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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - ORIGINAL ARTICLE

Botulinum neurotoxin injections for muscle-based (dystonia and spasticity) and non-muscle-based (neuropathic pain) pain disorders: a meta-analytic study

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Abstract

Apart from the known efficacy of Botulinum Neurotoxin Type A (BoNT/A) in hyperactive striated and smooth muscles, different pain states have become potential targets of toxin effects. This present study determined the comparative toxin effectiveness in pain reduction among those patients injected with BoNT/A in muscle-based and in non-muscle-based conditions. Randomized controlled trials (RCTs) on the effect of BoNT/A on selected pain conditions were included. The conditions were spasticity and dystonia for muscle-based pain. For non-muscle-based pain, conditions included were painful diabetic neuropathy (PDN), post-herpetic neuralgia (PHN), trigeminal neuralgia (TN), complex regional pain syndrome (CRPS), and spinal cord injury (SCI). In view of possibly differing pathophysiology, myofascial pain, temporomandibular joint (TMJ), other joint or tendon pains, cervicogenic and lumbar pains, migraine and visceral pain syndromes were excluded. Standardized mean difference was used as the effect measure and computed with STATA. 25 RCTs were analyzed. Pooled estimates showed significantly lower pain score in the Treatment group ($z = 5.23$, $p < 0.01$, 95% CI = −0.75, −0.34). Subgroup analyses showed that BoNT/A significantly reduced both muscle-based ($z = 3.78$, $p < 0.01$, 95% CI = −0.72, −0.23) and non-muscle-based ($z = 3.37$, $p = 0.001$, 95% CI = −1.00, −0.27) pain. Meta-regression using four covariates namely dosage, route, frequency and duration was done which revealed that dosage significantly affects standardized mean differences, while the other three covariates were insignificant. The joint F-test was found to be insignificant (p value = 0.1182). The application of the model with these covariates does not significantly explain the derived heterogeneity of standardized mean differences. In conclusion, BoNT/A can be effectively used in muscle-based and non-muscle-based pain disorders. We detected no difference between the presence and magnitude of pain relief favoring muscle-based compared to non-muscle-based pain. Thus, we cannot say whether or not there might be independent mechanisms of toxin-induced pain relief for pain generated from either muscle or nerve hyperactivity.

Keywords Botulinum neurotoxin · BoNT/A · Pain · Muscle-based pain · Non-muscle-based pain

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Introduction

Botulinum Neurotoxin Type A (BoNT/A) is a complex protein with a *neurotoxic part* which is proteolytically aimed at the synaptic proteins involved in vesicular neurotransmitter release, and the *auxiliary protein part*. The ability to purify BoNT paved the way for it to be used for multiple medical purposes, which in recent years, has included pain relief (Matak and Lackovic 2014). The best known mechanism of action of BoNT is by blocking the release of the neurotransmitter acetylcholine (Ach) from the pre-synaptic terminal at the neuromuscular junction (Matak and Lackovic 2014; Wheeler and Smith 2013). It exudes a temporary effect on the muscle fibers and hinders its contraction, leading to relaxation of hyperactive muscles. Intuitively, this may be a mechanism by which pain relief is generated, by relieving ischemia, lactate production, traction-related and positional pain. Additionally, BoNT may inhibit release of other local neuropeptides, that are involved in pain transmission such as substance P, calcitonin gene-related peptide (CGRP), glutamate, and transient receptor potential vanilloid 1 (TRPV1) (Wheeler and Smith 2013). Inhibition of the release of these neurotransmitters has been proposed to explain the relief of neuropathic and 'muscle-based' pain.

Literature suggests that BoNT can induce analgesia in many musculoskeletal disorders (Wheeler and Smith 2013). These nociceptive pain states lead to local, and even radiating, muscle spasms and pain ("pain-spasm-pain cycle"). Studies have documented effectiveness of the toxin in alleviating nerve-related or neuropathic pain such as trigeminal neuralgia (TN) (Ngeow and Nair 2010; Babiloni et al. 2016; Safarpour and Jabbari 2018), pain in post-herpetic neuralgia (PHN) (Safarpour and Jabbari 2018; Shackleton et al. 2016), painful diabetic neuropathy (PDN) and central neuropathic pain in multiple sclerosis (Habek et al. 2010), pain in traumatic brain injury (TBI)/spinal cord injury (SCI) and post-stroke pain (Safarpour and Jabbari 2018). BoNT has also been increasingly used "off-label" in several neuropathic pain states. In this present work, we specifically included BoNT subcutaneous injections for pain in clinical trials for TN (Ngeow and Nair 2010; Babiloni et al. 2016), pain in PHN (Shackleton et al. 2016), PDN, central neuropathic pain in multiple sclerosis (Habek et al. 2010), pain in TBI/SCI (Melnyk and Fineout-Overholt 2010) and post-stroke pain (Higgins and Thompson 2002; Sterne 2016; Valentine et al. 2010). Traumatic SCI produces dramatic changes of neuroanatomical and neurochemical shifts that result in maladaptive synaptic circuits in the spinal dorsal horn which contribute to the neuronal hyperexcitability in response to mechanical, chemical and thermal stimuli (Delnooz and Warrenburg 2012). Electrophysiologically, there is enhanced neuronal response properties to external stimuli applied and increased afterdischarge activity (Delnooz and Warrenburg 2012). In the somatosensory system, GABAergic descending pathways terminate in the spinal cord, where GABA, an inhibitory neurotransmitter, is widely distributed. GABA is a product of the decarboxylate of L-glutamate by glutamic acid decarboxylase (GAD). It plays a "counter balance" role against enhanced synaptic transmission in the spinal cord as a result of glutamate-mediated excitation of neurons following SCI (Delnooz and Warrenburg 2012). Neurons are not the only cells that synthesize GABA in the central nervous system. After an ischemic injury, forebrain region shows increased GFAP immunoreactivity (activated astrocytes) co-labeled with GABA and GAD which indicates that glial cells also synthesize GABA, since GAD is the enzyme necessary in GABA synthesis (Delnooz and Warrenburg 2012). These GABAergic neurons synapse axodendritically and axosomatically. The activation of NMDA receptors and other calcium channels triggers large influxes of calcium ions, dependent on the depolarization of the membrane and initiate subsequent calcium-dependent GABA release. Thus, the somatic and dendritic localized GABA release results in widespread inhibition in nociceptive transmission (Delnooz and Warrenburg 2012).

However, there is little exploration of whether BoNT/A might work differently in muscle-based compared to non-muscle-based pain. To date, meta-analytic studies on pain disorders, have focused primarily on neuralgia, migraine and other headaches, and diabetic neuropathy. They have not explored pain syndromes in general, or considered comparative efficacy and potentially different mechanisms of action. Data continue to accumulate so that a further summative meta-analysis is justified. Thus, we have conducted this present meta-analysis to address the clinical question: *how effective is BoNT/A in treating patients with muscle-based compared to non-muscle-based pains?*

Methods

Eligibility criteria

We used the P.I.C.O.T. framework (*population, intervention, comparison, outcome, and timeframe*) to develop our clinical question, guide the literature search, and evaluate eligibility of potentially relevant research papers (Melnyk and Fineout-Overholt 2010). Only papers written in English were included.

