of Findings: Effect Size (95% CI) or Pooled Effect Size (95% CI)	Clinical Impact, Absolute Benefit, Treatment Advantage, NNT	Quality
e. Cervicogenic headache — short-term followup										
Pain										
Freund[35]; chronic WAD with CGH (100%) Schnider[31]; chronic MND with CGH	RCT-ST	High (–1)	I^2 = 56% (–1)	A	–1	31	27	SMD_p –0.22 (95% CI random –1.02 to 0.58)	AB: BoNT-A 6.2, Pbo –0.8 TA 44%, NNT 3 AB: BoNT-A 10, Pbo 10 TA –1%, NNT 264	Very low
Disability										
Freund[35]; chronic WAD with CGH	RCT-ST	Low	NA	–1	–1	14	12	SMD 0.47 (95% CI random –0.31 to 1.26)	AB: BoNT-A 2.9, Pbo 1.7 TA 4%	Low
f. Cervicogenic headache — intermediate-term followup										
Pain										
Schnider[31]; chronic MND with CGH	RCT-IT	High (–1)	NA	–1	–1	17	15	SMD 0.00 (95% CI random –0.69 to 0.69)	AB: BoNT-A 11, Pbo 9 TA 3%, NNT 21	Very low
2. BoNT-A + exercise/medication vs placebo (saline) and exercise/medication*										
Short-term followup										
Pain										
Braker[32]; subacute WAD									AB: BoNT-A 1.2, Pbo 0.8 TA 7%, NNT 6	
Ferrante[25]; chronic MND (MPS) Lew[28]; subacute/chronic MND (MPS)	RCT-ST	Low	A	–2**	–1	55	59	SMDp –0.08 (95% CI random –0.45 to 0.29)	AB: BoNT-A 16.8, Pbo 10.4 TA 3%, NNT 15 AB: BoNT-A 2, Pbo 1.3 TA 6%, NNT 15	Very low
Intermediate-term followup										
Pain										
Braker[32]; subacute WAD Lew[28]; subacute/chronic MPS	RCT-IT	Low	A	–2**	–1	20	23	SMDp –0.66 (95% CI random –1.29 to –0.04)	AB: BoNT-A 3.5, Pbo 0.8 TA 45%, NNT 3 AB: BoNT-A 2.2, Pbo 0.8 TA 19%	Very low
3. BoNT-A + exercise vs exercise at short term										
Pain										
Esenyel[24]; chronic MND (MPS)	Quasi-RCT-ST	High (–1)	NA	–1	–1	18	18	SMD –0.50 (95% CI random –1.16 to 0.17)	AB: NA TA 7%	Very low
4. BoNT-A + exercise vs dry needling plus exercise at short term										
Pain										
Kamanli[27] vs dry needling; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	9	10	SMD –1.03 (95% CI random –2.01 to –0.06)	AB: BoNT-A 3.4, DNG 1.9 TA 29%, NNT 6	Very low
Disability										
Kamanli[27] vs dry needling; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	9	10	SMD –0.87 (95% CI random –1.82 to 0.09)	AB: BoNT-A 3, DNG 1.7 TA 28%	Very low
Quality of life										
Kamanli[27] vs dry needling; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	9	10	SMD –0.63 (95% CI random –1.56 to 0.30)	AB: BoNT-A 6.4, DNG 2 TA 27%	Very low
5. BoNT-A + exercise versus lidocaine plus exercise at short term										
Pain										
Esenyel[24] vs lidocaine; chronic MND (MPS)	Quasi-RCT or RCT-ST	High (–1)	A	–1	–1	27	28		AB: NA TA –3%	
Kamanli[27] vs lidocaine; chronic MND (MPS)								SMDp 0.35 (95% CI random –0.18 to 0.89)	AB: BoNT-A 3.4, LID 5 TA –16%	Very low

quality evidence from 1 trial, 19 participants[32], demonstrated no difference up to 6 months in pain (Figure 1) or GPE. Low-quality evidence from 2 trials, 63 participants[33,35], showed no difference at 4 weeks for disability associated

Table 1. Continued.

