Original Article

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# Efficacy of botulinum toxin for the management of orofacial pain and dysfunction : A Systematic review and Meta-analysis

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**Objective:** Orofacial pain (OFP) are the conditions that affect quality of life, psychological and socioeconomic status. The treatment goal is to reduce pain and function. The aim of this systematic review and meta-analysis was to determine the efficacy of botulinum toxin (BTX) for reduce pain and restore normal function that compared with placebo, standard treatment, and/or active treatment in orofacial pain (OFP) patients.
**Material and Methods:** Electronic search for randomized controlled trial (RCT) was made until March 2017. Search strategies and study selection was conducted following PRISMA guideline. Publications were assessed for risk-of-bias using the Cochrane Handbook. The outcomes were VAS score, MOA (mouth opening assessment), HD (headache day), and NDI (number of drug pills ingest). STATA was utilized to conduct direct meta-analysis.
**Results:** Eighteen RCT (946 patients) met the inclusion were divided into three groups for pooled outcomes. In group 1, BTX-A subjects had a significantly lower VAS score when compared to the NSS group (pooled WMD= -1.81, 95% CI: -3.23 to - 0.39). In group 2, the BTX-A subjects had significantly lower HD than the NSS subjects (pooled WMD = -1.66 95% CI: -2.64 to -0.69), and a significantly lower NDI than the NSS subjects (pooled WMD = -2.51 95% CI: -4.42 to -0.60). In group 3, we could not analyze the outcome because there were only 2 studies in this group.
**Discussion:** BTX-A subjects showed significant pain relief in group 1, and the BTX-A subjects had significantly lower HD and significantly lower NDI than the NSS subjects in group 2.
**Conclusion:** More rigorous design of trials should be carried out in future study to help the clinicians decisions.

**Keywords:** botulinum toxin, migraine, meta-analysis, myofascial pain, orofacial pain, tension-type headache

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## Introduction

Orofacial pain (OFP) is the pain associated with the hard and soft tissues of the head, face, and neck that affect motor and sensory transmission in the trigeminal nerve system [1]. Orofacial pain and dysfunction (OFD) can be subdivided into several subgroups. Our research classified OFD into three categories, first, musculoskeletal pain disorders (MSD), e.g., myofascial pain (MFP), temporomandibular disorders (TMDs), second, neurovascular pain disorders (NVD), e.g., tension-type headache (TTH), chronic daily headache (CDH), chronic migraine (CM), and third, neuropathic pain disorders (NPD), e.g., trigeminal neuralgia (TN), post-herpetic neuralgia (PHN).

OFD are common and present in many areas of the world. The prevalence of OFP in the population in United Kingdom was 26% [2]. The prevalence of migraine was 20.4-22.1% [3,4]. In Austria 56.5% had episodic headache, 38.3% had chronic headache [5]. Headache disorders

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were common in females [6,7] In summary, OFD, (especially migraine) is likely to be more prevalent in females than males [3,4,7-12]. The study showed that subjects living in Thailand are 1.5 – 4.5 times more likely to suffer from OFP symptoms compared to Finnish subjects [13]. Headache had negative impacts on different aspects of life: education, career and earnings, family, and social life. Each person with headache had lost on average 2.3 days from paid work, and 2.4 days from household work, and missed 1.2 days of social occasions, in the preceding 3 months [14].

The treatment goal is to reduce pain and restore normal function. The most common ways to manage pain included self-education and self-management program. Other treatment is occlusal stabilization [15-17]. Drugs for management OFD are analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, benzodiazepines, muscle relaxants, and low-dose antidepressants [18]. Carbamazepine is the most effective drug for TN, although its initial response is good but its effectiveness drops dramatically after 5 to 16 years of use [19]. Neurectomy, cryotherapy, and alcohol injection are peripheral surgical procedures. Gamma knife surgery are central surgical procedures. Many OFD patients who did not respond to conventional and surgical treatments may try to find alternative medicine approaches which can provide additional relief. These may include acupuncture, meditation, massage therapies, or botulinum toxin (BTX) injection.

In the last ten years, botulinum toxin type A (BTX-A) was the choice for preventive treatment of migraine [20-23]. Although BTX are quite expensive and its effects only last 3-6 months, but some studies indicated that BTX can relieve pain and reduce muscle stiffness, which improve the patients' quality of life. At present, BTX are widely used for treatment OFD but no research has been undertaken to determine the efficacy of BTX for OFD. At present, there are three studies about the efficacy of BTX for prophylactic treatment of migraine and TTH [24], efficacy of BTX-A for the prophylaxis of episodic migraine headaches [25], and the efficacy of BTX for the treatment of trigeminal and post-herpetic neuralgia [26]. Still, there is no study on the efficacy of BTX for OFD and/ or MFP of the face.

Our study was conducted to find out the treatment efficacy of BTX compare to placebo in OFD patients in adult aged 18-80 years. The outcomes measure at baseline and at the end of the study included visual analogue scale (VAS), mouth opening assessment (MOA), headache day (HD), number of drug pills ingest (NDI). The study utilized meta-analysis to benefit those who are still undecided whether to use BTX to treat OFP in the future.