In terms of the populations of interest, we included RCTs that examined use of BoNT for muscle-based or non-muscle-based pain syndromes, regardless of year of

publication, duration of treatment, or the respondent's age or sex. As exemplars, we designated spasticity and dystonia as muscle-based pain conditions, and central neuropathic pain, PDN, TN, complex regional pain syndrome [CRPS], and SCI as non-muscle-based pain conditions. In view of different pathophysiological processes in pain generation, migraine, chronic daily headache and tension type headache were excluded.

Control interventions accepted were placebo, usual or standard treatment. The primary outcome of interest was the pain scores of the study's respondents. No specific timeframe was set for the assessment of pain in the studies that were reviewed.

Information sources

We searched PubMed, Sciencedirect, EBSCO Host, and Google Scholar. We scrutinized the references of identified studies for further potentially relevant studies. We searched gray literature (*defined as reports produced by all levels of government, academics, business, and industry in print and electronic formats but are not controlled by commercial publishers*) ProQuest Dissertations and Theses Database and ClinicalTrials.gov.

Search procedure

We searched relevant literature on the search engines mentioned above. Multiple search techniques were employed including keyword search, controlled vocabulary or subject heading search, and Boolean logic search. For databases without controlled vocabulary, we searched for keywords, using the following phrases: "dystonia pain AND botulinum toxin," "spasticity pain AND botulinum toxin," "limb spasticity AND botulinum toxin," "botulinum toxin AND muscle pain," "botulinum AND non-muscle pain," "muscle-based pain AND botulinum toxin," "non-muscle based pain AND botulinum toxin," "botulinum toxin AND myofascial pain," "botulinum toxin AND cervicogenic pain," "botulinum toxin AND lumbar pain," "botulinum toxin AND neck pain," "botulinum toxin AND neuralgia," "botulinum toxin AND neuromuscular pain," and "botulinum AND neuropathic pain." Muscle-based pain studies exclusively referred to spasticity and dystonia. Other potential muscle-triggered pain such as myofascial pain, TMJ pain, cervicogenic and lumbar pains not associated with spasticity and dystonia were excluded. For databases with controlled vocabulary, we used the following Medicine Medical Subject Headings (MeSH) terms: "Botulinum toxin" OR "Botulinum Toxin A" OR "Botox" OR "BTX" AND "pain" OR "pain syndromes" OR "neuropathic pain" OR "neuralgia." The search was limited to researches on human data and on clinical trials.

Study selection

Two independent reviewers conducted literature search and eligibility assessment. One reviewer extracted research data and performed quality assessment of the identified articles. The second reviewer, checked the extracted data and also performed quality assessment. Disagreements in judgment between the reviewers were resolved by discussion.

Title, keywords, and abstract of publications identified according to the search strategies were independently screened by these reviewers. Inclusion criteria for title and abstract screening included trials or experimental studies on BoNT on pain (muscle or non-muscle based). The same reviewers independently scrutinized full-text papers for final inclusion in the study. Excluded research articles and the reasons for their exclusion were recorded and tabulated. Disagreements were managed through discussion.

Using the Cochrane Collaboration's tool, we assessed and rated the quality of each selected research article as either high, moderate, low, or very low. We appraised the following aspects of each RCT: *sequence generation, blinding, allocation concealment, incomplete outcome data, selective outcome reporting, and other sources of bias.* This Cochrane tool generally rates RCTs or other experimental studies as high quality. Quality scores are reduced by serious limitations in design, imprecision of results, unexplained heterogeneity, and indirectness of evidence and high probability of publication bias. In our own meta-analysis, we excluded BoNT/B to reduce data heterogeneity, and because some early studies reported that BoNT/B may induce pain during injection sessions.

Data collection process

We developed an abstraction form and pre-tested it on a number of five papers. Two reviewers independently extracted data from included studies.

Data items

The variable that was of primary interest in this present study was the pain score. The reviewers also extracted information regarding the authors, publication year, study design, study location, source of funding, duration of study, inclusion criteria, exclusion criteria, duration of pain, type of pain or pain syndrome, participation rate, attrition rate, dose of BoNT/A administered, outcomes, adverse effects, and other results.

Summary measures

We used the mean and standard deviation (SD) of pain scores to calculate the standardized mean difference (SMD)

for use in the meta-analysis. Regarding pain assessment, the pain scores extracted for this meta-analysis were the rating scores assessed at a given timeframe of the eligible study.

Synthesis of results

This study did not assume one effect size among all the studies that were included. Hence, the overall effect for each meta-analysis was derived using a random-effects model (REM), which takes within-study and between-study variation into account. We scrutinized statistical heterogeneity between studies using Q statistics test, I^2 statistics, and tau-squared (τ^2) statistics (Higgins and Thompson 2002).

We evaluated publication bias using contour-enhanced funnel pots. We performed formal statistical assessment of plot asymmetry using Egger's regression asymmetry test and Begg's adjusted rank correlation test (Sterne 2016). We conducted all analyses using STATA version 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.). A p value ≤ 0.05 was considered statistically significant.

Meta-regression

In considering potential effects of certain variables influencing current results from the derived studies, a meta-regression analysis was done using STATA. Thus, individual spread sheets containing the outcome measure of data interest were done. In this present study, we tabulated the 25 studies analyzed according to the dosage, frequency, route of administration, time of assessment post-injection, and study duration. To graph analysis in STATA, we used the command graph after the meta-regression analysis. A line graph of fitted values plotted against the first covariate was done, together with the estimates from each study represented by circles. By default, the circle sizes depend on the precision of each estimate, which is the weight given to each study in the fixed-effects model. A joint F-test was performed to demonstrate the significance of all covariates together.

Results

Study selection

The search retrieved 1102 articles between year 2000 and 2017. After applying our broad inclusion and exclusion criteria and checking these publications for duplicates, we screened the 55 remaining papers in more detail. From these articles, 29 were further removed due to the following: (1) 16 articles did not quantitatively report VAS scores; (2) 3 studies were case reports or studies; (3) 2 articles were repeated measures without a comparison; (4) 2 studies were qualitative studies; and, (5) 3 articles assessed bladder pain. As presented in the PRISMA Flow Diagram of Study Selection (see Fig. 1), a total of 25 articles were included in this meta-analytic study.

Study characteristics

All studies selected for this review were RCTs, with a total of 25 research papers. Using the formula recommended by Valentine et al. (2010), we calculated a statistical power of 99.92%, suggesting sufficiency of the extracted articles. Tables 1 and 2 summarize the characteristics of the included studies for both muscle-based and non-muscled-based pain disorders, separately.