Study; Disorder Subtype	Quality Assessment: Design* Followup Period	Limitations (Risk of Bias)*	Inconsistency*	Indirectness (Generalizability; Group Size)*	Imprecision (Sparse Data; Group Size)*	Patients, n: Int	Cntl	Summary of Findings: Effect Size (95% CI) or Pooled Effect Size (95% CI)	Clinical Impact, Absolute Benefit, Treatment Advantage, NNT	Quality
Disability										
Kamanli[27] vs lidocaine; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	9	10	SMD 0.21 (95% CI random –0.69 to 1.12)	AB: BoNT-A 3, LID 3.1 TA –7%	Very low
Quality of life										
Kamanli[27] vs lidocaine; chronic MND (MPS)	RCT-ST	High (–1)	NA	–1	–1	9	10	SMD 0.71 (95% CI random –0.22 to 1.65)	AB: BoNT-A 6.4, LID 12.1 TA –26%	Very low
6. BoNT-A + exercise vs conventional ultrasound plus exercise at short term										
Pain										
Esenyel[24] vs conventional US; chronic MND (MPS)	Quasi-RCT-ST	High (–1)	NA	–1	–1	18	18	SMD –0.50 (95% CI random –1.17 to 0.16)	AB: NA TA 8%	Very low
7. BoNT-A + exercise vs pain-threshold ultrasound plus exercise at short term										
Esenyel[24] vs pain-threshold US; chronic MND (MPS)	Quasi-RCT-ST	High (–1)	NA	–1	–1	18	18	SMD –1.41 (95% CI random –2.15 to –0.67)	AB: NA TA 23%	Very low

* Domains that may decrease the quality of the evidence are (1) the study design, (2) risk of bias (quality of evidence), (3) inconsistency of results among studies of the same subgroup, (4) indirectness (nongeneralizability), i.e., the extent to which the people, interventions, and outcome measures are similar to those of interest in the subgroup, and (5) imprecision (insufficient data). ** An additional source of bias for the trials on exercise and medication was the lack of standardization and systematic application to all participants. RCT: randomized controlled trial; NA: not applicable or not available; A: adequate; NC: not calculated, data not available; WAD: whiplash-associated disorders; MND: mechanical neck disorder; MPS: myofascial pain syndrome; CGH: cervicogenic headache; Pbo: placebo; BoNT-A: botulinum toxin type A; LID: lidocaine; US: ultrasound; DNG: dry needling group; ST: short term (4 weeks); IT: intermediate term (6 months); I^2: Iganen value; SMDp: standard mean difference pooled; RR: relative risk; AB: absolute benefit (difference between end of study mean and baseline mean in the same scale as the outcome concerned); TA: treatment advantage (positive value = advantage to the treatment group, negative value = advantage to the control group, 0% = no difference between the groups, 100% = maximum advantage for the treatment group, –100% = maximum advantage for the control group); NNT: number needed to treat (the number of patients a clinician needs to achieve a clinically important improvement in one); Int: intervention; Cntl: control.

Table 2. Risk of bias.

Study	Random Adequate (A)	Allocation Concealed (B)	Patient Blind (C)	Care Provider Blind (D)	Assessor Blind (E)	Dropouts (F)	All Analyzed (G)	Selective outcome (H)	Baseline Similar (I)	Cointervention Avoided (J)	Compliance Acceptable (K)	Timing of Outcome (L)	Total
Braker[32]	?	?	+	+	+	+	0	?	?	+	+	+	7
Carroll[33]	+	?	+	+	+	0	?	?	+	?	+	+	7
Cheshire[23]	?	?	+	?	?	+	+	?	+	+	+	+	7
Esenyel[24]	0	0	0	0	0	+	+	?	?	?	?	+	3
Ferrante[25]	+	+	+	+	+	?	+	?	+	+	?	+	9
Freund[35]	+	+	+	+	?	+	0	?	0	?	+	+	7
Gobel[26]	+	+	+	+	+	+	0	?	+	0	0	+	8
Kamanli[27]	?	0	0	0	0	0	+	0	+	?	+	+	4
Lew[28]	+	+	+	+	+	0	0	?	0	?	+	+	7
Ojala[29]	?	?	?	?	?	+	?	?	0	+	+	+	4
Padberg[34]	?	+	+	+	+	+	+	?	+	?	+	+	9
Schnider[31]	?	?	?	?	+	0	?	?	+	+	+	+	5
Wheeler[30]	?	?	+	+	+	0	+	?	0	0	+	+	6
Wheeler[36]	0	+	+	+	+	0	0	?	0	?	+	+	6
Totals, n = 14 (%)	5 (36)	6 (43)	10 (71)	9 (64)	9 (64)	7 (50)	6 (43)	0 (0)	7 (50)	5 (36)	11 (79)	14 (100)	
Weighted κ	0.4731	0.7154	0.7529	0.9412	0.6067	0.2317	0.7200	0	0.2446	0.3069	0.8923	1.0000	