## Materials and methods

### Search strategies and study selection

This study was conducted following PRISMA Guideline [27], and the protocol was registered at PROSPERO (CRD42017056954). PubMed and Scopus databases were used to identify previous meta-analysis studies and randomized controlled trial (RCT) of BTX for OFD, searched up to 17 March 2017. The search terms and strategies were constructed based on the following PICO terms; Patient (P), intervention (I), comparator (C), and outcome (O). (See Appendix 1)

### Inclusion and exclusion criteria

Any RCTs studied in adult-human was included if it met the following criteria: (1) adult patients aged 18-80 years who were diagnosed with MFP, myalgia, arthralgia, disc displacement, TTH, cluster headache, paroxysmal hemicranias, PHN or TN without surgical treatment (the criteria for diagnosis of OFD were defined according to those original studies, which mostly used clinical sign/symptoms recommended by International Headache Society (IHS). (2) comparing any pair of systematic administrations of BTX with active treatment (e.g., TCA, NSAIDs, low-level laser

(LLL), etc.), placebo (e.g., normal saline solution (NSS), and local anesthesia (LA), or standard treatment (routine care, fascial manipulation, traditional method, etc.). Studies were excluded if there was insufficient data for pooling after 3 attempts in contacting authors without the data being provided, or if the data is not published in English

Appendix 1 Search terms and results

Search results from PubMed (Cutoff date 17 March 2017)

| PICO | Search # | Search terms | #Results |
|---|---|---|---|
| P | #1 | myofascial pain | 3047 |
| | #2 | myalgia | 6345 |
| | #3 | arthralgia | 14527 |
| | #4 | “disc displacement” | 17844 |
| | #5 | migraine | 32941 |
| | #6 | headache | 75141 |
| | #7 | “paroxysmal hemicrania” | 403 |
| | #8 | “post herpetic neuralgia” | 720 |
| | #9 | “trigeminal neuralgia” | 7411 |
| | #10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 | 136380 |
| I | #11 | “botulinum toxin” | 11429 |
| | #12 | botox | 2437 |
| | #13 | dysport | 614 |
| | #14 | myobloc | 572 |
| | #15 | onabotulinumtoxin | 93 |
| | #16 | #11 OR #12 OR #13 OR #14 OR #15 | 12823 |
| O | #17 | pain | 681389 |
| | #18 | “range of motion” | 54160 |
| | #19 | “muscle tenderness” | 420 |
| | #20 | “jaw function” | 404 |
| | #6 | headache | 75141 |
| | #21 | #17 OR #18 OR #19 OR #20 OR #6 | 753217 |
| P AND I | #23 | #10 AND #16 | 880 |
| P AND I AND O | #24 | #22 AND #21 | 806 |
| | Limit | AND (English[lang]) | 732 |

| | |
|---|---|
| Pubmed | ((((myofascial pain) OR (myalgia) OR (arthralgia) OR (“disc displacement”) OR (migraine) OR (headache) OR (“paroxysmal hemicrania”) OR (“post herpetic neuralgia”) OR (“trigeminal neuralgia”)) AND ((“botulinum toxin”) OR (botox) OR (dysport) OR (myobloc) OR (onabotulinumtoxin))) AND (((pain) OR (“range of motion”) OR (“muscle tenderness”) OR (“jaw function”) OR (headache)))) AND (English[lang]) |

Search results from Scopus (Cutoff date 17 March 2017)

| PICO | Search # | Search terms | #Results |
|---|---|---|---|
| P | #1 | myofascial pain | 19,489 |
| | #2 | myalgia | 45,751 |
| | #3 | arthralgia | 47,900 |
| | #4 | “disc displacement” | 20,340 |
| | #5 | migraine | 93,089 |
| | #6 | headache | 269,821 |
| | #7 | “paroxysmal hemicrania” | 1,401 |
| | #8 | “post herpetic neuralgia” | 5,315 |
| | #9 | “trigeminal neuralgia” | 16,075 |
| | #10 | #1 OR #2 OR #3 OR #4 OR #5 | 207,485 |
| | #11 | #6 OR #7 OR #8 OR #9 | 285,396 |
| | #12 | #10 OR #11 | 412,097 |
| I | #13 | “botulinum toxin” | 46,766 |
| | #14 | botox | 8,912 |
| | #15 | dysport | 3,262 |
| | #16 | myobloc | 870 |
| | #17 | onabotulinumtoxin | 587 |
| | #18 | #13 OR #14 OR #15 OR #16 OR #17 | 47,762 |
| O | #19 | pain | 1,549,727 |
| | #20 | “range of motion” | 85,101 |
| | #21 | “muscle tenderness” | 2,634 |
| | #22 | “jaw function” | 777 |
| | #23 | headache | 269,821 |
| | #24 | #19 OR #20 OR #21 OR #22 OR #23 | 1,747,667 |
| P AND I | #25 | #12 AND #18 | 6.594 |
| P AND I AND O | #26 | #25 AND #24 | 6,196 |
| | Limit | AND (English[lang]) | 4,933 |

| | |
|---|---|
| Scopus | ((((myofascial pain) OR (myalgia) OR (arthralgia) OR (“disc displacement”) OR (migraine) OR (headache) OR (“paroxysmal hemicrania”) OR (“post herpetic neuralgia”) OR (“trigeminal neuralgia”)) AND ((“botulinum toxin”) OR (botox) OR (dysport) OR (myobloc) OR (onabotulinumtoxin))) AND (((pain) OR (“range of motion”) OR (“muscle tenderness”) OR (“jaw function”) OR (headache)))) AND ( LIMITTO ( SUBJAREA , "MEDI" ) OR LIMIT-TO (SUBJAREA, "DENT" ) ) AND ( LIMITTO ( LANGUAGE , "English" ) ) |

### Interventions

The interventions were BTX-A such as Dysport, Allergan, etc. The comparators could be active treatment, placebo, or standard treatment.

### Outcomes of interest

The outcome measures included 1.) VAS score (0-10 cm or 0-100 mm) with the endpoints “no pain” and “worse imaginable pain” Each treatment and control group measured pain intensity on a continuous scale by using the mean scores at baseline compared at the end of study.; and 2.) MOA (measured when patients open their mouth by using a ruler between the upper and lower central incisors or measured by original studies recorded. Secondary outcomes measure included 1.) HD (number of days with headache per month); and 2.) NDI (number of symptomatic pain medications used). These outcomes could be measured at any time before and after receiving the treatment, for example measured at 1 or 2 weeks, every 1-8 months, or at the end of the study.