Synthesis of results

Figure 2 suggests that the pooled data showed a significant difference in the mean pain scores between the use of BoNT/A and placebo treatment using random-effects model ($z = 5.23$, $p < 0.01$, 95% CI $= -0.75, -0.34$). The results favored the use of BoNT/A, in both muscle-based ($z = 3.78$, $p < 0.01$, 95% CI $= -0.72, -0.23$) and non-muscle-based ($z = 3.37$, $p = 0.001$, 95% CI $= -1.00, -0.27$) pain. They show that BoNT/A relieves both muscle-based and non-muscle-based pain better than placebo.

Risk of bias in studies

We assessed the risk of bias analysis using contour-enhanced funnel plots, as presented in Fig. 3. As shown, for both with and without subgroup analyses, there is funnel asymmetry and evidence strongly suggest that studies are suppressed on a single side (left side of the plot). In addition, statistical analysis using Begg's ($z = 3.13$, $p = 0.002$) and Egger's (bias $= -2.01$, $p = 0.012$) tests supports funnel asymmetry and possibility of publication bias. It is also notable that the sign of the bias coefficient was negative which suggests overestimation of the effect of the BoNT/A or underestimation of the comparison group's treatment.

Meta-regression

Meta-regression with dosage

Using SMD from 25 studies, meta-regression analysis showed that there is a positive association between dosage and difference between the effect of BoNT/A and placebo. This can be clearly seen in the bubble plot (Fig. 4) where increasing dosage is accompanied by increasing SMD. Where by increasing the SMD, the effect of BoNT/A moves farther from the effect of placebo. Increasing the dosage by a unit also increases the mean difference of pain scores

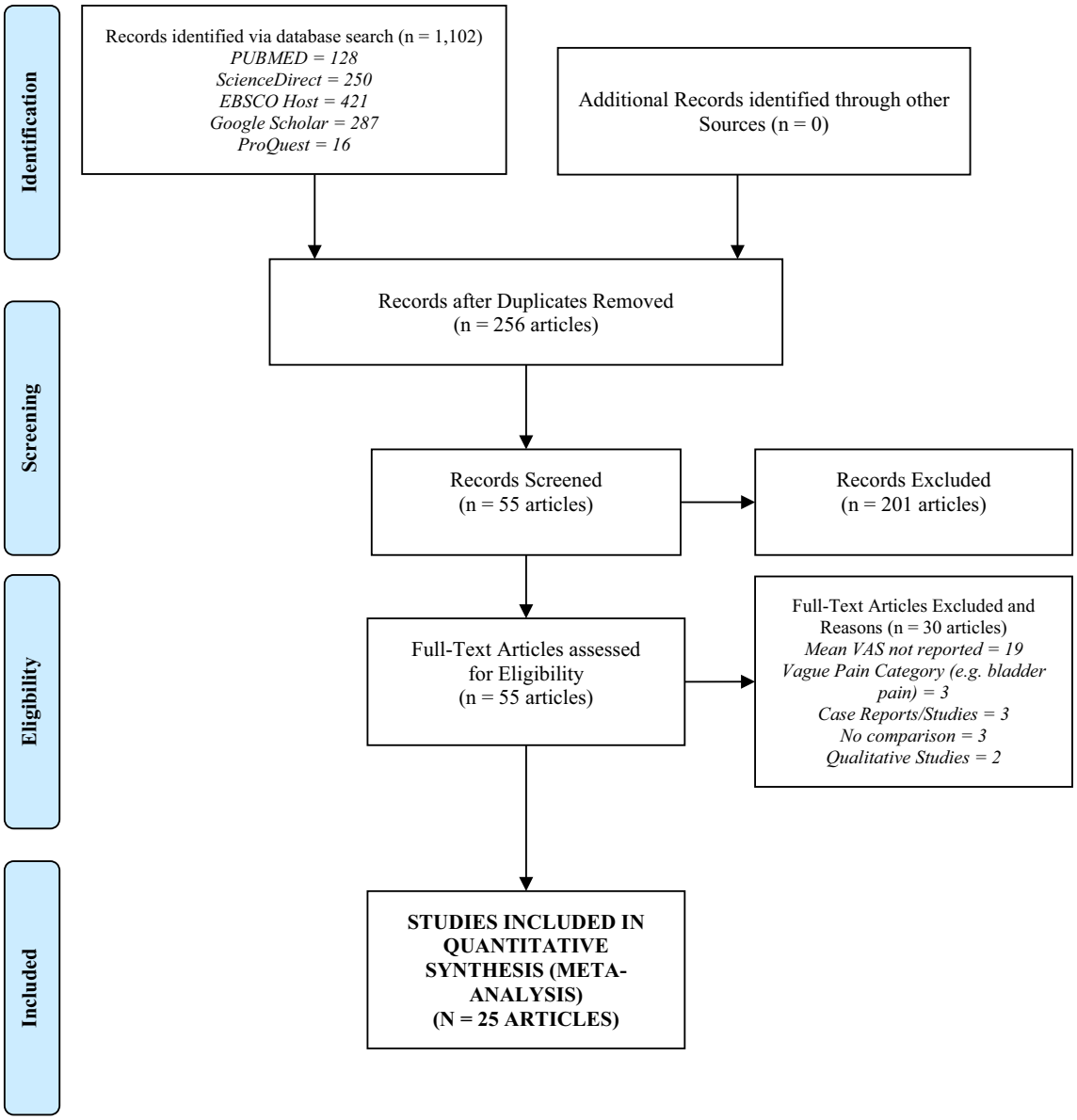

Fig. 1 PRISMA flow diagram of study selection

between the effect of BoNT/A and placebo treatments by 0.0009. Inversely, a decrease in dosage will decrease the SMD; hence, decreasing difference in pain scores between the effect of BoNT/A and placebo treatments. This effect of dosage was found to be significant at 10% alpha (p value = 0.063).

The weighted overall SMD − 0.5463 favors BoNT/A over placebo. On the average, weighted SMD varies by as much as 0.4567 from this weighted overall SMD if dosage is taken into account. The estimate of between-study variance was found to be significantly different from zero based from the Likelihood-ratio test (p value − 0.0017). Results showed that dosage explains 21.85% of the overall heterogeneity. The remaining 78.15% is explained by other factors. From this 78.15% variation unexplained by dosage, 64.83% is due to heterogeneity of studies signifying more covariates are affecting the advantage of BoNT/A over placebo (see Table 3).

