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REVIEW ARTICLE

Intramuscular injections of botulinum toxin for the treatment of upper back myofascial pain syndrome: A systematic review of randomized controlled trials

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Abstract

Background and Objective: Myofascial pain syndrome (MPS) is a chronic musculoskeletal disorder characterized by the presence of trigger points. Among the treatment options, botulinum toxin injections have been investigated. The aim of this paper was to provide a synthesis of the evidence on intramuscular botulinum toxin injections for upper back MPS.

Databases and Data Treatment: A systematic review of the literature was performed on the PubMed, Scopus and Cochrane Library, using the following formula: ("botulinum") AND ("musculoskeletal") AND ("upper back pain") OR ("myofascial pain").

Results: Ten studies involving 651 patients were included. Patients in the control groups received placebo (saline solution) injections, anaesthetic injections + dry needling or anaesthetic injections. The analysis of the trials revealed modest methodological quality: one "Good quality" study, one "Fair" and the other "Poor". No major complications or serious adverse events were reported. Results provided conflicting evidence and did not demonstrate the superiority of botulinum toxin over comparators. Most of the included trials were characterized by a small sample size, weak power analysis, different clinical scores used and non-comparable follow-up periods. Even if there is no conclusive evidence, the favourable safety profile and the positive results of some secondary endpoints suggest a potentially beneficial action in pain control and quality of life.

Conclusion: The currently available studies show conflicting results. Their overall low methodological quality does not allow for solid evidence of superiority over other comparison treatments. Further insights are needed to properly profile patients who could benefit more from this peculiar injective approach.

Significance: The randomized controlled trials included in this review compared using botulinum toxin to treat upper back MPS with placebo or active treatments (e.g.,

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dry needling or anaesthetics) showing mixed results overall. Despite the lack of clear evidence of superiority, our study suggests that the use of botulinum toxin should not be discouraged. Its safety profile and encouraging results in pain control, motor recovery and disability reduction make it an interesting treatment, particularly in the subset of patients with moderate to severe chronic pain and active trigger points. To support the safety and efficacy of botulinum toxin, further high-quality studies are needed.

1 | INTRODUCTION

Myofascial pain syndrome (MPS) is a chronic musculoskeletal disorder of multifactorial aetiology characterized by the presence of areas of muscle tenderness and stiffness, known as trigger points, which cause localized and radiating pain in the surrounding regions and reduce range of motion (ROM) (Gobel et al., 2006). This muscle pain, which can last up to 6–12 months, can be associated with sensory, motor and autonomic symptoms that limit motor function (Bordoni et al., 2023). When this clinical condition occurs in the neck and/or upper back muscles (e.g. trapezius, latissimus dorsi, levator scapulae, rhomboids), it is referred to as upper back myofascial pain syndrome (UBMPS) (Geri et al., 2022; Ziaeifar et al., 2019). Beyond traumatic and posture-related causes, UBMPS can also be a consequence of an excessive release of acetylcholine (ACh) (Mendes et al., 2019), which leads to spasms and prolonged muscle contraction, resulting in an increased concentration of inflammatory and nociceptive factors within the trigger point (Nicol et al., 2014). This persistent stimulus could lead to central sensitization, which is characterized by altered sensory processing with abnormal response of nociceptive neurons, even to non-painful stimuli, and pain hypersensitivity (Graboski et al., 2005; Nicol et al., 2014). The combination of peripheral nociceptor activation, changes in the pain modulation process, and an inflammation-painful state leads through unclear evolutionary mechanisms, to the symptoms chronicization and to nociplastic pain onset (Clark et al., 2017; Fitzcharles et al., 2021). Early UBMPS symptoms may be sudden or may worsen progressively, lasting for more than 6 months, manifesting as deep aching pain in specific upper body muscle areas or with referred pain limiting motor function (Lu et al., 2022). This clinical condition must be distinguished from others (e.g. muscle cramps), which cause pain and transient functional limitation due to temporary muscle shortening and do not always require therapeutic management (Tantanatip et al., 2021). For example, in muscle cramps, the pain is associated with a continuous, involuntary and localized contraction of a few muscle fibres up to an entire muscle group, limited to a few seconds to a few minutes, due to idiopathic or known causes (Bordoni et al., 2023; Shah et al., 2015).

Nowadays, there are no standard diagnostic criteria for UBMPS, so local manual palpation is used to identify tenderness, twitching and/or tightness (Myburgh et al., 2011). Conventional therapeutic approaches to relieve myofascial pain are conservative and include stretching exercises, massage and manual myofascial release techniques, with transitory and partial results in terms of long-term pain relief and full functional recovery (Harden et al., 2009). In addition, minimally invasive treatments such as dry needling (Navarro-Santana et al., 2020), local anaesthetics or isotonic saline solution injections (Tantanatip et al., 2021) or pharmacotherapy with steroids, nonsteroidal anti-inflammatory agents and antidepressants are frequently used as therapeutic alternatives, especially for chronic pain (Harden et al., 2009; Shah et al., 2015). Among these, botulinum toxin (BTX) intramuscular injections have been investigated as an alternative therapy for chronic MPS (Kwanchuay et al., 2015). BTX is a neurotoxin protein produced by *Clostridium botulinum* that downregulates neuropeptides and neurotransmitters' receptors (e.g., substance P and CGRP) (Mahowald et al., 2006; Sconza et al., 2023) and their responses by inhibiting ACh release at the neuromuscular junction with important anti-nociceptive effects in chronic pain (Ferrante et al., 2005; Letizia Mauro et al., 2021). Based on this evidence, a possible explanation of BTX pain inhibition in UBMPS is that it modulates the activity of muscle spindles, resulting in relaxation of the painful muscle and offering a long-lasting effect (3–4 months) compared with conventional modalities (Nicol et al., 2014). Thus, BTX has been demonstrated to possess antinociceptive and muscle-relaxant properties, so that it would be useful in chronic musculoskeletal pain (Casale & Tugnoli, 2008; Ernberg et al., 2011). This effect may not be limited to the injection site; in fact, considering the documented spread through the muscle fascia and to contiguous non-injected sites, BTX could lead to modifications in length-force muscles characteristics (Shaari et al., 1991; Yaraskavitch et al., 2008). This mechanism of action of BTX could interrupt the pain cycle, suggesting possible efficacy in the treatment of UBMPS (Eisele et al., 2011), as demonstrated by initial exploratory studies (Benecke et al., 2011), stimulating the interest of authors to explore this topic further. However, there is no