### Data extraction

Data extractions were performed independently by the two reviewers (S.S. and T.I.). Characteristics of studies and patients extracted include demographic data e.g., percentage of female subject, mean age of total subject, types of OFD, total number of injected muscle, type and dose of intervention, type and dose of comparators, setting center, country, and follow up weeks of each study. The outcomes such as VAS score, MOA, HD, and NDI were recorded by mean and standard deviation (SD). Data were pooled with continuous outcomes. Any disagreement was resolved by discussion among the reviewers. We divided RCT into three groups for pooled outcomes. Group 1 was MSD group that represented MFP, group 2 was NVD group that represented TTH, CDH, and CM, and group 3 was NPD group that represented PHN and TN.

### Risk of biased assessment

The quality of the included studies was assessed independently by the two reviewers (S.S. and T.I.) as recommended by the Cochrane Collaboration's risk of bias tool [28]. Six domains were assessed including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Each domain was graded as ‘high risk’ and ‘low risk’ if there was evidence of high and low risk of bias, respectively. If there was insufficient information to judge, it was classified as ‘unclear risk’. Disagreements were resolved by consensus and discussion with a third party (S.M.).

### Statistical analysis

STATA was utilized to conduct direct meta-analysis. First, we chose the number of participants (N) in each treatment and control groups, mean differences and SD differences from continuous outcome of interested such as VAS, MOA, HD, and NDI. Next step, unstandardized mean differences (USMD) was used to assessed for differences in efficacy of each outcome, because the outcomes were measured in the same scale. Random-effect model was used if heterogeneity was present. If there are homogeneity in all outcomes, mean difference of the outcomes will be estimated and pooled using the fixed-effect model. To check for heterogeneity, we used the Cochran Q test and quantified the degree of heterogeneity. A meta-regression analysis was done to explore the source of heterogeneity by adding the co-variables (e.g., dose of BTX, and number of muscle) into the model one by one, if the studies reported the co-variables needed. If adding the variable could decrease the between-study variation, or the $I^2$ decreased, this would indicate that added variable may be a source of heterogeneity. A subgroup analysis by this variable was done next. Publication bias was assessed using the Egger’s test and funnel plot [29].

## Results

### Identifying studies

A total of 732 and 4,933 studies were respectively located from Pubmed and Scopus. After 498 duplicates were removed, 5,167 studies were screened on titles or abstracts, and 21 studies were eligible. After reading the full text of those studies, 18 studies remain due to duplicated studies and insufficient data (see Figure 1).

### Characteristics of included studies

The characteristics of these 18 studies [30-47] are described in Table 1.

In MSD group, we divided the number of injected muscles into 2 groups as (≤ 1 muscles versus >1 muscles), and divided the number of injected doses into 2 groups as (< 100 Mu versus ≥ 100 Mu). In NVD group, we divided the number of injected muscles into 2 groups as (≤ 3 muscles versus > 3 muscles), and divided the number of injected doses into 2 groups as (< 100 Mu versus ≥ 100 Mu), respectively.*Risk of bias assessment* The quality of the included studies was assessed by the Cochrane Collaboration's risk of bias tool shown in Table 2.

