Critique author	**Ed Whitney**

Bibliographic Data	
Authors	Marques RE, Duarte GS, et al
Title	Botulinum toxin type B for cervical dystonia.
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Other information if relevant	

Methods	
Aim of study	To compare the effectiveness and safety of botulinum toxin type B (BtB) versus placebo in the treatment of cervical dystonia
Design	Meta-analysis of randomized clinical trials

PICOS	
Population from which participants are drawn	Adults over 18 with a clinical diagnosis by any physician of idiopathic cervical dystonia (trials which also enrolled patients with other forms of dystonia were eligible for inclusion)
Intervention being evaluated	Intramuscular injection of BtB by any technique with or without guidance by EMB or echography
Comparison or control intervention	Placebo injection Injection of different doses of BtB were compared in a subgroup analysis 10,000 U was considered high dose; 5000 units was considered medium dose; 2500 U was considered low dose
Outcomes	Overall improvement on any validated symptom rating scale such as Cervical Dystonia Severity Scale (CDSS) or the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) measure between week 3 and week 6 after the injection TWSTRS scores are a composite of torticollis severity as assessed by an observer (35 points), disability as reported by the patient (30 points), and pain scale (20 points), 0 is the best score and 85 is the worst score

Study types	Randomized parallel group double blind trials of any duration Crossover trials were excluded due to concerns about the appropriateness of these trial designs for the evaluation of cervical dystonia

Study selection	
Search date of literature review	26 October 2015
Databases in literature search	EMBASE, MEDLINE, CENTRAL were the computerized databases; the authors also did some hand searching of international meetings and reference lists of published articles
How authors assessed study quality (risk of bias and other considerations	The core domains of the Cochrane Risk of Bias Tool (randomization sequence generation, allocation concealment, blinding of patients and personnel, blinding of outcome assessment, completeness of followup, and selective outcome reporting were used The authors added one criterion thought to relate to risk of bias: whether the studies used enriched enrollment (such as selecting patients on the basis of their response or their non-response to previous injections with botulinum toxin type A
Additional information if relevant	Because the clinical effect of botulinum toxin injection is readily perceived by the patient, most non-naïve patients are likely to recognize their own treatment group, and the potential for bias among patients who have had prior injections of botulinum toxin were considered to be a potential source of bias whenever studies included primarily non-naïve patients

Results	
Number of studies screened	1450 records screened, 12 full text articles assessed for eligibility
Number of studies selected for analysis of results	4 studies with a total of 441 patients, three of which were published in the 190s (1997, 1999, and 1999) and one which was published in 2013
Whether authors elected to perform meta-analysis to pool study results statistically and type of meta-analysis done (fixed effect or random effects, heterogeneity, etc)	The preferred comparison for meta-analysis was mean difference between groups with respect to improvement in TWSTRS scores. Fixed effect models were used to pool most of these treatment effects. Relative risks were preferred when the outcome was adverse events, and most of these analyses used fixed effect models

Quality of studies as assessed by authors	Only 2 studies adequately described their randomization and allocation methods All were considered at risk of bias for blinding of subjective outcome reporting Only two studies adequately described methods for blinding of objective outcome assessment
Effect sizes reported for primary outcomes (mean differences, standardized mean differences, response ratios, etc)	For improvement in TWSTRS scores from baseline to week 4, BtB was superior to placebo; the difference in improvement was 6.78 points (95% CI 4.54 to 9.01), based on pooled data from three trials The subgroup analyses for TWSTRS improvement did not appear to show differences between low, medium, and high doses of BtB; the improvement for the 10,000 U dose was 8.72 points and for 2500 U the improvement was 6.95 points
Effect sizes reported for additional outcomes (mean differences, standardized mean differences, response ratios, etc)	Withdrawals due to adverse events were rare in both BtB (1.3%) and placebo (1.4%) groups Dry mouth was much more common with BtB (19.6%) than placebo (2.2%) Dysphagia was also much more common with BtB (16.6%) than with placebo (2.2%) Dry mouth was more common with high doses of BtB (29%) than with low doses (1.5%) Dysphagia was more common with high doses of BtB (26.6%) than with low doses (9.2%) Other adverse events were not statistically greater with BtB than placebo for nausea, injection site pain, headache, and infection, but these events were numerically more common with BtB than placebo
Additional information if relevant	Duration of effect was assessed as the time until TWSTRS scores returned to baseline; this appeared to be between 12 and 18 weeks However, in all of the studies, repeat injections were not allowed; only one treatment session was performed