Meta-regression with route

Meta-regression analysis showed that SMD is lower if the route is non-muscle based [coded with two on the bubble plot]. This implies that the effects of BoNT/A and placebo treatments have lower difference in non-muscle-based route compared to muscle-based route. Bubble plot (Fig. 5) shows the very slow decreasing trend as route goes from muscle based to non-muscle based. If the route is non-muscle based,

Table 1 Characteristics of research studies on muscle-based pain disorders included in the meta-analysis ($N = 13$)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Bhakta et al. (2000) United Kingdom	Double-Blind RCT	Post-stroke spasticity (PSS)	Patients with stroke and chronic hemiparesis referred to a rehabilitation unit for consideration of BoNT for arm spasticity	1000 Units of Abo-BoNT/A Intramuscular 3 Months	Numerical Rating Scale (NRS)	*Control group*: 8.25 (± 5.25) with 20 respondents *Treatment group*: 7.00 (± 4.00) with 20 respondents
Gracies et al. (2015) Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia, and USA	Double-Blind RCT	PSS and TBI	Patients 18–80 years old, hemiparetic for < 6 months PSS and TBI with a MAS score in the primary target muscle group of at least two for patients who had no previous BoNT/A injection in the paretic limb	500 Units of Abo-BoNT/A Intramuscular 5 Months	Global Self-Assessment (GSA) Pain	*Control group*: 2.10 (± 0.80) with 79 respondents *Treatment group*: 1.80 (± 0.70) with 79 respondents
Hesse et al. (2011) Germany	RCT-Parallel	PSS	Patients who were first time supratentorial stroke (4–6 weeks after onset); on rehabilitation; partly independent with ADLs; with a Barthel Index > 25; non-functional upper extremity with a Fugl-Meyer motor score < 20; no volitional wrist or finger extensor activity; with finger and/or wrist flexor stiffness with a MAS (0–5) of 1 or 2	150 Units of Inco-BoNT/A Intramuscular 1 Month	5-point Ordinal Scale (0–4)	Finger extension: *Control group*: 1.80 (± 0.70) with 9 respondents *Treatment group*: 0.70 (± 0.70) with 9 respondents Wrist extension: *Control group*: 2.10 (± 0.90) with 9 respondents *Treatment group*: 0.90 (± 0.80) with 9 respondents
Kong et al. (2007) Singapore	RCT	PSS	Patients, > 3 months post-stroke, with hemiplegic shoulder pain associated with shoulder adductor and elbow flexor spasticity	500 Units of Abo-BoNT/A Intramuscular 3 Months	Visual Analog Scale (0 – 10)	*Control group*: 4.00 (± 1.43) with 9 respondents *Treatment group*: 3.00 (± 2.00) with 8 respondents

Table 1 (continued)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Lim et al. (2008) South Korea	Double-Blind RCT	Hemiplegic shoulder pain	Patients with hemiplegic shoulder pain aged 18 to 78 years	100 Units of Abo-BoNT/A Intramuscular 3 Months	Numerical Rating Scale (NRS)	*Control group*: 5.50 (± 1.00) with 11 respondents *Treatment group*: 3.20 (± 0.50) with 14 respondents
Marco et al. (2007) Spain	Double-Blind RCT	PSS	Post-stroke patients with spastic shoulder pain	500 Units of Abo-BoNT/A Intramuscular 6 Months	Visual Analog Scale (0 – 10)	*Control group*: 48.30 (± 29.40) with 15 respondents *Treatment group*: 30.10 (± 26.90) with 14 respondents
McCory et al. (2009) Australia	Multi-Centre RCT	PSS	Patients who were > 18 years, had a stroke at least 6 months in the past, had moderate to severe spasticity of the arm as defined by the MAS	1000 Units of Abo-BoNT/A Intramuscular 6 Months	Visual Analog Scale (0 – 10)	*Control group*: 30.90 (± 37.90) with 42 respondents *Treatment group*: 34.40 (± 43.20) with 54 respondents
Mordin et al. (2014) USA and Russia	Double-Blind RCT	CD	Patients with CD with symptoms for at least 18 months, as well as the following baseline TWSTRS scores: a total score of at least 30; a Severity domain score of at least 15; and a Disability domain score of at least 3	500 Units of Abo-BoNT/A Intramuscular 2 Months	Visual Analog Scale (0 – 10)	*Control group*: 48.10 (± 22.00) with 61 respondents *Treatment group*: 38.20 (± 20.40) with 55 respondents
Quagliato et al. (2010) Brazil	Double-Blind RCT	CD	Patients ≥ 18 years of age with primary CD, with no previous BoNT/A injections, and no BoNT/A application within the prior 24 weeks	300 Units of Abo-BoNT/A Intramuscular 4 Months	Pain Subscale of the TWSTRS	*Control group*: 7.20 (± 4.90) with 12 respondents *Treatment group*: 5.80 (± 5.01) with 8 respondents

Table 1 (continued)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Rosales et al. (2012) Philippines, Hong Kong, Malaysia, Singapore, Thailand	RCT	PSS	<3 months upper limb spasticity MAS 1.5 and above	500 Units of Abo-BoNT/A Intramuscular 3 Months	Pain using VAS 0 – 100	*Control group*: 20.72 (± 21.53) with 83 respondents *Treatment group*: 13.57 (± 21.53) with 80 respondents
Shaw et al. (2010) United Kingdom	Multi-center RCT	PSS	Patients with chronic upper limb spasticity	1000 Units of Abo-BoNT/A Intramuscular 12 Months	Pain using VAS 0 – 10	*Control group*: 4.20 (± 3.51) with 92 respondents *Treatment group*: 2.80 (± 3.51) with 97 respondents
Truong et al. (2010) USA and Russia	International Multi-center, Double-Blind RCT	CD	Male and female patients, aged 18 years or older with cervical dystonia, no previous BoNT/A injections, if previously treated with BoNT/A or BoNT/B, have a minimum interval of 16 weeks since last injection or returned to pre-treatment status	500 Units of Abo-BoNT/A Intramuscular 3 Months	Visual Analog Scale (0–10)	*Control group*: 45.10 (± 31.50) with 61 respondents *Treatment group*: 39.50 (± 27.50) with 55 respondents
Yelnik et al. (2007) France	Double-Blind RCT	PSS and hemiplegic shoulder pain	PSS with shoulder pain	500 Units of Abo-BoNT/A Intramuscular 1 Month	Visual Analog Scale (0–10)	*Control group*: 1.50 (± 2.21) with 10 respondents *Treatment group*: 1.00 (± 1.40) with 10 respondents

PSS post-stroke Spasticity, *TBI* Traumatic Brain Injury Spasticity, *CD* Cervical Dystonia, *Abo-Bont/A* Abobotulinum Toxin A, *Inco-Bont/A* Incobotulinum Toxin A, *TWSTRS* Toronto Western Spasmodic Torticollis Rating Scale, *RCT* Randomized Clinical Trial, *ADL* Activities of Daily Living, *MAS* Modified Ashworth Scale