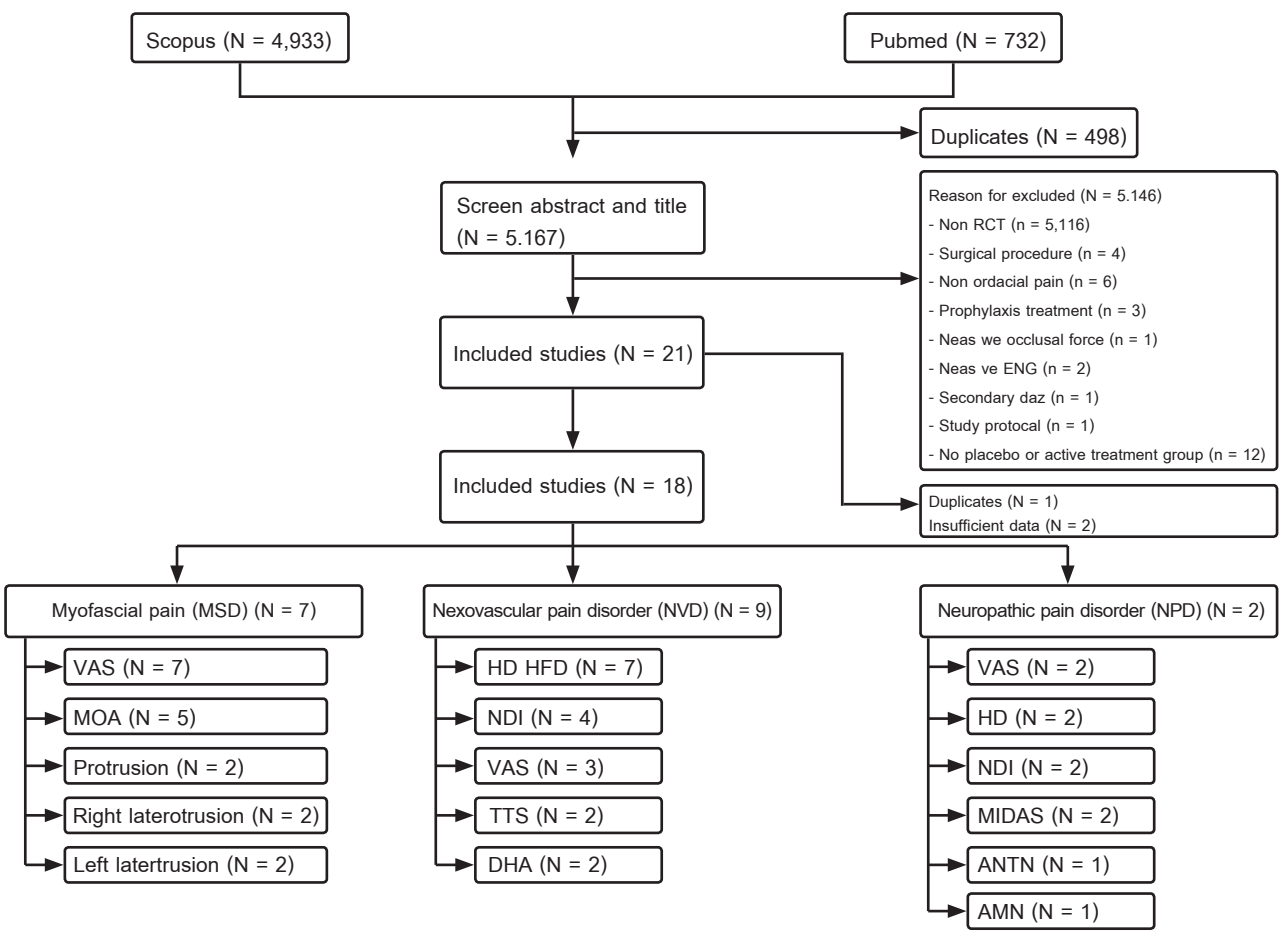


Figure 1 Flow Chart of the Study Selection

Table 1 Characteristics of included RCTs

| Author | Year | Type of OFD | Mean age±SD | % of female | Intervention | Dose of BTX (Mu) | Comparator | Dose of comparator | Number of injected muscles | Setting (center) | Country | F/U (Wks) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Rollnik JD [40] | 2000 | NVD | 37.4±14.1 | 61.9 | BTX-A | 200 | NSS | 1 ml | 3 | Single | Germany | 12 |
| Schmitt WJ [41] | 2001 | NVD | 46.4±15.6 | 61.02 | BTX-A | 20 | NSS | 0.4 ml | 2 | Single | Switzerland | 8 |
| Nixdorf DR [37] | 2002 | MSD | 33±N/A | 100 | BTX-A | 75 | NSS | N/A | 2 | Single/crossover | Canada | 8 |
| Von Lindern JJ [47] | 2003 | MSD | N/A | N/A | BTX-A | 35 | NSS | 0.7 ml | 3 | Single | Germany | 4 |
| Ondo WG [38] | 2004 | NVD | 47±11 | 81.67 | BTX-A | 200 | NSS | N/A | 2 | Single | USA | 12 |
| Padberg M [39] | 2004 | NVD | 44.5±N/A | 70 | BTX-A | 100 | NSS | 2 ml | 7 | Single | Netherlands | 12 |
| Schulte-Mattler WJ [42] | 2004 | NVD | 45.5±14 | 45.79 | BTX-A | 200 | NSS | 5 ml | 7 | Multi | Germany | 6 |
| Freitag FG [33] | 2008 | NVD | 42.3±N/A | 73.17 | BTX-A | 100 | NSS | N/A | 5 | Single | USA | 16 |
| Guarda-Nardini L [34] | 2008 | MSD | N/A | 50 | BTX-A | 100 | NSS | N/A | 2 | Single | Italy | 24 |
| Straube A [44] | 2008 | NVD | 41.75±N/A | 55.08 | BTX-A | 210 and 420 | NSS | 2.1 ml | 5 | Multi | Germany | 12 |
| Magalhaes E [36] | 2010 | NVD | 34±10 | 97.22 | BTX-A | 250 | amitriptyline | 25-50 mg/day | 5 | Single | Brazil | 12 |
| Xiao L [46] | 2010 | 8 | 67.33±13.9 | 53.33 | BTX-A | <200 | NSS and Lidocaine | <40 ml | N/A | Single | China | 12 |
| Ernberg M [32] | 2011 | MSD | 38±12 | 90.5 | BTX-A | 100 | NSS | 1 ml | 1 | Single/crossover | Sweden | 12 |
| Guarda-Nardini L [35] | 2012 | MSD | 45.45±14.1 | 73.33 | BTX-A | 150 | Fascial manipulation | N/A | 2 | Single | Italy | 12 |
| Wu CJ [45] | 2012 | NPD | 58.6±14.62 | 54.76 | BTX-A | 75 | NSS | 1.5 ml | N/A | Single | China | 12 |
| Song JH [43] | 2015 | NVD | 36.9±8.05 | 71.43 | BTX-A | N/A | Nimodipine and infrared polarized light | 30 mg | 2 | Single | China | 24 |
| De Carli BMG [31] | 2016 | MSD | 38±N/A | 86.67 | BTX-A | 500 | low level laser GaAlAs | N/A | 2 | Single | Brazil | 4 |
| Al-Wayli H [30] | 2017 | MSD | 45.5±10.8 | 100 | BTX-A | 20 | Traditional method | N/A | 1 | Single | Saudi Arabia | 48* |

*Pick up data at 8 weeks

Table 2 Risk of Bias Assessment

| Author | Year | Random sequence generation | Allocation concealment | Blinding of participant and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective outcome reporting | Other bias |
|---|---|---|---|---|---|---|---|---|
| Rollnik JD [40] | 2000 | unclear | unclear | low | low | unclear | low | unclear |
| Schmitt WJ [41] | 2001 | low | unclear | low | low | low | low | unclear |
| Nixdorf DR [37] | 2002 | low | unclear | low | low | high | low | unclear |
| Von Lindern JJ [47] | 2003 | unclear | unclear | unclear | unclear | high | low | unclear |
| Ondo WG [38] | 2004 | high | unclear | low | low | low | low | unclear |
| Padberg M [39] | 2004 | unclear | low | low | low | low | low | unclear |
| Schulte-Mattler WJ [42] | 2004 | low | unclear | unclear | unclear | unclear | low | unclear |
| Freitag FG [33] | 2008 | unclear | unclear | low | low | low | low | unclear |
| Guarda-Nardini L [34] | 2008 | unclear | unclear | unclear | unclear | low | low | unclear |
| Straube A [44] | 2008 | high risk | unclear | low | low | low | low | unclear |
| Magalhaes E [36] | 2010 | low | unclear | high | high | unclear | low | unclear |
| Xiao L [46] | 2010 | high | unclear | low | low | low | low | unclear |
| Ernberg M [32] | 2011 | low | low | low | low | low | low | unclear |
| Guarda-Nardini L [35] | 2012 | unclear | high | high | high | low | low | unclear |
| Wu CJ [45] | 2012 | high | unclear | low | low | low | low | unclear |
| Song JH [43] | 2015 | unclear | unclear | high | high | low | low | unclear |
| De Carli BMG [31] | 2016 | low | unclear | high | unclear | low | low | unclear |
| Al-Wayli H [30] | 2017 | unclear | high | high | high | high | low | unclear |