+: yes, item adequately addressed; 0: no, not adequately addressed; and ?: unsure if adequately addressed. A: Was the method of randomization adequate? B: Was the treatment allocation concealed? C: Was the patient blinded to the intervention? D: Was the care provider blinded to the intervention? E: Was the outcome assessor blinded to the intervention? F: Was the dropout rate described and acceptable? G: Were all randomized participants analyzed in the group to which they were allocated? H: Are the reports of the study free of suggestion of selective outcome reporting? I: Were the groups similar at baseline regarding the most important prognostic indicators? J: Were cointerventions avoided or similar? K: Was the compliance acceptable in all groups? L: Was the timing of the outcome assessment similar in all group?

Table 3. Characteristics of included studies and main outcomes.

Author/ Participant	Intervention	Main Outcomes
Braker[32] N(A/R) 19/20 Subacute WAD	BoNT-A vs placebo (saline) Duration treatment: 1 session; duration followup: 24 weeks Cointervention: analgesics (NSAID and paracetamol) and physiotherapy used concurrently	Pain intensity (VAS, 0 to 10) BM (SD): BoNT-A 6 (1), saline 6 (2) ESM (SD) BoNT-A 2.5 (3), saline 5.2 (3.5) AB: BoNT-A 3.5, saline 0.8 Report results: not significant at 3 wks or 24 wks SMD short term –0.15 (95% CI random –1.05 to 0.75) SMD intermediate term –0.79 (95% CI random –1.74 to 0.15) Patient global assessment: ESM (SD): BoNT-A 7.5 (2), saline 5.5 (2) Reported results: not significant SMD –0.96 (95% CI random –1.92 to 0.01)
Carroll[33] N(A/R) 31/37 Subacute WAD I and II	BoNT-A vs placebo (saline) Duration treatment: 1 session; duration followup: 3 mo	Pain intensity (VAS, 0 to 10) BM (SD): BoNT-A 6 (1.70), saline 6 (1.77) ESM (SD): BoNT-A 4 (3.3), saline 4 (3.5) AB: BoNT-A 2, saline 2 Reported results: no significant difference SMD short term 0.00 (95% CI random –0.65 to 0.65) Disability (Vernon-Mior Index, 0 to 50) BM (SD): BoNT-A 32 (?), saline 36.5 (?) ESM (SD): BoNT-A 23 (23.3), saline 25.5 (22.8) AB: BoNT-A 9, saline 11 Reported results: not significant SMD short term –0.07 (95% CI random –0.75 to 0.54)
Cheshire[23] N(A/R) 6/6 Chronic NP (myofascial pain)	BoNT-A vs placebo (saline) Duration treatment: 2 sessions; duration followup: 8 wks	Pain intensity (VAS, 0 to 100) BM (SD): BoNT-A 70 (21.1), saline 62 (18.9) ESM (SD) BoNT-A 65 (15.1), saline 73 (15.1) AB: BoNT-A 5, saline –11 Reported results: no significant difference SMD short term –0.53 (95% CI random –1.69 to 0.63) SD were estimated using the observed effect size and the level of statistical significance reported, under the assumption of no order effect
Esenyel[24] N(A/R) 90/90 Chronic NP (myofascial pain)	BoNT-A (10 U) vs 4 groups: (1) lidocaine 0.5% ml (LID), (2) conventional ultrasound (US), (3) high power pain threshold US (PtUS), (4) stretching exercises (STC). All patients had stretching and home exercises Duration treatment: 1 session; duration followup: 1 mo	Pain intensity (0 absent to 3 severe) BM and ESM: Not reported Reported results: Significant favoring BoNT-A vs PtUS. Not significant for the 3 other groups SMD short term (BoNT-A vs LID) 0.28 (95% CI random –0.38 to 0.93) SMD short term (BoNT-A vs US) –0.50 (95% CI random –1.17 to 0.16) SMD short term (BoNT-A vs PtUS) –1.41 (95% CI random –2.15 to –0.67) SMD short term (BoNT-A vs STC) –0.50 (95% CI random –1.16 to 0.17)
Ferrante[25] N(A/R) 132/132 Chronic NP (myofascial pain)	BoNT-A (10 U, 25 U, 50 U) vs placebo (saline) Duration treatment: 1 session; duration followup: 12 wks Cointervention for all groups: amitriptyline, ibuprofen, acetaminophen, physiotherapy	Pain intensity (VAS, 0 to 100) BM: BoNT-A (10 U) 58.5, BoNT-A (25 U) 63.2, BoNT-A (50 U) 67.8, saline 59.7 ESM: BoNT-A (10 U) 52.2, BoNT-A (25 U) 50.2, BoNT-A (50 U) 51, saline 49.3 AB: BoNT-A (10 U) 6.3, BoNT-A (25 U) 13.0, BoNT-A (50 U) 16.8, saline 10.4 Reported results: Not Significant SMD short term (BoNT-A 10 U vs Pbo) 0.09 (95% CI random –0.39 to 0.57) SMD short term (BoNT-A 25 U vs Pbo) 0.03 (95% CI random –0.44 to 0.50) SMD short term (BoNT-A 50 U vs Pbo) 0.06 (95% CI random –0.43 to 0.54)