standardized protocol in the literature for the intramuscular use of BTX in the treatment of MPS with different methods of administration and dosages (Avendano-Coy et al., 2014).

The aim of this paper was to review the actual evidence on the use of BTX intramuscular injections for the treatment of UBMPS to understand its real therapeutic effect and compare it with other conservative treatments.

2 | LITERATURE SEARCH METHODS

2.1 | Literature searches and databases

A systematic review of the literature was performed on the use of injective treatment with intramuscular botulinum neurotoxin in UBMPS. We conducted the search for English articles published up to the end of September 2023 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) principles. The electronic databases PubMed, Scopus and Cochrane Library were investigated, using the following formula: ("botulinum") AND ("musculoskeletal") AND ("upper back pain") OR ("myofascial pain").

2.2 | Eligibility criteria

Authors met the following inclusion criteria: (1) randomized controlled trials (RCTs), (2) English language, (3) from indexed journals in the last 20 years (2003–2023) and (4) use of intramuscular injections of BTX for the treatment of UBMPS. Exclusion criteria were RCTs including other muscle regions, other minimally invasive treatments beyond BTX or physical and instrumental therapy.

2.3 | Data extraction

Database searching was supplemented by screening reference lists and tracking citations included in articles to identify any additional studies. Three independent observers (A.A., B.D.M. and S.R.) conducted the screening by deciding which articles to read in full text. Any disagreement was solved by the authors. Then, the data extraction was performed independently by the other two authors (E.K., G.L.) that also contributed to the analysis process. The accuracy of the extracted data was confirmed by another author (C.S.). Any disagreement was solved by consensus. Articles were initially screened using the title and abstract. After reading the full text, other articles were excluded following the previously established criteria. The PRISMA flowchart is represented in Figure 1. Relevant data were then collected into a database with the consensus of the two observers on (1) treatment groups, (2) sample size and characteristics, (3) BTX preparation method, (4) therapeutic protocols, (5) outcome measures, (6) time points of follow-up evaluations and (7) clinical outcomes. The authors considered whether RCTs showed adverse effects. The primary outcome of this review was the analysis of patient-reported subjective scores and pain at 1-month follow-up.

2.4 | Assessment of the quality of evidence

The risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs, as detailed in Table 2. The results were then converted to Agency for Healthcare Research and Quality (AHRQ) standards, which ultimately classify RCTs as "good quality", "fair quality" or "poor quality" as follows: "good quality": all criteria met (i.e., low for each domain); "fair quality": one criterion not met (i.e., high risk of bias for one domain) or two criteria unclear and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; and "poor quality": one criterion not met (i.e., high risk of bias for one domain) or two criteria unclear and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results; two or more criteria are listed as high or unclear risk of bias.

3 | RESULTS

A total of 10 studies published from 2003 to 2023 dealing with the use of BTX injective treatment for UBPMS were ultimately included in this review. A detailed description of each study is provided in Table 1.

3.1 | Study design and quality

All studies were, as per inclusion criteria, RCTs. The studies' designs were extremely variable, since patients in the control groups received different injections or treatments: placebo (saline solution) injections in eight studies (Benecke et al., 2011; Ferrante et al., 2005; Gobel et al., 2006; Kwanchuay et al., 2015; Lew et al., 2008; Nicol et al., 2014; Ojala et al., 2006; Qerama et al., 2006), anaesthetic injections + dry needling in one study (Kamanli et al., 2005) and anaesthetic injections in one study (Graboski et al., 2005).

Looking at the quality of the available literature by AHRQ standard, we found that one study reached a "good quality" standard (Lew et al., 2008), one was ranked as "fair quality" (Kwanchuay et al., 2015) and the remaining