## Synthesis of the results

### *MSD group*

*Evaluate VAS outcome*. There were 7 studies in MSD group. We classified the studies into 2 subgroups. First, there were 4 studies that used NSS in control groups [32, 34, 37, 47]. A forest plot showed that the point-estimated Weight Mean Difference (WMD) of all trials were lower than 0. The pooled WMD was -1.81 (95% CI: -3.23 to -0.39), with a highly heterogeneous ($I^2$ = 89.7%), Chi-square = 29.20, d.f. = 3, P = 0.000, as presented in figure 2(a). From these findings, it could be interpreted that BTX subjects had a significantly lower VAS score than NSS group. Subgroup analysis in co-variables has been done. For the number of injected muscle (≤ 1 muscle versus > 1 muscle) in the meta-regression model reduces the $tau^2$ from 1.47 to 0, and reduces the degree of heterogeneity ($I^2$ from 89.7% to 0 %). Coefficients of the variables were statistically significant (p = 0.03). Sensitivity analysis was done by excluding 1 study in group ≤ 1 muscle [32], which resulted in the decrease of the degree of heterogeneity from 89.7% to 0%, with pooled WMD of –2.73 (95% CI: -3.21 to –2.24). This result suggested that the number of injected muscles were the source of heterogeneity of this group in meta-regression model. For injection dose of BTX (< 100 Mu versus ≥ 100 Mu) in the meta-regression model reduces the $tau^2$ from 1.47 to 0, and reduces the degree of heterogeneity ($I^2$ from 89.7% to 0 %). Coefficients of the variables were statistically significant (p = 0.03). A subgroup analysis was performed according to the number of injection doses. The degree of heterogeneity was 0% in both groups (< 100 Mu versus ≥ 100 Mu). This result suggested that the injection dose was source of heterogeneity of this group. Publication bias was assessed by funnel plot and Egger's test. These results agreed with the Egger's tests, which indicated no evidence of asymmetry of funnels. The coefficients of asymmetry was -0.10 (SE = 3.35, P = 0.98). Contour-enhanced funnel plots were further constructed. The graph shows the missing studies in both significant and non-significant areas of the funnels, an asymmetry might be more likely caused by heterogeneity ($I^2$ = 89.7%) than publication bias (see figure 2(b)). Second, there were 3 studies that used active and standard treatment [30, 31, 34] (LLL with GaAlAs active medium, fascial manipulation, and traditional method) in control groups. A forest plot presented in figure 3(a).

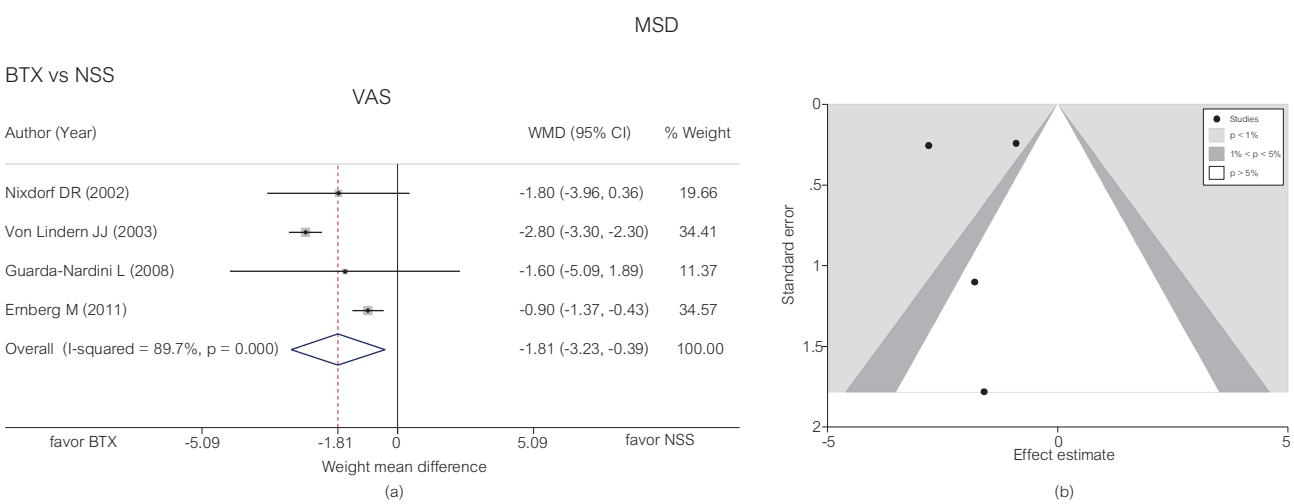


Figure 2 Forest plot of the mean difference of VAS score in MSD patients (a) and contour-enhanced funnel plot of pooling VAS score at the end of study minus baseline of BTX group compare to NSS group in MSD patients (b).