with WAD grade II. Additionally, low-quality evidence from 1 trial, 39 participants[34], noted no short-term difference for GPE for chronic WAD grades I or II.

Cervicogenic headache, BoNT-A vs placebo. Very low-quality evidence from 2 trials, 58 participants[35,31], showed no difference for short-term pain and one of the trials, 32 participants[31] also showed no benefit over 6 months of BoNT-A for CGH. The same trial[31] provided low-quality evidence of no difference for CGH-associated disability in the short term.

Combination with exercise and medication. Very low-quality evidence from 3 trials, 114 participants[25,28,32], suggested no difference in the short term for chronic NP or WAD [SMD –0.08, (95% CI –0.45 to 0.29)] when BoNT-A was

Table 3. Continued.

Author/ Participant	Intervention	Main Outcomes
Freund[35] N(A/R) = 26/30 Chronic WAD with CGH	BoNT-A vs placebo (saline) Duration treatment: 1 day; duration followup 4 wks	Pain intensity (combined scores for headache, neck, shoulder, VAS 0 to 100) Baseline median: BoNT-A 16.2, saline 13.3 End of study median: BoNT-A 10, saline 14.1 AB: BoNT-A 2.1, saline –0.8 Reported results: significant improvement from baseline in treatment group but not placebo group; our analysis, however, showed no significant difference between the groups SMD short term: –0.65 (95% CI random –1.45 to 0.14) Disability (Vernon-Mior Index, 0 to 50) End of study median: BoNT-A 18.1, saline 12.0 AB: BoNT-A 2.9, saline 1.7 Reported results: not significant SMD short term: 0.47 (95% CI random –0.31 to 1.26)
Gobel[26] N(A/R) 145/120 Chronic NP (myofascial pain; moderate to severe)	BoNT-A vs placebo (saline) Duration treatment: 1 day; duration followup: 12 wks	Pain intensity (4 point scale: 1 no pain to 4 severe pain) BM (SD): Unknown Mean change from baseline: BoNT-A –19(30%), saline –16(17%) AB: Unknown Reported results: not statistically significant for short term SMD –0.12 (95% CI random –0.48 to 0.24)
Kamanli[27] N(A/R) 29/29 Chronic NP (myofascial pain)	BoNT-A vs dry needling (DNG) BoNT-A vs LID Duration treatment: 1 day; duration followup: 4 wks Cointervention: passive stretch, home exercise, and information on prevention of postural problems given to all groups	Pain intensity (VAS, 0 to 10) BM (SD): BoNT-A 6.1 (1.70), LID 6.9 (1.77), DNG 7.0 (1.77) ESM (SD): BoNT-A 2.7 (1.04), LID 1.9 (1.67), DNG 5.1 (2.94) AB: BoNT-A 3.4, LID 5.0, DNG 1.9 Reported results: significant favoring BoNT-A vs DNG and not statistically significant vs LID SMD short term (BoNT-A vs DNG) –1.03 (95% CI random –2.01 to – 0.06) SMD short term (BoNT-A vs LID) 0.49 (95% CI random –0.42 to 1.41) Disability (VAS, 0 to 10) BM: BoNT-A 5.5, LID 5.1, DNG 6.8 ESM: BoNT-A 2.5, LID 2.0, DNG 5.1 AB: BoNT-A 3.0, LID 3.1, DNG 1.7 Reported results: corrected value not significant for all comparisons SMD short term (BoNT-A vs LID) 0.21 (95% CI –0.69 to 1.12) SMD short term (BoNT-A vs DNG) –0.87 (95% CI –1.82 to 0.09) Quality of life (Nottingham Health Profile, 0 to 38) BM: BoNT-A 16.6, LID 18.5, DNG 16.2 ESM: BoNT-A 10.2, LID 6.4, DNG 14.2 AB: BoNT-A 6.4, LID 12.1, DNG 2.0 Reported results: not significant for all comparisons SMD short term (BoNT-A vs DNG) –0.63 (95% CI random –1.56 to 0.30) SMD short term (BoNT-A vs LID) 0.71 (95% CI random –0.22 to 1.65)
Lew[28] N(A/R) 30/29 Subacute/ Chronic NP (myofascial pain)	BoNT-A vs placebo (saline) Duration treatment: 1 day; duration followup: 6 mo Cointervention: Use of concomitant pain medication and physical therapy was allowed and no instructions were given to subjects to alter their current regimen	Pain intensity (VAS, 0 to 10) BM (SD): BoNT-A 6.06 (2.00), saline 4.77 (1.52) ESM (SD): BoNT-A –2.21 (2.42), saline –0.72 (2.65) AB: BoNT-A 2.21, saline 0.72 Reported results: not statistically significant for short and intermediate terms SMD short term –0.32 (95% CI random –1.10 to 0.47) SMD intermediate term –0.56 (95% CI random –1.39 to 0.27)