Table 2 Characteristics of research studies on non-muscle-based pain disorders included in the meta-analysis ($N=12$)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Apalla et al. (2013) Greece	RCT	PHN	Men or women, over 18 years of age with PHN	100 Units of Abo-BoNT/A Subcutaneous 1 Month	Visual Analog Scale 0–10	*Control group*: 8.20 (±2.80) with 10 respondents *Treatment group*: 3.90 (±2.80) with 15 respondents
Attal et al. (2016) France	Double-blind RCT	Neuropathic pain	Patients with neuropathic pain, based on a score of at least four out of ten on the DN4 questionnaire	100 Units of Abo-BoNT/A Subcutaneous 6 Months	Numerical Rating Scale	*Control group*: 5.80 (±2.20) with 32 respondents *Treatment group*: 4.80 (±2.60) with 34 respondents
Ghasemi et al. (2014) Iran	Double-blind RCT	PDN	Patients diagnosed with diabetes mellitus and diabetic neuropathy confirmed using the DN4 questionnaire and nerve conduction velocity patterns	100 Units of Abo-BoNT/A Intradermal 0.75 Month	Numerical Rating Scale	*Control group*: – 0.10 (±2.97) with 20 respondents *Treatment group*: – 1.80 (±3.11) with 20 respondents
Han et al. (2016) South Korea	Double-blind RCT—Parallel	Neuropathic pain from SCI	Patients with SCI were recruited from the community and clinical settings and by referrals from clinicians	200 Units of Abo-BoNT/A Subcutaneous 2 Months	100 mm Visual Analog Scale	*Control group*: 76.80 (±20.40) with 20 respondents *Treatment group*: 63.80 (±27.50) with 20 respondents
Li et al. (2017) China	Double-blind RCT	Neuropathic pain from SCI	Patients with > 1 year post SCI with neuropathic pain lasting more than 3 months, and VAS score ≥ 40, aged 18–65 years old, ASIA impairment scale A to D	200 Units of Abo-BoNT/A Subcutaneous 2 Months	100 mm Visual Analog Scale	*Control group*: 0.40 (±2.50) with 22 respondents *Treatment group*: 12.10 (±40.6) with 22 respondents
Safarpour et al. (2010) USA	Double-blind RCT	CRPS	Patients meeting the IASP diagnostic criteria for CRPS	Max of 200 Units of Abo-BoNT/A Intradermal or Subcutaneous 2Mmonths	Visual Analog Scale 0 – 10	*Control group:* 6.00 (±2.00) with 6 respondents *Treatment group*: 7.30 (±1.70) with 8 respondents

Table 2 (continued)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Shehata et al. (2013) Egypt	RCT	Idiopathic TN	Patients with idiopathic TN which fulfilled the IHS criteria	40 – 60 Units of Abo-BoNT/A SC Subcutaneous 3 Months	Visual Analog Scale 0 – 10	*Control group*: 8.20 (±2.88) with 10 respondents *Treatment group*: 1.80 (±2.88) with 10 respondents
Wu et al. (2012) China	RCT	Idiopathic TN	Patients were diagnosed with TN according to the IHS criteria	75 Units Abo-BoNT/A Subcutaneous 3 Months	Visual Analog Scale 0 – 10	*Control group*: 5.00 (±6.41) with 20 respondents *Treatment group*: 1.00 (±6.41) with 22 respondents
Xiao et al. (2010) China	RCT	PHN	Patients with PHN who had pain for > 3 months following lesion healing and failed medical management	Max of 200 Units of Abo-BoNT/A Subcutaneous 3 Months	Visual Analog Scale 0 – 10	*Control group*: 5.00 (±1.15) with 20 respondents *Treatment group*: 4.00 (±1.15) with 20 respondents
Yuan et al. (2009) Taiwan	Randomized double-blind crossover trial	Diabetic Neuropathy	Patients with Type II DM for at least 3 years and with neuropathic pain that did not change over the last 1 month	50 Units of BoNT/A Intradermal 3 Months	Visual Analog Scale 0 – 10	*Control group*: 5.86 (±2.04) with 18 respondents *Treatment group*: 4.20 (±2.24) with 18 respondents
Zhang et al. (2014) China	Randomized controlled trial (RCT)	TN	Participants (> 18 years), who had failure of recent treatment for TN at baseline (pain intensity mean score > 4; mean attack frequency > 4 per day; course > 4 months), good general health, and understanding the possible complications, such as transient facial weakness	25 Units of BoNT/A Subcutaneous 1 Month	Visual Analog Scale 0–10	*Control group*: 4.00 (±5.24) with 16 respondents *Treatment group*: 1.90 (±5.24) with 27 respondents

Table 2 (continued)

Study (year) and country	Design	Diagnosis	Participants	Maximum or dose range, route of administration, and time of assessment post-injection	Outcome measurement	Results
Zuniga et al. (2013) Brazil	Randomized controlled trial (RCT)	TN	Men and women, older than 18 years, with a clinical diagnosis of classic or essential trigeminal neuralgia (TN)	50 Units of Ona-BoNT/A Subcutaneous 2 Months	Visual Analog Scale 0–10	*Control group*: 6.94 (±2.41) with 16 respondents *Treatment group*: 4.75 (±2.53) with 20 respondents

PHN Postherpetic Neuralgia, *PDN* Painful Diabetic Neuropathy, *TN* Trigeminal Neuralgia, *SCI* Spinal Cord Injury, *CRPS* Complex Regional Pain Syndrome, *Abo-Bont/A* Abobotulinum Toxin A, *ASIA* American Spinal Injury Association, *IASP* International Association for the Study of Pain

the mean difference between the effect of BoNT/A and placebo treatments is lower by 0.1003 compared when the route is muscle based. This effect of route was found to be not significant (p value −0.740).

Weighted overall SMD of −0.5463 favors BoNT/A over placebo. On the average, weighted SMD varies by as much as 0.4637 from this weighted overall SMD if route is taken into account. This estimate of between-study variance was found to be significantly different from zero based from the Likelihood-ratio test (p value = 0.0011). Results showed that route does not contribute to the overall heterogeneity (0.00%). The other 100.00% is explained by other factors. From this 100.00% variation unexplained by route, 67.62% is due to heterogeneity of studies signifying more covariates are affecting the advantage of BoNT/A over placebo (see Table 4).

Meta-regression with frequency

Meta-regression analysis showed that SMD is higher if the frequency is not a single dose [coded with one in the bubble plot]. This implies that the effects of BoNT/A and placebo treatments have lower difference in single dose. The bubble plot (Fig. 6) shows the increasing trend as frequency goes from single dose to 12 weeks to 12–16 weeks. If the frequency is not a single dose, the mean difference between the effect of BoNT/A and placebo treatments is higher by 0.3034 compared when the frequency is single dose. This effect of frequency was found to be not significant (p value = 0.294).

Weighted overall SMD of −0.5463 favors BoNT/A over placebo. On the average, weighted SMD varies by as much as 0.5117 from this weighted overall SMD if frequency is taken into account. This estimate of between-study variance was found to be significantly different from zero based from the Likelihood-ratio test (p value = 0.0018). Results showed that frequency explains 1.93% only of the overall heterogeneity. From this 98.07% variation unexplained by frequency, 66.31% is due to heterogeneity of studies signifying more covariates are affecting the advantage of BoNT/A over placebo (see Table 5).