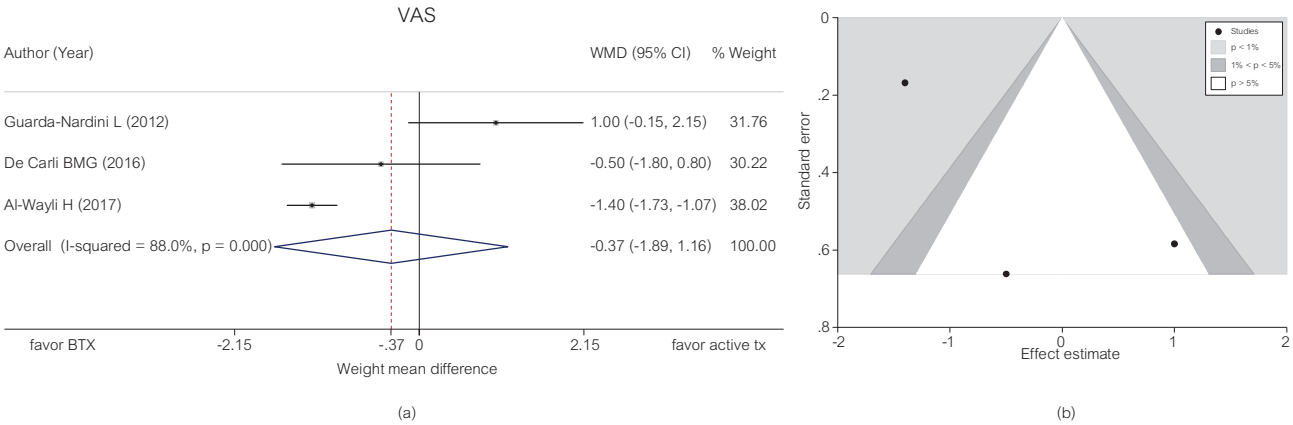


Figure 3 Forest plot of the mean difference of VAS score in MSD patients (a) and contour-enhanced funnel plot of pooling VAS score at the end of study minus baseline of BTX group compare to active standard treatment group in MSD patients (b).

It could be interpreted that BTX subjects had lower VAS score compared at the end of study minus at baseline than active treatment subjects but not significantly (Z = 0.47, p= 0.64). After the forest plot had been interpreted, sensitivity analysis was then conducted. One study was excluded [35] due to point estimated WMD being greater than 0, this result showed the decrease in the degree of heterogeneity from 88.0% to 42.4% (moderately heterogeneity), with pooled WMD of -1.18 (95% CI: -1.94 to –0.42). It is concluded that this study may contribute to heterogeneity. Publication bias was assessed but there was no evidence of correlation between the effect sizes and variances. These results agreed with the Egger's tests, which indicated no evidence of asymmetry of funnels. The coefficients of asymmetry was 3.68 (SE= 2.11, P = 0.33). Contour-enhanced funnel plots were further constructed. The graph shows the missing studies in both significant and non-significant areas of the funnels, an asymmetry might be more likely caused by heterogeneity ($I^2$ = 88.0%) than publication bias (see figure 3 (b)).

*Evaluate MOA outcome.* There were 5 studies in MSD group that presented MOA outcomes. Due to differentiation of substance in control group, only 3 studies that use NSS could be analyzed in the meta-analyses. A forest plot showed in figure 4(a) could be interpreted that NSS subjects had greater MOA than BTX subjects but not significantly (Z = 0.54, p= 0.59). Sensitivity analysis was done by excluding one study due to point-estimated WMD being lower than 0 [37], this result showed that the degree of heterogeneity decreased from 59.0% to 0% (no heterogeneity), with pooled WMD of 1.52 (95% CI: -3.85 to 6.90). It is concluded that this study may contribute to heterogeneity. Publication bias indicated no evidence of asymmetry of funnels. The coefficients of asymmetry was -12.89 (SE = 9.89, P = 0.42). The graph of contour-enhanced funnel plots shows the missing studies in both significant and non-significant areas of the funnels, an asymmetry might be more likely caused by heterogeneity ($I^2$ = 59.0%) thanpublication bias.

***NVD group***

*Evaluate HD outcome.* There were 9 studies in this group [33, 36, 38-44], with only 7 studies that assessed HD. We analyzed 6 studies that use BTX in treatment group and use NSS in control groups. A forest plot presented in figure 4(b) could be interpreted that BTX subjects had a significantly lower HD than NSS subjects. The result of the sensitivity analysis of duration of treatments of 4-12 weeks (excluded one study that showed

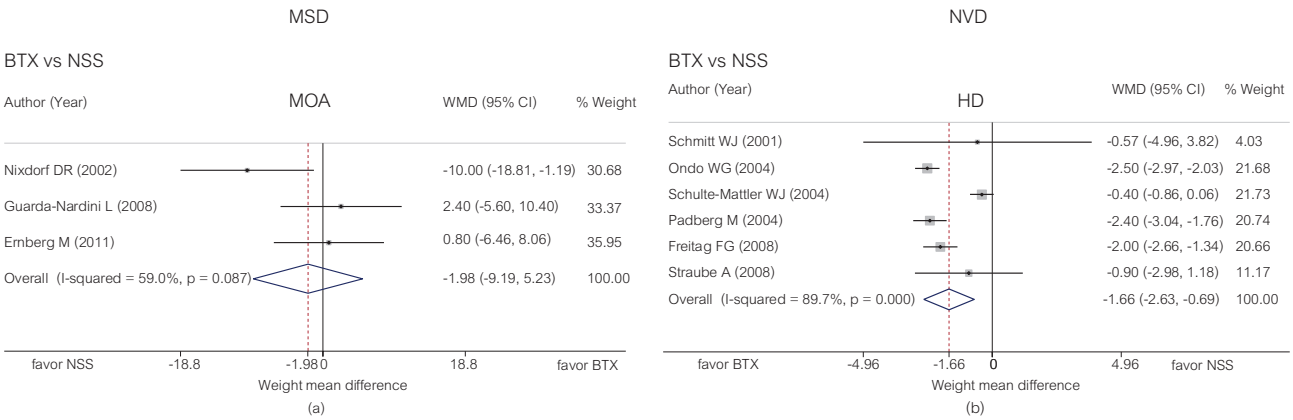


Figure 4 Forest plot of the mean difference of MOA in MSD patients (a) and forest plot of the mean difference of HD in NVD patients (b).