combined with exercise/medication versus exercise/medication alone (Figure 1). However, very low-quality evidence from 2 trials, 43 participants[28,32], indicated a difference of 6 months, favoring BoNT-A plus exercise/medication for pain [SMD_p –0.66 (95% CI –1.29 to –0.04)] in subacute or chronic NP or subacute WAD (Figure 1).

Combination with exercise. Very low-quality evidence from 1 trial, 36 participants[24], demonstrated no short-term differ-

Table 3. Continued.

Author/ Participant	Intervention	Main Outcomes
Padberg[34] N(A/R) 40/40 Chronic NP (myofascial pain)	BoNT-A vs placebo (saline) Duration treatment: 1 day; duration followup: 12 wks Cointervention: Analgesics were allowed	Pain intensity (VAS, 0 to 100) BM (SD): BoNT-A 64.5 (14.8), saline 62.1 (20.3) ESM (SD): BoNT-A 52.0 (29.2), saline 56.7 (29.6) AB: BoNT-A 12.5, saline 5.4 Reported results: not significant SMD short term –0.16 (95% CI random –0.78 to 0.46) Global perceived effect: ESM: BoNT-A 11/20, saline 7/20 Reported results: not significant Risk ratio, short term: 1.05 (95% CI random 0.64 to 1.73)
Schnider[31] N(A/R) 32/33 Chronic CGH	BoNT-A plus standardized PT vs placebo (saline) plus standardized PT (massage and hot packs) Duration treatment: 1 session; duration followup: 16 wks	Pain intensity (VAS 0 to 100) BM (SD): BoNT-A 53 (17.0), saline 51 (17.7) ESM (SD): BoNT-A 42 (?), saline 42 (?) AB: BoNT-A 11, saline 9 Reported results: not significant SMD short term 0.16 (95% CI random –0.53 to 0.86) SMD intermediate term 0.00 (95% CI random –0.69 to 0.69)
Wheeler 1998[30] N(A/R) 22/22 Chronic NP +/– NP-R (myofascial)	BoNT-A 50 U vs BoNT-A 100 U Duration treatment: 1 session; duration followup: 4 mo	Neck pain and disability (NPAD 0 to 100) BM: 50 U BoNT-A 54, 100 U BoNT-A 63, saline 65 ESM: Not reported Reported results: not significant Global perceived effect Reported results: not significant
Wheeler 2001[36] N(A/R) 45/50 Chronic NP	BoNT-A vs placebo (saline) Duration treatment: 1 session; duration followup: 16 wks	NPAD 0 to 100 BM (SD): BoNT-A 54.2 (14.8), saline 48.2 (12.0) ESM (SD): BoNT-A 40.1 (16.7), saline 32.9 (16.5) AB: BoNT-A 14.1, saline 15.3 Reported results: not significant SMD intermediate term 0.43 (95% CI random –0.17 to 1.02) Global perceived effect [scale from –4 (100% worse) to +4 (100% better)] ESM (SD): BoNT-A 1.0 (1.4), saline 1.2 (1.5) Reported results: not significant SMD intermediate term 0.14 (95% CI random –0.45 to 0.72)