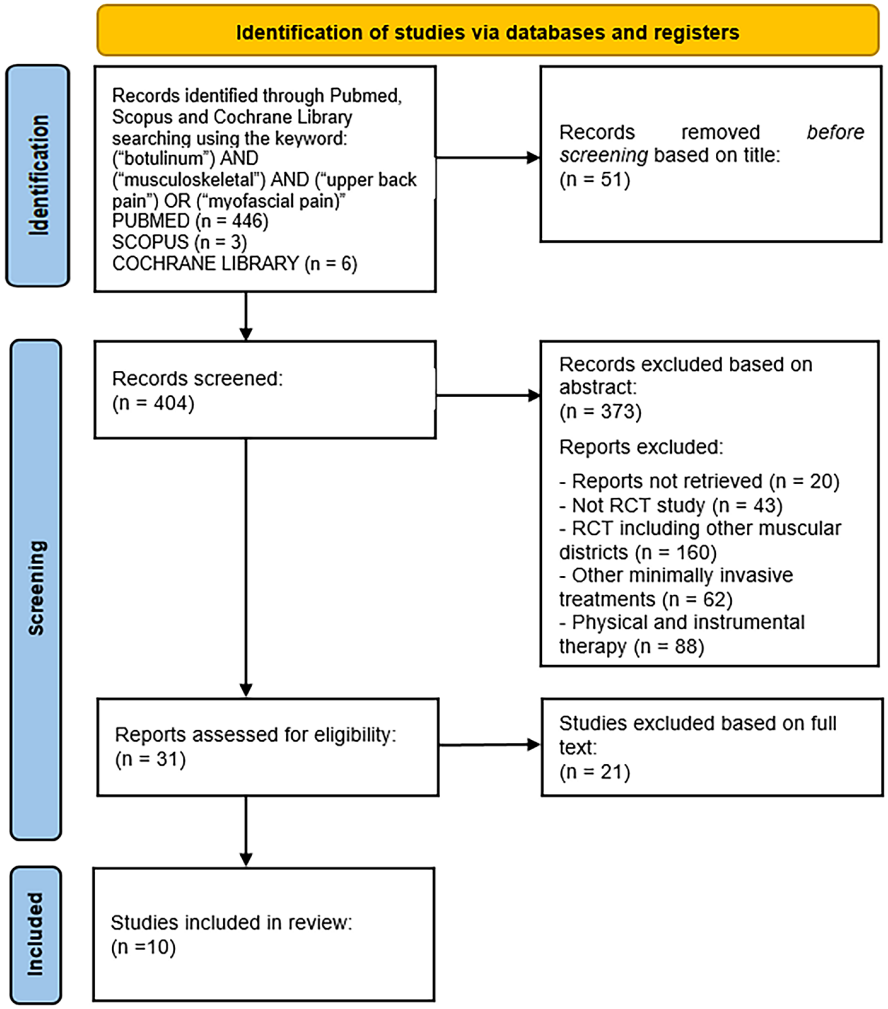

FIGURE 1 Preferred reporting items for systematic reviews and meta-analyses flowchart resuming the paper's selection process. RCT, randomized controlled trial.

eight were considered as "poor quality". The results of the analysis performed with the Cochrane Risk of Bias tool for RCT are detailed in Table 2. Regarding the random sequence generation process, it was specified in eight papers (Benecke et al., 2011; Gobel et al., 2006; Graboski et al., 2005; Kwanchuay et al., 2015; Lew et al., 2008; Ojala et al., 2006; Qerama et al., 2006). The method of allocation concealment was described in six studies (Benecke et al., 2011; Gobel et al., 2006; Graboski et al., 2005; Kwanchuay et al., 2015; Lew et al., 2008; Qerama et al., 2006). Two papers reported outcomes incompletely (Benecke et al., 2011; Qerama et al., 2006). Regarding sample size calculation, in eight trials, the power analysis methods were not fully clarified (Benecke et al., 2011; Ferrante et al., 2005; Gobel et al., 2006; Graboski et al., 2005; Kamanli et al., 2005; Nicol et al., 2014; Ojala et al., 2006; Qerama et al., 2006). Eight trials were double-blinded (Benecke et al., 2011; Ferrante et al., 2005; Gobel et al., 2006; Graboski et al., 2005; Lew et al., 2008; Nicol et al., 2014; Ojala et al., 2006; Qerama et al., 2006); one was single-blinded (Kamanli et al., 2005) and the other was unblinded (Kwanchuay et al., 2015). Moreover, the risk of attribution bias was unclear for most of the studies: all studies specified the number of patients screened, but not all of them clarified how many were excluded from randomization and why, how many were lost to follow-up and for what specific reason. Flow diagrams depicting the patients' selection process were reported in all studies except for two studies (Ferrante et al., 2005; Kamanli et al., 2005). Finally, none of the trials were registered in a public clinical trial registry, which should be mandatory according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.

3.2 | Patients and evaluation methods

Ten studies involving a total of 651 patients with UBMPS were included. In most of the papers, patients enrolled were affected by UBMPS diagnosed through clinical examination by tender nodule palpation for trigger point identification, local twitch contraction response and specific patterns of referred pain associated with each trigger point. Baseline and follow-up assessments were based on clinical scores in all studies.

Pain evaluation was performed in most of the studies (Ferrante et al., 2005; Graboski et al., 2005; Kwanchuay et al., 2015; Lew et al., 2008) by using the visual analogue scale (VAS); also, other authors used the visual numeric scale (Nicol et al., 2014) and the numerical rating scale (Qerama et al., 2006). Moreover, concerning functional assessment, the following scales were used: the Neck Disability Index (NDI) (Lew et al., 2008; Nicol et al., 2014) and the ROM measurement (Qerama et al., 2006). The impact of UBMPS on quality of life was analysed using the Short-Form (36) Health Survey (SF-36) (Ferrante et al., 2005; Lew et al., 2008; Nicol et al., 2014) and the Nottingham Health Profile (NHP) (Kamanli et al., 2005). In addition to clinical questionnaires, five trials reported the assessment of trigger point sensitivity by measurement of the Pain Pressure Threshold (PPT) (Fischer, 1986) using a pressure algometer (Ferrante et al., 2005; Kwanchuay et al., 2015; Ojala et al., 2006; Qerama et al., 2006).