week 16 at the end of study [33] showed increasing of the degree of heterogeneity from 89.7% to 91.6%, with pooled WMD of 1.55 (95% CI: -2.78 to -0.33). It is concluded that the duration of treatments of 4-12 weeks may not contribute to heterogeneity. Subgroup analysis in co-variables such as number of injected muscles and injection dose of BTX has also been conducted. Adding number of injected muscles (≤ 3 muscles versus > 3 muscles) in the meta-regression model increased the tau$^2$ from 1.08 to 1.12, and reduce the degree of heterogeneity ($I^2$ from 89.7% to 87.27 %). Coefficients of the variables were not statistically significant (p = 0.57). A subgroup analysis was performed according to number of injected muscles. The degree of heterogeneity ($I^2$) were 0% in group ≤ 3 muscles, and 90.2% in group > 3 muscles). This result suggested that the number of injected muscle in group ≤ 3 muscles may be the source of heterogeneity. Adding number of injected dose (< 100 Mu versus ≥ 100 Mu) in the meta-regression model increases the tau$^2$ from 1.08 to 1.10, and increase the degree of heterogeneity ($I^2$ from 89.7% to 91.75%). Coefficients of the variables was not statistically significant (p = 0.68). A sensitivity analysis was performed by excluding one study that use injection dose < 100 Mu [41], the result showed increasing degree of heterogeneity from 89.7% to 91.8%, with pooled WMD of -1.71 (95% CI: -2.71 to -0.71). It is concluded that injected dose may not contribute to heterogeneity in this group. There was no evidence of correlation between the effect sizes and variances. These results agreed with the Egger's tests, which indicated no evidence of asymmetry of funnels. The coefficient of asymmetry was -1.66 (SE = 0.96, P = 0.16). Contour-enhanced funnel plots were further constructed. The graph shows the missing studies in both significant and non-significant areas of the funnels, an asymmetry might be more likely caused by heterogeneity ($I^2$ = 89.7%) than publication bias.

*Evaluate NDI outcome.* There were 5 studies in NVD group that presented outcome in NDI but only 4 studies could be analyzed in meta-analyses due to differentiation of substance in control group. These studies use BTX in treatment group and use NSS in control groups [33, 39, 41, 44]. A forest plot presented in figure 5(a) could be interpreted that BTX subjects had a significantly lower NDI than NSS subjects.

Sensitivity analysis of duration of treatments of 4-12 weeks (excluded one study that showed week 16 at the end of study [33] showed an increase in the degree of heterogeneity from 97%

to 97.3%, with pooled WMD of -3.29 (95% CI: -6.31 to –0.26). It is concluded that duration of treatments of 4-12 weeks may not contribute to heterogeneity. Adding number of injected muscles (≤ 3 muscles versus > 3 muscles) in the meta-regression model increased the $tau^2$ from 2.85 to 2.87, and increase the degree of heterogeneity ($I^2$ from 97% to 98%). Coefficients of the variables were not statistically significant (p = 0.78). A sensitivity analysis was performed by excluding one study that had number of injected muscles ≤ 3 muscles [41], result presented increasing of the degree of heterogeneity from 97% to 98%, with pooled WMD of -2.45 (95% CI: -4.39 to -0.51). It is concluded that number of injected muscles may not contribute to heterogeneity in this group. Adding number of injected dose (< 100 Mu versus ≥ 100 Mu) in the meta-regression model increases the $tau^2$ from 2.85 to 2.87, and increase the degree of heterogeneity ($I^2$ from 97% to 98%). Coefficients of the variables were not statistically significant (p = 0.78). A sensitivity analysis was performed by excluding one study that use injection dose < 100 Mu [41], with the result showing an increasing in the degree of heterogeneity from 97% to 98%, with pooled WMD of -2.45 (95% CI: -4.39 to -0.51). It is concluded that injection dose may not contribute to heterogeneity in this group. There was no evidence of correlation between the effect sizes and variances. These results agreed with the Egger's tests, which indicated no evidence of asymmetry of funnels. The coefficients of asymmetry was -1.28 (SE = 1.76, P = 0.54). Contour-enhanced funnel plots were further constructed. The graph shows the missing studies in both significant and non-significant areas of the funnels, an asymmetry might be more likely caused by heterogeneity ($I^2$ = 97%) than publication bias.

*Evaluate VAS outcome.* There were only three studies in NVD group that assessed effect of pain intensity as VAS score that compared VAS between BTX group and NSS group [39-41]. A forest plot in figure 5(b) could be interpreted that BTX subjects had greater VAS score than NSS subjects but not significantly greater (Z = 0.59, p = 0.56). Publication bias was assessed by funnel plot and Egger's test. There was no evidence of correlation between the effect sizes and variances. These results agreed with the Egger's tests, which indicated no evidence of asymmetry of funnels. The coefficients of asymmetry was -0.37 (SE = 1.41, P = 0.84). Contour-enhanced funnel plots were further constructed. The graph shows the missing studies in non-significant area of the funnels, asymmetry may be due to publication bias.