NP: neck pain; CGH: cervicogenic headache; NP-R: neck pain with radiculopathy; WAD: whiplash-associated disorder; N MPS: myofascial pain syndrome; N(A/R): sample number analyzed/randomized; VAS: visual analog scale; SMD: standard mean difference; NNT: number needed to treat; NR: not reported; Pbo: placebo; BoNT-A: botulinum toxin type A; NSAID: nonsteroidal antiinflammatory drug; U: units; US: ultrasound; PT: physiotherapy; BM: baseline mean; ESM: end of study mean; AB: absolute benefit; NPAD: Neck Pain and Disability Scale.

ence for chronic NP with BoNT-A plus exercise versus exercise alone.

BoNT-A plus exercise versus dry needling/lidocaine plus exercise. Very low-quality evidence from 1 trial, 19 participants[27], showed a short-term difference for pain [SMD –1.03 (95% CI –2.01 to –0.06)] but not for disability or QOL, comparing BoNT-A plus exercise versus dry needling plus exercise, in chronic NP. Very low-quality evidence from 2 trials, 55 participants[24,27], showed no short-term difference in pain [SMD_p 0.35 (95% CI –0.18 to 0.89)] and 1 trial, 19 participants[27], showed no short-term difference in disability or QOL comparing BoNT-A plus exercise with lidocaine plus exercise for chronic NP.

BoNT-A plus exercise versus ultrasound plus exercise. Very low- quality evidence from 1 trial, 36 participants[24], demonstrated no short-term difference for BoNT-A plus exercise versus conventional ultrasound plus exercise for chronic NP. This trial showed a difference between BoNT-A plus exercise compared to pain-threshold ultrasound plus exercise [SMD –1.41 (95% CI –2.15 to –0.67)].

Adverse events. Pooled data from the 14 trials reported an adverse event rate estimated at 30% (109/360 participants treated with BoNT-A). Adverse event reports included transient effects of injection site soreness, shoulder or arm weakness, fatigue, heaviness, numbness, flu-like symptoms, systemic fever, shivering, generalized muscle soreness, vertigo, and headache. For comparison intervention participants, mild adverse events were reported and estimated at 21% (71/343 subjects). Adverse event reporting was poorly done in general across trials. Cost of care was not reported