3.3 | Treatments

The injected BTX volume and concentration were not uniform in the studies, and the dosage ranged from 10 up to 300 IU depending on the number of active treated trigger points. Regarding the methods of BTX administration, treatment protocols were different in terms of the number of injections and temporal frequency. In all trials, BTX was injected directly into the trigger points clinically identified during the physical examination, except in one trial where BTX was injected into the painful muscle (Nicol et al., 2014). The most sensitive trigger points identified were used as the injection sites. In addition, in two studies, the trigger point positions were mapped with a marker pen and recorded against anatomical reference points, creating true anatomical maps to ensure consistency and accuracy of injection (Ojala et al., 2006; Qerama et al., 2006). The BTX preparation method and therapeutic protocol are detailed in Table 1.

3.4 | Complications

All the RCTs reported data on adverse events. Patients were systematically asked about adverse events at follow-up. Only transient and mild adverse events were reported, such as local flushing, flu-like symptoms, localized tenderness or stiffness, arthralgia, mild muscle weakness or soreness and headache. No major complications or serious adverse events were reported in any of the included trials. A summary of adverse events is shown in Table 1.

3.5 | Reported clinical outcome

Three studies (Benecke et al., 2011; Gobel et al., 2006; Nicol et al., 2014) showed that BTX treatment met primary endpoints in pain management. In two studies (Kwanchuay et al., 2015; Lew et al., 2008), the BTX experimental group did not meet the primary endpoint, but there was a slight positive trend towards improvement in VAS scores compared with the placebo control group.

Three studies (Ferrante et al., 2005; Ojala et al., 2006; Qerama et al., 2006) showed no significant differences between BTX treatment of trigger points in the experimental group and placebo in the control group in terms of VAS score, PPT and reduction in drug intake; thus, they do not support a specific antinociceptive and analgesic effect of BTX. In the study by Ojala et al., the subjective outcome of treatment after the first injections was significantly in favour of BTX, whereas after the second injections it was better for saline, but the difference was not statistically significant. In addition, the Qerama study showed that BTX reduced motor endplate activity and Electromyography interference patterns without altering trigger point pain, thus challenging the proposed paradigm of the relationship between endplate activity and trigger point pain.

In the study by Kamanli et al. (2005), treatment with lidocaine injection in the control group was found to be more convenient, quicker and to cause less discomfort than dry needling in the experimental group treated with BTX injection. Graboski et al. partially confirmed this finding, claiming that there was no significant difference between BTX and local anaesthetic treatment, either in the duration and intensity of pain relief, or in patient function and satisfaction. However, given the high cost of BTX, Graboski et al. (2005) identified anaesthetic injections as a more cost-effective solution for UBMPS.

4 | DISCUSSION

The main findings of the present systematic review are as follows: (1) the overall "poor" quality of studies comparing the use of botulinum toxin with other treatments and (2) the lack of univocal results for the intramuscular use of BTX for the treatment of UBMPS.

BTX injections were tested against placebo (saline solution) and other common mini-invasive treatments such as anaesthetic injections and dry needling. Unfortunately, the small number of studies found and the lack of clinical scores used in many studies did not allow the authors to perform a meta-analysis of the results. Most of the RCTs included were characterized by a small sample size and weak power analysis, in some cases lacking a clear indication of the numerical data used to calculate the sample

TABLE 1 Data extracted from included studies.

Publication	Study design	Score	Patients features	BTX preparation method
Kwanchuay et al. (2015)	BTX injection vs. placebo (saline) injection Open-label study	VAS, PPT by using the Fisher algometer	48 (BTX: 24 vs. CG: 24) *Age*: BTX: 39.8 (±10.1) vs. CG: 38.8 (±10.8) *Sex*: BTX: F: 20 (83.3%) vs. CG: F: 22 (91.7%)	*V & Conc*: 100 IU of BTX in 1 mL of 0.9% NaCl
Nicol et al. (2014)	BTX injection vs. placebo (saline) injection	VNS, SF-36, NDI, BPI	54 (BTX: 29 vs. CG: 25) *Age*: BTX: 48.8 (±16.2) vs. CG:47.4 (±14.9) *Sex*: BTX: F: 23 (79%) vs. CG: F: 19 (76%)	*V & Conc*: 25 IU of BTX diluted in 4-mL sterile saline
Benecke et al. (2011)	BTX injection vs. placebo (saline) injection	Rated pain on a 4-point scale: 1, no pain; 2, mild pain; 3, moderate pain and 4, severe pain; changes in pain intensity and the number of pain-free days per week	148 (BTX: 76 vs. CG: 72) *Age*: BTX: 48 (±13) vs. CG: 45 (±10) *Sex*: BTX: M: 32 (42%) vs. CG: M: 20 (28%)	*V & Conc*: 40 IU of BTX in 0.4 mL of saline solution
Lew et al. (2008)	BTX injection vs. placebo (saline) injection	VAS, NDI, SF-36	29 (BTX: 14 vs. CG: 15) *Age*: BTX: 48.7 (±9.4) vs. CG: 48.5 (±13.4) *Sex*: BTX: F: 6 (42.9%) vs. CG: F: 3 (20.0%)	*V & Conc*: 100 IU of BTX reconstituted by 2 mL of normal saline
Gobel et al. (2006)	BTX injection vs. placebo (saline) injection	Mean weekly score of at least three points on an ordinal self-rating pain scale (1 = no pain to 4 = severe pain)	144 (BTX: 74 vs. CG: 70) *Age*: BTX: 44 (±12) CG: 45 (±11) *Sex*: BTX: M: 13 (18%) vs. CG: M: 16 (23%)	*V & Conc*: 40 IU per site of BTX into the 10 most tender trigger points
Ojala et al. (2006)	BTX injection vs. placebo (saline) injection	Severity of neck-shoulder pain from 0 to 10 (no pain [0] to unbearable pain [10]) about half an hour before each treatment session. Patient's self-assessment of the efficacy of each treatment assessed using a verbal rating scale (1 = very good; 2 = rather good; 3 = some; 4 = rather small; 5 = none). The PPT of TPs and the reference point measured in the sitting position with a algometer	31 (BTX: 15 vs. CG: 16) *Age*: BTX: 44.9 (±7.6) vs. CG: 43.8 (±8.1) *Sex*: NA	*V & Conc*: The total dose varied from 15 to 35 IU of BTX depending on the number of active treated TPs The mean total dose of BTX was 28 (±6)
Qerama et al. (2006)	BTX injection vs. placebo (saline) injection	NRS, PPT using a hand-held pressure electronic algometer, ROM shoulder measurement	29 (BTX: 14 vs. CG: 15) *Age*: BTX: mean age 54.5 (range 31–72) vs. CG: mean age 46.7 (range 23–76) *Sex*: F: 18 (62%)	*V & Conc*: 50 IU in 0.25 mL of saline solution