Meta-regression with duration

Meta-regression analysis showed a positive association between duration and difference between the effect of BoNT/A and placebo. This can be clearly seen in the bubble plot (Fig. 7) where increasing duration is accompanied by increasing SMD. Hence, increasing SMD increases the difference in pain scores between BoNT/A and placebo. Increasing the duration by 1 month also increases the mean difference between the effect of BoNT/A and placebo treatments by 0.0433. This effect of duration was not significant (p value = 0.165).

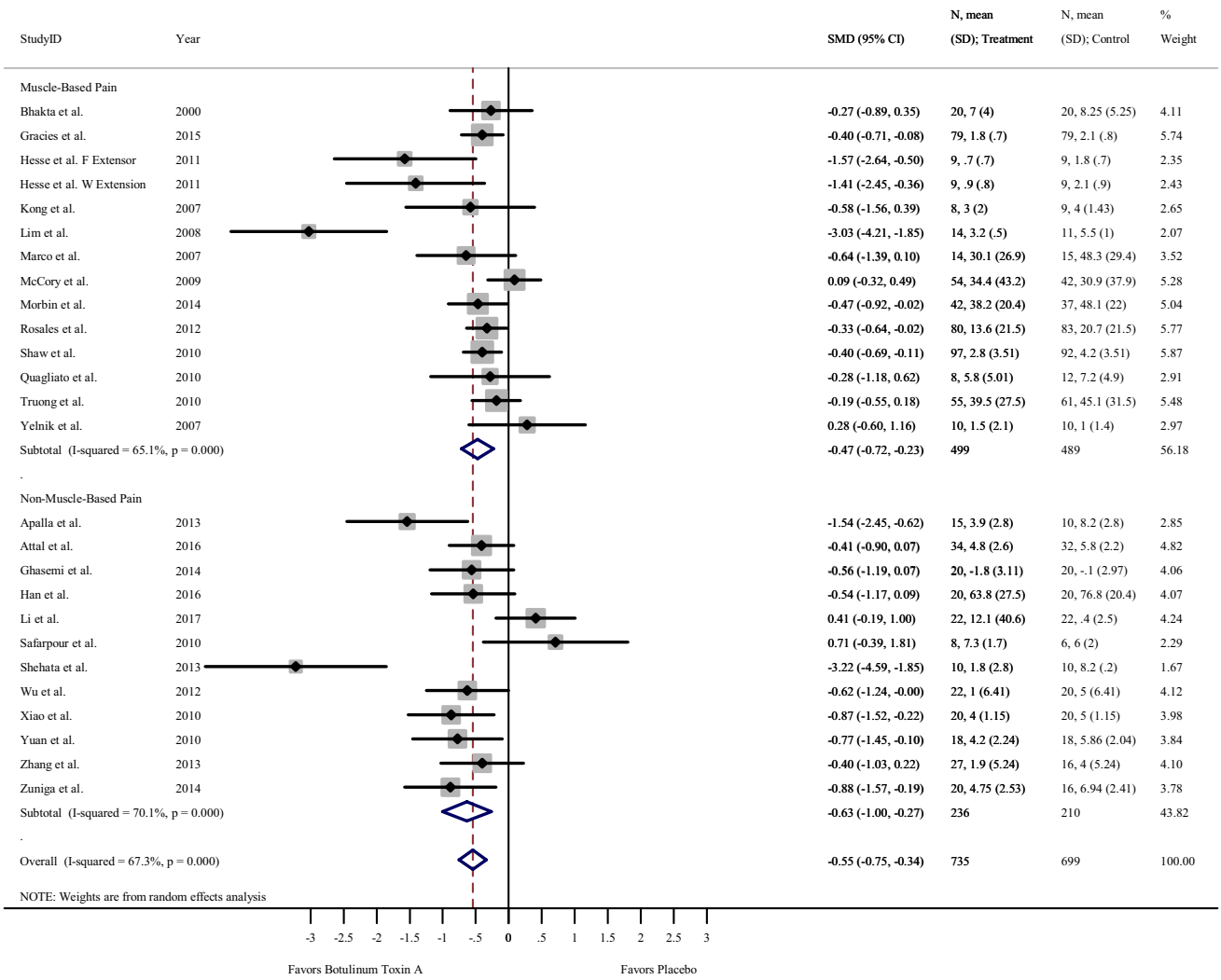

Fig. 2 Comparison of pain scores between muscle-based and non-muscle-based pain disorders

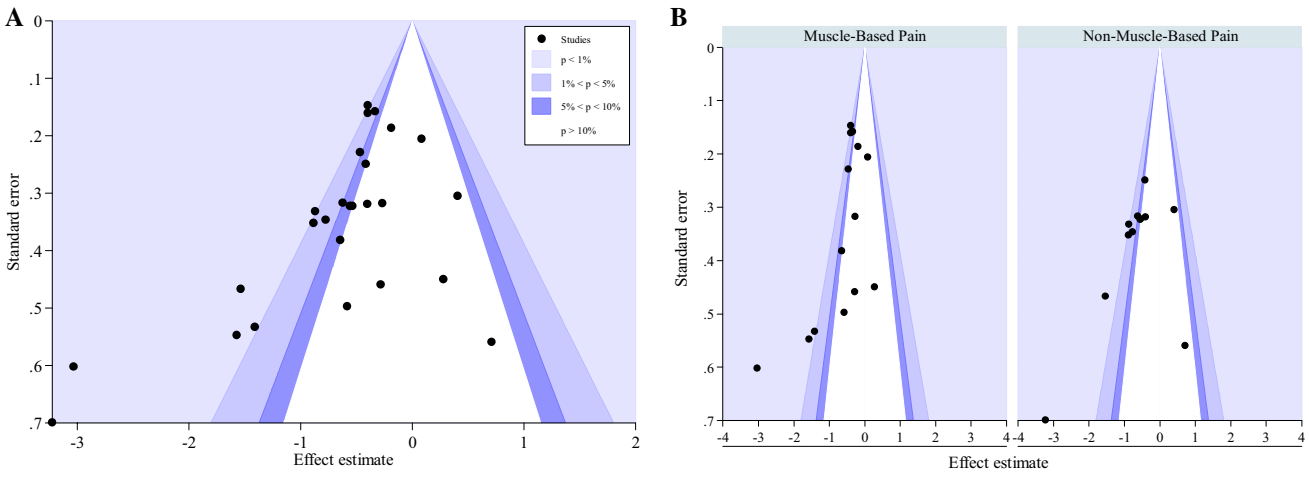

Fig. 3 Contour-enhanced funnel plots of **a** all studies included and **b** studies included according to type of pain (muscle-based and non-muscle-based)