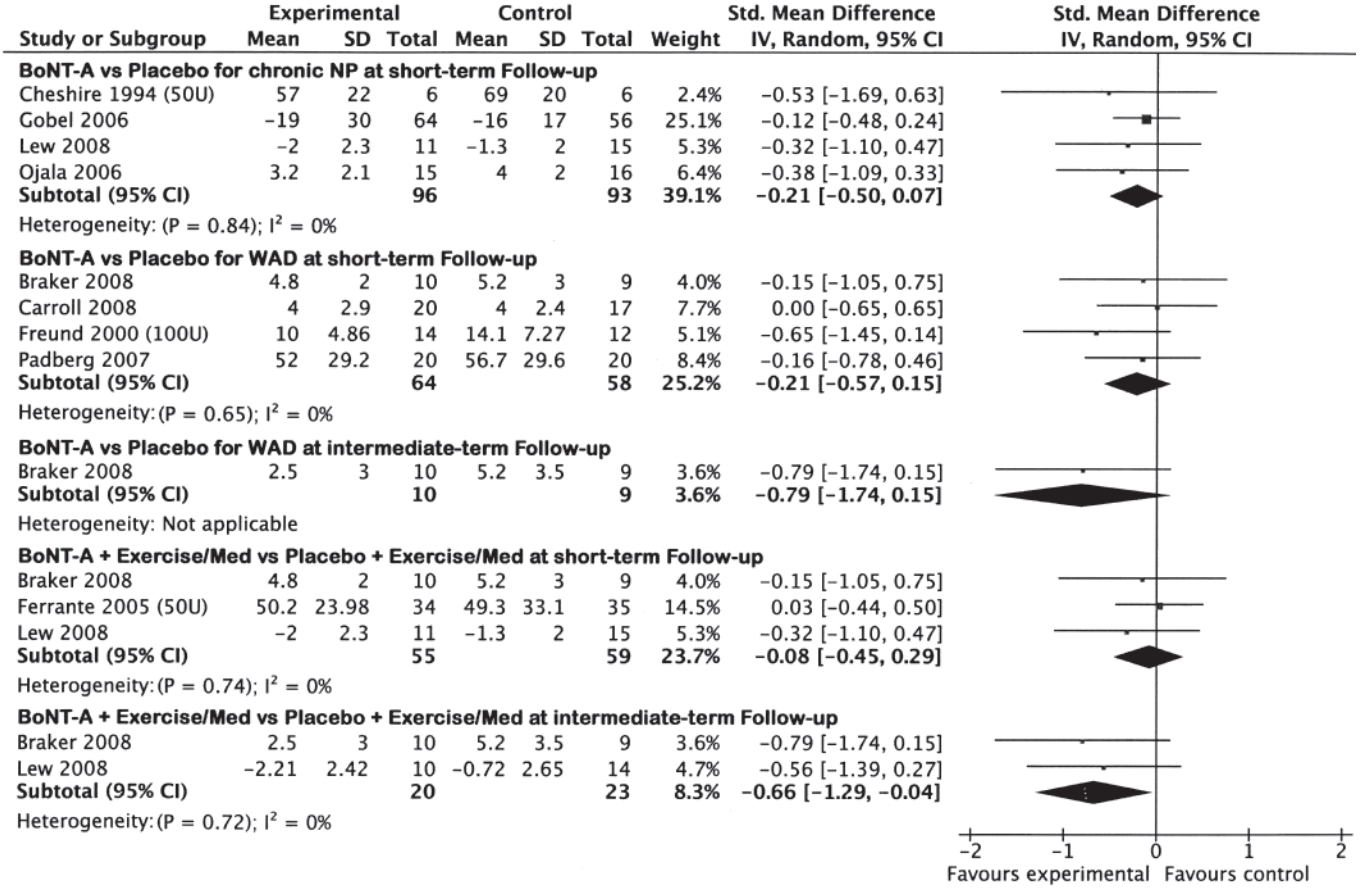

Figure 1. Pain outcomes for botulinum toxin type A (BoNT-A) versus placebo for chronic neck pain (NP) and whiplash-associated disorder (WAD) at short term and intermediate term, with and without adjunctive treatment (exercise, medication). IV: inverse variance.

in most studies. Strategies recommended to reduce costs included single low-dose injections[27] or very restricted patient numbers[29]. A benchmark cost of $335 US per 100 units was noted[37].

Clinical applicability. All studies were assessed to determine whether readers could implement the findings into clinical practice. Six criteria (participant description, interventions, outcomes, relevance, benefits vs harms, timing of evaluation) were developed for this review[16,17]. Considering this, the study population was adequately described in 13/14 studies. One did not detail exclusion criteria, 8 provided sufficient detail for protocol replication, and 6 omitted necessary details of treatment administration or provider training. Twelve studies evaluated outcomes at clinically sensible times, while 2 studies used a 4-week evaluation period, limiting understanding of intermediate-term treatment effects. In 85% of the studies, the treatment effects were rated as not clinically important based on the MCID standards, and in 100% of the studies, the treatment benefits as reported were not considered greater than the potential harms.

DISCUSSION

In a previous review[37] we found moderate evidence of no benefit for BoNT-A over saline for chronic neck pain (7 trials; 270 participants). Since the 2007 publication, data on 7 additional trials, 396 participants, with BoNT-A have been identified. This review found high-quality (4 trials/183 participants)[23,26,28,29] and moderate-quality evidence (4 trials/122 participants)[32,33,34,35] demonstrating a lack of benefit for BoNT-A over saline injections for subacute or chronic NP in the short term. Very low-quality evidence from 2 studies, 143 participants[28,32], showed benefit of BoNT-A plus exercise/medication over placebo plus exercise/medication at 6 months. These results extend the findings of our prior review and suggest that BoNT-A is not effective as a standalone agent in subacute or chronic neck pain. While Colhado, *et al*[4] advocated use of BoNT-A in chronic pain disorders, our data do not support its use as a standalone treatment for chronic neck pain. Our analysis differs from that of Jeynes and Gauci[38], who noted that the Gobel study[26] reported superior pain benefits for BoNT-A versus placebo at 5–8 weeks. However, analysis of earlier and later timepoints shows no significant differences. Given these mixed results, accompanied with a 17% dropout rate, we disagree that "there is level 2A evidence in support of using of BoNT-A in the treatment of myofascial pain"[38]. Our conclusions

are in agreement with the qualitative systematic review of Ho and Tan[39], who concluded that the evidence did not support the use of BoNT-A in myofascial pain syndrome. Interestingly, in low back pain, Chou, *et al*[5] noted positive short-term results (3 weeks) for low back pain and disability, with cessation of benefit after 3–4 months. Additionally, we suggest that whether BoNT-A has utility as an adjunctive agent to exercise requires further study. A review by Lang[40] suggested that BoNT-A, used as part of a multifaceted approach, may improve the results in chronic pain associated with muscle disorders.