Therapeutic protocol and follow-up (F-up)	Results	Safety	AHRQ standard	Overall performance
20 IU/TP. F-up at baseline, and at 3 and 6 weeks after injection	The efficacy in VAS reduction of a single 20 IU of BTX injection was not different from 0.9% NaCl for myofascial TP at the upper trapezius muscle. However, BTX showed a statistically significant increase in PPT at 6 weeks after injection	11 patients in the BTX group (45.8%) had non-severe, transient effects (1 skin redness, 2 feverish sensations, 4 local tightness, 3 local stiffness, 1 skin redness + stiffness)	Fair	*BTX +/−* BTX failed to reach the primary endpoint (VAS) but achieved positive secondary endpoints (PPT)
Painful muscles were injected with a maximum of 300 IU. F-up at baseline, 6, and 12 weeks after the first injection, until completion of the study after 26 weeks	BTX group improved average pain scores, reduced number of headaches per week and BPI interference scores for general activity and sleep compared to placebo in patients experiencing severe cervical and shoulder girdle myofascial pain	No major adverse effects. Transient flu-like illness (9), arthralgia (1), fatigue (4), mild neck weakness (25), modest neck weakness (4)	Poor	*BTX +* BTX reached the primary endpoint (VNS) in subjects who received a second dose, but also improved the secondary endpoints (SF-36, NDI, BPI)
40 IU in 10 TP. F-up at baseline and at 5, 8 and 12 weeks after injection	Duration of daily pain was reduced in the BTX group compared with the placebo group at weeks 9 and 10. Fixed-location treatment with BTX led to a significant improvement of the main target parameter only in week 8	Adverse effects mild or moderate 31 (41%) in the BTX group and 28 (39%) in the CG	Poor	*BTX +* BTX reduced pain duration and intensity in the medium term in primary outcomes (Rated pain on a 4-point scale). Secondary parameters (physicians 'and patients' global assessment) significantly favoured BTX over placebo
50 IU/site with a maximum of 200 IU. F-up at 2 weeks and at months 1, 2, 3, 4 and 6	Trends towards improvements in VAS and NDI scores in the BTX group are encouraging, but they were possibly due to a placebo effect and were not statistically significant. The BTX subjects, at certain time points, showed statistically significant improvements in the bodily pain and mental health scales of the SF-36 compared with controls	No serious adverse event reported	Good	*BTX +/−* BTX does not significantly improve primary outcomes (VAS), but reached statistically significant positive improvements in secondary endpoints (NDI, SF-36)
F-up at 4, 5, 6, 8, 11, 12 weeks	At week 5, 51% of BTX patients reported mild or no pain. Compared with placebo, BTX resulted in a significantly greater change from baseline in pain intensity during weeks 5–8 and significantly fewer days/weeks without pain between weeks 5 and 12. In patients with UBMPS, BTX injections at 10 individualized TPs significantly improved pain levels 4–6 weeks after treatment	No serious adverse events occurred during the study. Two muscles soreness	Poor	*BTX +* BTX reached positive results in primary outcomes (ordinal self-rating pain scale) and in secondary outcomes (changes in pain intensity and the number of pain-free days per week)
F-up at baseline, 4 weeks after the first injections, and 4 weeks after the second injections	There was no difference between the effect of small doses of BTX and those of physiological saline in the treatment of myofascial pain syndrome	No serious adverse event reported	Poor	*BTX =* BTX and placebo groups do not reach statistically significant changes in primary outcomes (Neck-shoulder pain, PPT) and in the subjective assessment of the efficacy of the treatment (verbal rating scale)
50 IU in a TP F-up at 3 and 28 days after injection	BTX reduced motor endplate activity and the interference pattern of Electromyography significantly but had no effect on either pain (spontaneous or referred) or pain thresholds compared with isotonic saline. The results do not support a specific antinociceptive and analgesic effect of BTX	No severe or persistent adverse effects. Headache and neck pain (BTX: 4; CG: 3)	Poor	*BTX =* BTX and placebo groups do not reach statistically significant changes in primary outcomes (NRS) and secondary outcomes (PPT, median spontaneous and evoked referred pain intensity, ROM, pain relief)