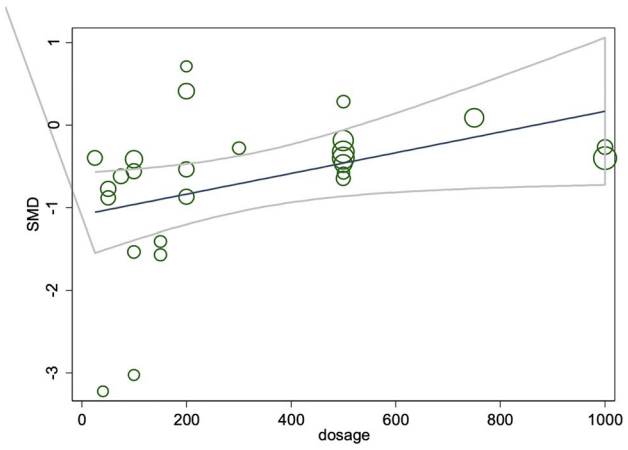

Fig. 4 Bubble plot (meta-regression with dosage)

Weighted overall SMD of − 0.5463 favors BoNT/A over placebo. On the average, weighted SMD varies by as much as 0.4591 from this weighted overall SMD if duration is taken into account. This estimate of between-study variance was found to be significantly difference from zero based from the Likelihood-ratio test (p value = 0.0036). Results showed that duration explains 21.05% of the overall heterogeneity. The remaining 78.95% is explained by other factors. From this 78.95% variation unexplained by duration, 65.39% is due to heterogeneity of studies signifying more covariates are affecting the advantage of BoNT/A over placebo (see Table 6).

Multiple meta-regression

Using all four covariates simultaneously in a single model revealed that dosage significantly affects SMD, while all other three do not have significant effects. Adjusting for route, frequency and duration, the effect of dosage is now higher from 0.0009 to 0.0014. Increasing the dosage by one unit increases the mean difference between the effect of BoNT/A and placebo treatments by 0.0014. However, joint F-test of these four covariates is not significant for p value is high 0.1182. This implies that the model with these four covariates does not significantly explain the heterogeneity of SMD. Other important factors can define the difference in the effects of BoNT/A and placebo treatments observed in the 25 studies analyzed.

On the average, weighted SMD varies by as much as 0.1913 from the weighted overall SMD if all four covariates are taken into account. This estimate of between-study variance was found to be significantly different from zero based

Table 3 Meta-regression with dosage

Covariate	Effect	p value	Remark
Dosage	0.0009	0.063	Significant at 10%
Overall SMD			− 0.5463
Between-study standard deviation (τ)			0.4567
Likelihood-ratio test of $\tau = 0$			p value = 0.0017
Residual variation due to heterogeneity (I^2 res)			64.83%
Proportion of between-study variance explained			21.85%

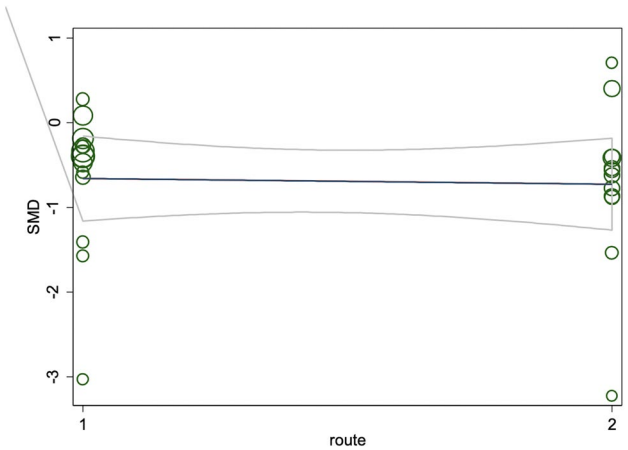

Fig. 5 Bubble plot (meta-regression with route/mode)

Table 4 Meta-regression with route/mode

Covariate	Effect	p value	Remark
Route	− 0.1003	0.740	Not significant
Overall SMD			− 0.5463
Between-study standard deviation (τ)			0.4637
Likelihood-ratio test of $\tau = 0$			p value = 0.0011
Residual variation due to heterogeneity (I^2 res)			67.62%
Proportion of between-study variance explained			0.00%

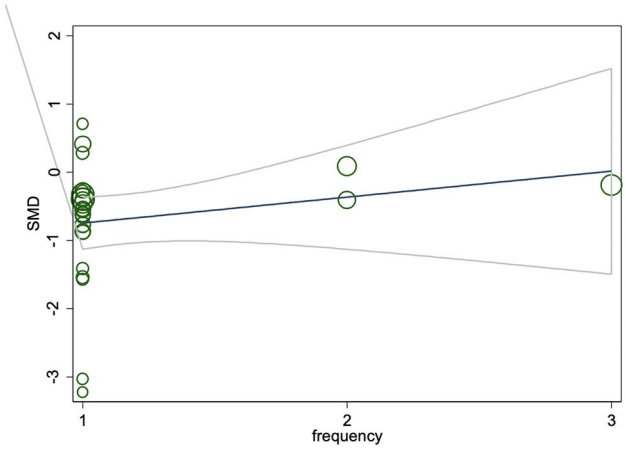

Fig. 6 Bubble plot (meta-regression with frequency)

from the Likelihood-ratio test (p value = 0.0017). Results showed that, collectively, these four covariates explain 28.33% of the overall heterogeneity. From the remaining 71.67% variation unexplained by these four covariates, 63.99% is due to heterogeneity of studies signifying more covariates are affecting the advantage of BoNT/A over placebo (see Table 7).

Discussion

This present meta-analytic study demonstrated that BoNT/A is effective in reducing pain from both muscle- and non-muscle-based triggers. The contention of dichotomizing muscle from non-muscle-based pain is hinged upon the knowledge of BoNT effects along the muscle where it is directly

Table 5 Meta-regression with frequency

Covariate	Effect	p value	Remark
Frequency	0.3034	0.294	Not significant
Overall SMD			− 0.5463
Between-study standard deviation (τ)			0.5117
Likelihood-ratio test of $\tau = 0$			p value = 0.0018
Residual variation due to heterogeneity (I^2 res)			66.31%
Proportion of between-study variance explained			1.93%