Conclusions	
Key conclusions of study authors	- A single injection of BtB is effective and well-tolerated for patients with cervical torticollis, whether they have or have not responded well to BtA injections - Even though the analysis did not detect a statistical dose-response effect for treatment effects, it should be borne in mind that these were not designed as dose-response studies, and the division into high, medium, and low dose levels was somewhat arbitrary, and adverse events appear to occur more commonly with higher than with lower doses - Dry mouth and dysphagia are common adverse effects, but did not result in study discontinuation - Although the TWSTRS scale is validated for research into cervical dystonia, the minimum clinically important difference (MCID) has not been established, and a new outcome scale with an MCID is being planned for future research - It is uncertain whether the effect of BtB decays over time or with repeated injections
Additional information if relevant	

Comments by DOWC staff

- The status of research into the effectiveness of BtB for cervical dystonia is not clear; no RCTs have been published since the search date for this meta-analysis, and there was a gap of 14 years between the study published in 1999 and the one published in 2013; there appear to be only four blinded parallel group randomized trials of BtB in this setting
- The authors had to impute the standard deviations for TWSTRS improvement for one of the 1999 studies, because the authors of that study did not report them; this probably increases the uncertainty of the effect of BtB for that outcome
- The adverse event "withdrawals due to adverse events" was rare, but it is not clear what this would mean when the treatment intervention is an injection which is done only once at the outset of the trial
- The Cochrane review of BtA (Costa 2005) has not been updated, and that review had 13 studies (5 parallel group and 13 crossover studies); it used only the first period data for the crossover studies in order to avoid potential problems with crossover effects, while this review excluded crossover studies altogether
- The authors reported numbers needed to treat (NNT) for improvement in TWSTRS scores, but NNT is defined in terms of dichotomous variables when the outcome is prevention of one "event" which will or will not occur during the course of the study; NNT for a continuous variable would require some explanation which the authors did not supply
- The subgroup in Analysis 1.23 (the occurrence of dry mouth according to high, medium, or low dose) appears to be dose-related, with a relative risk of 11.47 for high dose and 0.97 for low dose; however, the statistical test for subgroup differences is indeed non-significant
- TWSTRS is a composite of clinician-observed and patient-reported outcome data, and is apparently being replaced with a new outcome measurement tool in the near future; it is important to have a scale with an MCID since the clinical importance of an improvement difference of 6.78 points on an 85 point scale was not clear to the authors
- Because of the suboptimal reporting of outcome data by the authors of the included studies, the overall evidence for the beneficial effect of BtB on cervical dystonia is probably best regarded as "good" rather than "strong"

Assessment by DOWC staff	
Overall assessment as suitability of evidence for the guideline ☒ High quality ☐ Adequate ☐ Inadequate	The systematic review is of high quality, but the included studies are only of adequate quality for the benefits of BtB There is good evidence that a single injection of botulinum toxin type B is more effective than placebo in alleviating the severity and pain of idiopathic cervical dystonia There is good evidence that botulinum toxin type B commonly induces dry mouth and dysphagia, which are reported from 15% to 20% of the time following a single injection The duration of effect of botulinum toxin type B is not certain, but appears to be approximately 12 to 18 weeks

If inadequate, main reasons for recommending that the article not be cited as evidence	

Additional references if relevant
- Costa J, Espirito-Santo CC, et al. Botulinum toxin type A therapy for cervical dystonia (Review). Cochrane Database of Systematic Reviews 2005,Issue 1, Art. No. CD003633.