TABLE 1 (Continued)

Publication	Study design	Score	Patients features	BTX preparation method
Ferrante et al. (2005)	BTX injection 10 IU/TP vs. 25 IU/TP vs. 50 IU/TP placebo (saline) injection	VAS, PPT measured by pressure algometry, SF-36	122 (10 IU/TP: 32 vs. 25 IU/TP: 34 vs. 50 IU/TP: 31 vs. CG: 35) *Age*: 10 IU/TP: 43.3 (±10.9) vs. 25 IU/TP: 46.6 (±15.1) vs. 50 IU/TP: 46.5 (±12.2) vs. CG: 45.3 (±10.1) *Sex*: 10 IU/TP: M: 13 (41%) vs. 25 IU/TP: M: 13 (38%) vs. 50 IU/TP: M: 11 (35%) vs. CG: M: 15 (43%)	*V & Conc*: 10, 25, or 50 IU of BTX diluted in 0.5 mL of saline solution into up to 5 active TPs. Maximum dose was 0, 50, 125, 250 IU respectively
Kamanli et al. (2005)	Lidocaine injection vs. DN vs. BTX injection	PPT, VAS, HDRS, NHP	29 (Lidocaine: 10 vs. DN: 10 vs. BTX: 9) *Age*: Lidocaine: 37.30 (±9.76) vs. DN: 37.20 (±8.08) vs. BTX: 38.3 (±5.26) *Sex*: F: 23 (79%)	*V & Conc*: 10–20 IU of BTX in 1 mL of saline solution
Graboski et al. (2005)	BTX injection vs. bupivacaine injection	VAS	17 (BTX: 9 vs. Bupivacaine: 8) *Age*: 51.1 (±13.4) *Sex*: F: 9 (52.94%)	*V & Conc*: 25 IU of BTX mixed with 0.5 cc normal saline per TP

Note: The use of BTX in the treatment of UBMPS: data extracted from the 11 RCTs included in the review.

Abbreviations: ACPA, American Chronic Pain Association's quality of life scale; ADP, average daily pain; AKPS, anterior knee pain scale; AOFAS, American Orthopaedic Foot and Ankle Society Ankle/Hindfoot Score; AOS, Ankle Osteoarthritis Scale; BDI, Beck Depression Inventory; BPI, Brief Pain Inventory scale; BTX, Botulinum Toxin; CG, control group; CHFS, Cochin Hand Function Scale; conc., concentration; CS, corticosteroids; CTTH, chronic tension-type headache; DN, Dry Needling; F, female; FANS, non-steroidal anti-inflammatory drugs; FU, follow-up; GIC, global impression of change; HAD-A and HAD-D, Hospital Anxiety and Depression scale; HDRS, Hamilton Depression and anxiety Rating Scale; HHS, Harris Hip Score; IA, intraarticular; KOOS, The Knee injury and Osteoarthritis Outcome Score; LD, large dose group; M, male; MPQ-SF, McGill Pain Questionnaire-Short Form; MPS, Myofascial pain syndrome; MRC, Medical Research Council; NA, not available; NDI, Neck Disability Index; NHP, Nottingham health profile; NRS, numerical rating scale; PG, Placebo Group; OA, osteoarthritis; ODI, Oswestry Disability Index; OLBPQ, Oswestry Low Back Pain Questionnaire; OMERACT, Outcome Measures in Rheumatology criteria; OWQ, Oswestry questionnaire; PA, patient; PDI, Pain Disability Index; PGA, patient global assessment; PGIC, patient global impression of change; PPT, pain pressure threshold; PRTEE, grip strength and Patient-Rated Tennis Elbow Evaluation; PS, pain scores; RCT, randomized controlled trial; ROM, range of motion; SD, small-dose group; SF-36, the 36-Item Short Form Health Survey; SF-MPQ, Short-form McGill Pain Questionnaire; SG, study group; SLS, single leg stance test; SPADI, Shoulder Pain and Disability Index; STAI, Spielberger State–Trait Anxiety Index; TG, Treated Group; TH, triamcinolone hexacetonide; TKA, Total Knee Arthroplasty; TP, Trigger point; TST, Timed-stands test; TUG, A Timed "Up-and-Go" test; UBMPS, Upper Back Myofascial Pain Syndrome; US, Ultrasound; V, Volume; VAS, visual analogue scale; VASm, VAS for pain during movement; VASr, VAS for pain at rest; VNS, Visual Numerical Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; +, better results in the experimental group compared to the control group; +/−, better results only in secondary endpoints; −, worse results in the experimental group compared to the control group; =, no differences between experimental and control groups.

size. The different clinical scores adopted in the studies, the non-comparable periods of follow-up in different populations and the poor homogeneity of the data made the results unreliable. In addition, there was a general partial adherence to CONSORT guidelines for reporting methods and results in RCTs, thus generating a series of consecutive biases responsible for the modest rating of the studies according to the AHQR standard; in fact, only one of them could be rated as "good quality" RCTs. Despite the methodological limitations, some clinical considerations can be drawn from the analysis of the literature. Overall, three out of 10 trials (Benecke et al., 2011; Gobel et al., 2006; Nicol et al., 2014) showed a more effective outcome for BTX treatment than the control group. In two studies, the BTX group failed to reach significant control pain, only achieving secondary endpoints (i.e., PPT, NDI and SF-36) (Kwanchuay et al., 2015; Lew et al., 2008). In two studies (Graboski et al., 2005; Kamanli et al., 2005), BTX did not show significant superiority over the control group. Finally, three trials showed no significant differences compared with placebo, a finding that certainly needs to be investigated further (Ferrante et al., 2005; Ojala et al., 2006; Qerama et al., 2006). The effects of BTX have mostly been evaluated in the short to medium term, with a lack of data on the prolonged duration of benefits. Only a few studies have evaluated patients with a follow-up of more than 3 months, such as 6 months in Lew's trial and up to 26 weeks in Nicol's paper (Lew et al., 2008; Nicol et al., 2014).