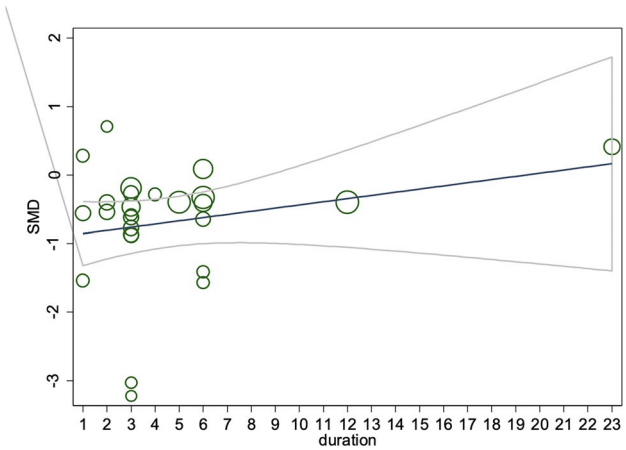

Fig. 7 Bubble plot (meta-regression with duration)

applied. BoNT has been increasingly used "off-label" in neuropathic pain states. Here, we specifically included subcutaneous injections for pain in TN (Ngeow and Nair 2010; Babiloni et al. 2016), PHN (Shackleton et al. 2016), TBI/SCI (Melnyk and Fineout-Overholt 2010), PDN, central neuropathic pain in multiple sclerosis (Habek et al. 2010), and post-stroke pain (Higgins and Thompson 2002; Sterne 2016; Valentine et al. 2010). In dystonia, the abnormally sustained muscle activity may eventually lead to pain which is said to be present in 65–75% of patients with dystonia which also causes significant disability among patients (Shaw et al. 2010). On the other hand, spasticity complicates and disable neurologic patients with stroke, multiple sclerosis, and TBI/SCI, with pain occurring in 65% of cases. Spasticity-related pain is derived from severe muscle spasms, co-contraction, abnormal posturing and setting-in of biomechanical forces

Table 6 Meta-regression with duration

Covariate	Effect	p value	Remark
Duration	0.0433	0.165	Not significant
Overall SMD			−0.5463
Between-study standard deviation (τ)			0.4591
Likelihood-ratio test of $\tau = 0$			p value = 0.0036
Residual variation due to heterogeneity (I^2 res)			65.39%
Proportion of between-study variance explained			21.05%

Table 7 Multiple meta-regression

Covariates	Effect	*p* value	Remark
Dosage	0.0014	0.047	Significant at 5%
Route	0.5732	0.159	Not significant
Frequency	0.2721	0.291	Not significant
Duration	0.0273	0.362	Not significant
Joint F-test			p value = 0.1182
Overall SMD			−0.5463
Between-study standard deviation (τ)			0.1913
Likelihood-ratio test of $\tau = 0$			p value = 0.0017
Residual variation due to heterogeneity (I^2 res)			63.99%
Proportion of between-study variance explained			28.33%

along the musculoskeletal region from immobility (Yelnik et al. 2007).

In our present work, we have showed that BoNT/A reduced pain scores greater with increasing sufficient and therapeutic amount of dosage used and among patients injected with BoNT/A whether directly to the muscle (muscle-based), intradermal or subcutaneously (non-muscle based). BoNT/A proved to be efficacious in reducing pain by affecting cholinergic transmission by blocking acetylcholine release from the pre-synaptic terminal at the neuromuscular junction, hindering muscle fiber contraction and leading to muscle relaxation and pain reduction. BoNT is successful in treating pathologies characterized by hyperexcitability of peripheral nerve terminals (Caleo et al. 2018; Pellet 2012; Pirazzini et al. 2017). However, substantial experimental and clinical evidence indicates that not all BoNT/A effects can be explained solely by silencing of the neuromuscular junction (Caleo et al. 2018). It also acts by inhibiting neuropeptides involved in pain transmission, namely substance P, CGRP, glutamate, and TRPV1 (Wheeler and Smith 2013). Hence, it may be effective in pain relief of non-muscle-based pain disorders. BoNT has a direct anti-nociceptive effect to muscle pain receptors including receptors for proprioception and spinal cord circuitry modulation through gamma efferent block, direct muscle relaxation and reduction of muscle spasm (Higgins and Thompson 2002). Some studies assumed that the effect of BoNT/A is through a retrograde axonal transport of BoNT/A via central neurons and motor neurons which offered novel pathways of BoNT/A trafficking with neurons (Bach-Rojecky et al. 2010). Hence, it can, therefore, be concluded that the anti-nociceptive effect of BoNT/A may be associated with processes of central sensitization (Bach-Rojecky et al. 2010). These effects may be the consequence of hematogenic spread, a retrograde neural transport of BoNT to the central nervous system, or an indirect action secondary to denervation and changes of afferent input resulting in the plastic reorganization of the CNS (Gwak and Hulsebosch 2011). Studies reported different effects of BoNT at the level of spinal cord and brain circuits contributing to its therapeutic benefits (Caleo et al. 2018). Several other animal studies provide evidence for a retrograde transport of BoNT (Aoki 2005; Bach-Rojecky and Lackovic 2005). In one study, radioactivity was found successively in the sciatic nerve, the ipsilateral spinal ventral roots and the spinal cord with a distal–proximal segment following intramuscular injection of radiolabeled BoNT in the cat gastrocnemius muscle (Gwak and Hulsebosch 2011; Weise et al. 2019) which demonstrated functional changes on parts of the soma membrane of the alpha-motoneuron on follow-up neurophysiological study (Gwak and Hulsebosch 2011; Weise et al. 2019; Akaike et al. 2013; Lackovic et al. 2018). In a recent study, it showed that BoNT acted at facial nucleus neurons after injection in the whisker muscles (Gwak and Hulsebosch 2011; Wiegand and Wellhöner 1977; Akaike et al. 2013; Lackovic et al. 2018). Consistent with other studies, they were able to detect cleaved SNAP25 [synaptosomal nerve associated protein at distant cells, upstream from the initial uptake neurons] indicating a catalytic action following retrograde interneuronal transport via transcytosis (Gwak and Hulsebosch 2011; Wiegand and Wellhöner 1977; Antonucci et al. 2008; Bomba-Warczak et al. 2016; Akaike et al. 2013; Lackovic et al. 2018). There is functional evidence of bilateral muscle relaxation after unilateral injection of BoNT in the rat paw. Here, BoNT arrived at the contralateral muscle to similar extents via neural pathways and the hematogenous route, which suggests transport within neuronal networks as an additional mechanism for BoNT's action at distant sites.

BoNT primarily acting on the neuromuscular junction results in a biochemical denervation and muscle weakness of the injected muscle, this mechanism undoubtedly constitutes the main action and cause for the reliable clinical effect of BoNT in several neurological and pain disorders. Nevertheless, alongside its peripheral action, strong clinical evidence exists indicating additional BoNT-related central effects. Current literature suggests that indirect effects of BoNT on the brain may be more prominent (Lackovic et al. 2018). Here, the changes to the afferent input are thought to

result in short- and long-term plastic changes to the CNS. This reorganization of the brain may have an additional therapeutic effect. It may potentially be responsible for the long-lasting clinical effect of BoNT or its effect in non-treated muscles (Weise et al. 2019).

Conclusion

In conclusion, the peripheral blocking effects of BoNT/A impact in reducing pain from both muscle-based and non-muscle-based pain conditions, be it administered intramuscularly (for muscle-based pain) or subcutaneously/intradermal (for non-muscle-based pain) accordingly. The fact that BoNT/A effects on pain did not favor one over the other, injection approach addressing the specific disease state argues toward independent effects in pain mechanisms. The development of new and engineered toxins that are specifically targeted for pain neurotransmitters will be an interesting new chapter and innovation in the management of painful conditions.

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