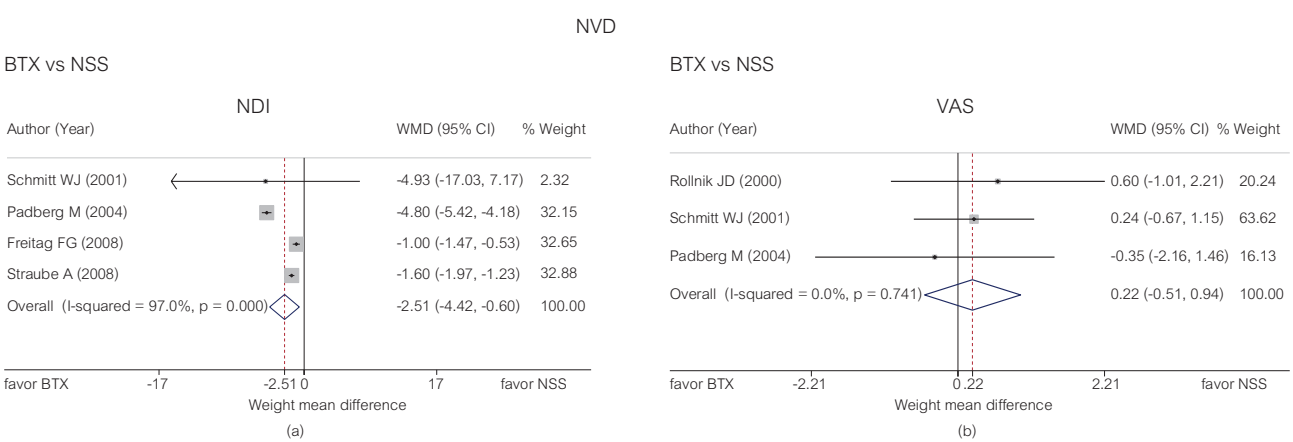


Figure 5 Forest plot of the mean difference of NDI in NVD patients (a) and forest plot of the mean difference of VAS in NVD patients (b).

## Discussion

### Summary of findings

Our results found that BTX-A subjects experienced significantly less pain than NSS subjects in MSD patients (pooled WMD= -1.81, 95% CI: -3.23 to -0.39), and had clinically significant change in pain intensity at VAS score 18.1 mm (the minimum clinically significant change over a VAS is 9 mm [48]). This is consistent with the current hypothesis that BTX can inhibit the secretion of neurotransmitters that caused pain in MSD condition. MSD is related to inappropriate activity of ACh at the neuromuscular junction, which produces a sustained contraction of the sarcomere called "taut band", and the nociceptive neurotransmitters initiate the cascade of pain neurotransmission that causes local pain and referred pain. In MSDgroup, BTX-A subjects had lower VAS score than standard active treatment subjects but not significantly lower (pooled WMD = -0.37, 95% CI: -1.89 to 1.16). As OFD can be caused by various etiology and needs multidisciplinary approach in the treatment such as self-education and self-management program combined with pharmacotherapy for reduced muscular tension and pain, it is difficult to find the obvious result from a single treatment. The result showed BTX-A subjects had less MOA than NSS group but not significantly lower (pooled WMD = -1.98, 95% CI: -9.19 to 5.23) than in MSD patients. These results may be caused by adverse effects of BTX such as difficulty chewing or opening the mouth, which results from local muscle weakness and is usually dose dependent.

In NVD group, 9 studies with difference methodology were included. In order to differentiate the outcomes, this study divides selected studies into three groups; HD, NDI, and VAS. 3 studies were analyzed for VAS outcomes [39, 40, 41]. BTX-A subjects had greater VAS score than NSS subjects but not significantly greater (pooled WMD = 0.22, 95% CI: -0.51 to 0.94), with no heterogeneity ($I^2$ = 0%). Publication bias was assessed, with contour-enhanced funnel plots showing the missing studies in non-significant area of the funnels, while asymmetry may be due to publication bias. For the significance of results, in the future, we need more RCT studies with more rigorous design. 6 studies were analyzed for HD outcomes [33,38,39,41,42,44]. BTX-A subjects had significantly lower HD than NSS subjects (pooled WMD = -1.66, 95% CI: -2.64 to -0.69). This is consistent with mechanism of action of BTX that can inhibit the release of several pain-related neurotransmitters including substance P, glutamate, and calcitonin gene-related peptide. These properties had been tested in Phase Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) trials [20].

4 studies were analyzed for NDI outcomes [33, 39, 41, 44]. BTX-A subjects had significantly lower NDI than NSS subjects (pooled WMD = -2.51, 95% CI: -4.42 to -0.60) corresponding to mechanism of action of BTX that can inhibit the release of several pain-related neurotransmitters as mentioned above.

Our study attempted to extract the data and pool the outcomes that represent pain intensity such as VAS, HD, and NDI, outcome that represents range of motion such as MOA from RCT. VAS is the most commonly used measures of pain intensity in clinical and research settings with high validity. In addition, there is no study about the treatment efficacy of BTX in OFD patients before. Our study was designed to collect the data from all samples that represent OFD. However, our study also has some limitations. First, we could not control for study design, methodology, confounding factors because we worked on primary data. For example, dose of BTX and number of injected muscles were not consistent across all of the included studies. Although our strategy was to divide the studies into three groups e.g., number of injected muscles in MSD group (≤ 1 muscle versus > 1 muscle), number of injected muscles in NVD group (≤ 3

muscle versus > 3 muscle), number of injected doses in MSD and NVD groups (< 100 Mu versus ≥ 100 Mu), second, there were only 2 studies in NPD group, we could not pool the outcome in meta-analysis, and third, there were not many studies in this trial, hence some groups that exhibited heterogeneity could not be properly analyzed in subgroup analysis. From our study, we can imply that BTX-A might be an alternative treatment to those patients who are either unable to manage their pain medically or would like adjunct therapy.

## Conclusions

There are not many RCT that study the efficacy of BTX compared with placebo, the standard treatment, and/or active treatment in OFD patients. Each trial used different methodological design, different characteristics of sample e.g., number of samples, age, duration of disease, duration of treatment, follow up period, etc. The results showed moderate to high heterogeneity, so more rigorous design of trials should be carried out in future studies.

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