Therapeutic protocol and follow-up (F-up)	Results	Safety	AHRQ standard	Overall performance
F-up at 1, 2, 4, 6, 8 and 12 weeks	No significant differences occurred between the placebo and BTX groups in VAS scores, PPT and rescue medication Injection of BTX directly into TPs did not improve cervicothoracic myofascial pain	No serious adverse events reported. Transient flu-like symptoms (BTX: 3)	Poor	*BTX* = No significant differences occurred between BTX and placebo with respect to primary outcomes (VAS, PPT), only a trend towards improvement in secondary endpoints (SF-36)
10–20 IU/TP. F-up at baseline and 1 month after treatment	In the lidocaine group, PPT values were significantly higher than in the DN group, and pain scores were significantly lower than in both the BTX and DN groups. In all, VAS scores significantly decreased in the lidocaine injection and BTX groups and did not significantly change in the DN group. BTX could be selectively used in MPS patients resistant to conventional treatments	No serious adverse events. Transient fatigue (5), transient muscle pain (3), headache (1) in the BTX group	Poor	*BTX* – BTX showed much less improvement than Lidocaine in primary outcomes (VAS, PPT) and overlapping or positive improvements, respectively, in NHP and HDRS secondary outcomes
25 UI/TP F-up at until patient's pain returned to 75% or more of their pre-injection pain for two consecutive weeks	There was no significant difference between the BTX and 0.5% bupivacaine groups in duration or magnitude of pain relief, function, satisfaction, or cost of care. Considering the high cost of BTX, bupivacaine is deemed a more cost-effective injectate for MPS	Adverse events in the BTX group were transient and none required specific treatment. Regional weakness (2), numbness of limbs (2), coldness of limbs (1), sore throat (1), nausea (1)	Poor	*BTX* – Both BTX and Bupivacaine treatments were effective in reducing pain in primary outcomes (VAS). However, BTX lost in cost in comparison with Bupivacaine

The treatment protocols used in the included trials were neither uniform nor fully described. In fact, volumes of BTX ranged from 10 to 100 units and the degree of dilution varied from 0.25 to 4 mL of saline solution.

The analysis of the included RCTs (Kwanchuay et al., 2015; Ojala et al., 2006) revealed that low doses of BTX (5–10 IU) may be inadequate to affect UBMPS trigger points, although it has been shown that even low doses of BTX can spread through the fascia. Therefore, a muscle-specific dose needs to be standardized to achieve better results and fewer side effects (Soares et al., 2014).

The promising results of BTX therapy in providing pain relief, improvement of motor function and quality of life were difficult to extend to the general population because of the lack of specific clinical outcomes, preferring in almost all studies the assessment of PPT by algometer evaluation and self-perceiving pain using the VAS scale. Moreover, some studies analysed pain using poor-discriminating non-standardized rating scales. In addition, not all included studies analysed UBMPS's psychological impact and patient's quality of life, outlining the need to investigate these data more thoroughly. This was especially true in patients with a pre-existing motor disability (e.g., Parkinson's disease, multiple sclerosis or stroke), in whom spinal pain is often related to the presence of motor compensations from poor posture or gait deficits, which can further worsen the patient's level of independence and quality of life (Lo Buono et al., 2017;

TABLE 2 Quality assessment of the included studies by using the Cochrane risk of bias tool for randomized controlled trials and the AHRQ (Agency for Healthcare Research and Quality) standards.

Publication	Random sequence generation	Allocation concealment	Selective reporting	Other bias	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	AHRQ standard
Kwanchuay et al. (2015)	Low	Low	Low	Unclear	Low	Low	Unclear	Fair
Nicol et al. (2014)	High	High	Unclear	Unclear	Low	Unclear	Low	Poor
Benecke et al. (2011)	Low	Low	Unclear	Unclear	Low	Low	High	Poor
Lew et al. (2008)	Low	Low	Low	Low	Low	Low	Low	Good
Gobel et al. (2006)	Low	Low	Unclear	Unclear	Low	Low	Unclear	Poor
Ojala et al. (2006)	Low	Unclear	Unclear	Unclear	Low	Unclear	Low	Poor
Qerama et al. (2006)	Low	Low	Unclear	Unclear	Low	Unclear	High	Poor
Ferrante et al. (2005)	High	High	Unclear	High	Low	Unclear	Unclear	Poor
Kamanli et al. (2005)	High	High	Unclear	High	High	High	Low	Poor
Graboski et al. (2005)	Low	Low	Unclear	Unclear	High	Unclear	Unclear	Poor

Note: "Good quality": All criteria met (i.e., low for each domain); "Fair quality": One criterion not met (i.e., high risk of bias for one domain) or two criteria and the assessment that this was unlikely to have biased the outcome, and there is no known important limitation that could invalidate the results; "Poor quality": One criterion not met (i.e., high risk of bias for one domain) or two criteria unclear and the assessment that this was likely to have biased the outcome, and there are important limitations that could invalidate the results; Poor quality: two or more criteria listed as high or unclear risk of bias.