Further, our study estimated transient adverse events at a rate of 30%, consistent with reports by Mejia, *et al*[41] (36%), Kessler, *et al*[42] (22%), and Naumann and Jankovic[43] (25%). While BoNT-A appeared generally safe to administer, case reports of allergic reactions, including fatal anaphylaxis, have been reported[5].

Whether there is value in transient effects at 5 to 8 weeks is a point of conjecture[26]. Given the lack of superiority to lidocaine injections, lack of effects earlier and later, as well as costs and transient adverse events, we suggest that BoNT-A is not recommended in the treatment of chronic neck pain, CGH, or WAD. Also, the pharmacological action of BoNT-A is limited to muscle tissue, and does not directly influence the commonly affected articular or neuromeningeal tissues. Given the varied etiologies in the development of "myofascial" pain, it is possible that poor diagnostics contributed to the limited results of the injections.

Limitations of our study. Some limitations are inherent in the primary literature. For instance, we principally considered pain, since there was limited information on disability, GPE, and QOL. Further, it is not clear that an optimal dose, or the dose-response, has been adequately defined for BoNT-A for NP. Finally, there may be some patient subgroups that do respond, although there is not sufficient information on responders and their prediction from the current data. In spite of the increased number of studies since our prior review, the overall sample size is still limited. Our ability to metaanalyze results was restricted by variable trial quality, insufficient subject numbers, and lack of standardization of adjunctive treatments.

Nevertheless, our review has several strengths. Database searches had no language restriction. At least 2 independent reviewers from diverse professional backgrounds selected studies, minimizing both selection and professional bias. Data abstraction and risk of bias assessment were performed independently and final scores represent the group's consensus. We also searched extensively for unpublished work, and contacted authors and known experts to find further studies.

We calculated that an additional 2 studies, each having active and placebo study arms of size, n = 100, with a similar mean and SD to the 4 high-quality pooled studies[23,26,28,29] (6 studies in total) would be needed to show a statistically significant difference from placebo. This result, however, would still fall below established thresholds for clinically important differences from placebo.

Future trials should define responder criteria *a priori* as well as examine predictors of response to facilitate patient selection. While the current evidentiary basis is not methodologically compelling enough to recommend BoNT-A plus exercise or medications in the clinic, there is weak evidence that these combinations could be effective. Therefore future studies should explore the combination of BoNT-A with a cointervention such as exercise[44] and analgesics, where to date limited data suggest a benefit of this combination, to refute or clarify whether BoNT-A might have clinical value. Different designs would be appropriate, such as the use of a 2 × 2 factorial design with double placebo, exercise alone, BoNT-A alone, and the combination. We might even suggest that a BoNT-A-alone arm is not necessary, since it is known to be ineffective versus placebo, based on our findings.

Inclusion criteria should be tightened to ensure that patients have defined trigger points[45] and to reduce the possible confounding factor of age-related degenerative changes in the cervical spine. Collection of outcomes, such as disability and GPE, would help place the pain findings in context. Further, trial reporting must improve, with clear descriptions of randomization, allocation, and blinding procedures, as well as the use of ITT analysis and both qualitative and quantitative analysis of baseline differences and treatment outcomes. Authors should provide sufficient details to allow beneficial interventions to be implemented in the clinic.

BoNT-A intramuscular injections produced pain relief similar to saline for chronic neck pain and for whiplash-associated disorder, as assessed on pain, function, and patient global perceived effect. Consequently, for these populations, we do not recommend use of BoNT-A in the clinic, either alone or combined with any other therapy. Any further investigation of BoNT-A for neck pain should combine BoNT-A with physiotherapy (exercise) and medication in a well constructed design study, as the potential for a positive result would be more likely and could inform clinical practice.

ACKNOWLEDGMENT

We thank the Faculty of the MClSc (Manipulative Therapy) Program, School of Physical Therapy, Faculty of Health Sciences, The University of Western Ontario, London, Ontario, Canada, for their guidance, and Annie Moran and Lina Santaguida for their consultation on this review.

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