Naro et al., 2020; Sardella et al., 2022; Sconza et al., 2021; Zhao et al., 2021).

The repetitive peripheral nociceptive stimuli occurring in UBMPS could stimulate the production of various inflammatory mediators and neuropeptides (i.e., substance P, prostaglandins, histamine and glutamate) that act on the free nerve ending receptors activating the C- and A-delta fibres (Montero-Marin et al., 2019). These mechanisms play an important role in peripheral sensitization first and central sensitisation later (Ardoino et al., 2020; Sconza et al., 2023), resulting in the onset of chronic pain that is difficult to control only with conventional therapy (e.g., physical therapy, drugs) (Urits et al., 2020). In this light, BTX appears to be able to block central and peripheral sensitisation, playing a crucial role in modulating nociplastic pain that occurs in MPS (Rawicki et al., 2010) by reducing inflammatory mediators that also act on pain receptors (Galasso et al., 2020). Although BTX injections have a long history of safe use in the treatment of various conditions, serious adverse events have been reported, including dysphagia, generalized muscle weakness, respiratory compromise and increased cervical spine instability (Bhatia et al., 1999; Crowner et al., 2010; Yiannakopoulou, 2015). There is a unique study illustrating the case of an elderly woman who developed severe cervical kyphotic deformity secondary to loss of residual paraspinal muscle tone following BTX injections into the cervical extensor muscles (Agyei et al., 2019). This treatment was used to treat headache and neck pain following the patient's car accident. The complication of cervical spine instability, previously reported only in patients with a history of cervical spine fusion, demonstrates the potential risk of using BTX in the neck of an elderly patient. This case highlights the importance of pre-assessing whether patients are predisposed to developing cervical kyphotic deformities.

The most common BTX side effects were transient muscle pain and weakness with spontaneous resolution (Galasso et al., 2020), and no major adverse events (e.g., arrhythmia, anaphylactic shock, autonomic dysreflexia and skin rash) related to injection treatment were reported in the included studies. As the best results are known to be obtained with the combination of pharmacological and nonpharmacological therapy, the use of BTX could be integrated into a multidisciplinary setting involving physiotherapy and physical activity to enhance the effects of a single approach (Fujita et al., 2019; Kamanli et al., 2005; Loudovici-Krug et al., 2022; Pratelli et al., 2017).

Moreover, further insights are needed to better analyse the mechanisms of pain reduction at various times of the intervention. Given the BTX long-lasting relaxing muscular effects (Benecke et al., 2011), several authors showed an additional immediate effect of needling in pain reduction on active muscle trigger points (Dommerholt et al., 2020;

Gerber et al., 2015; Qerama et al., 2006). Thus, the injection technique, even with saline or dry needling, could also play a role in pain modulation, explaining the short-term pain reduction (Calvo-Lobo et al., 2018). This effect could allow the authors to speculate about an additional positive, prolonged effect of BTX injection in patients with UBMPS, which, however, should be further investigated.

Interestingly, some authors found that multiple BTX injections in the same region could lead to better pain control than one due to toxin diffusion through muscle fascia (Kaya Keles & Ates, 2022; Yaraskavitch et al., 2008). BTX distribution induces local chemical denervation, reducing peripheral nociceptive signals and thus decreasing central sensitization, limiting stimuli to the cortex (Aoki, 2005; Mathew, 2011). The cost of BTX, even in small doses, is much higher than that of saline, anaesthetics or dry needling, suggesting that it should only be used in patients with chronic pain that is resistant to physiotherapy and medication or with recurrent pain (Kamanli et al., 2005). However, some studies show a longer pain-free period and fewer active trigger points at follow-up (Benecke et al., 2011), making it difficult to define the most correct indication for treatment. Considering the UBMPS clinical manifestation heterogeneity with different pain onset and chronicization mechanisms, we can hypnotize that BTX injections could be integrated into multimodal UBMPS treatment, particularly in patients with nociplastic pain.

4.1 | Limitations

This manuscript has several shortcomings. First, no meta-analysis of the data was performed; the only possible attempt in this respect would have been to compare BTX with placebo, but the small number of trials, with different clinical scores and poor homogeneity of the data, would have resulted in an unreliable evaluation. Furthermore, the modest quality of the trials prevented the authors from defining clear indications for the use of BTX, and few of the included RTCs compared BTX with conservative approaches. Another limitation is that the authors only considered the last 20 years of research. Finally, grey literature was not considered and only published, peer-reviewed RCTs were included to avoid potential methodological errors.

5 | CONCLUSION

The evidence from the analysis of currently available RCTs that have compared the treatment of UBMPS by BTX with other different therapies is conflicting and does not allow the superiority of BTX over the comparators to be affirmed. The evaluation of the methodological characteristics of the included RCTs showed an overall modest quality, making the measurement of treatment effectiveness more complex. Even if there was no conclusive evidence that BTX is beneficial for UBMPS, the favourable safety profile and the positive results of some secondary endpoints, such as SF-36, NDI and Brief Pain Inventory scale, suggested a potentially beneficial action in terms of pain control, improvement of motor function and patients' quality of life. Given the high cost of BTX, this treatment might be reserved for a subgroup of more responsive patients: those with moderate to severe chronic pain and active trigger points. Further large, high-quality studies are needed to support the safety and efficacy of BTX, standardize treatment protocols and better identify patients who may benefit most from this therapeutic approach.

AUTHOR CONTRIBUTIONS

Conceptualization: C. Sconza, S. Portaro and G. Leonardi. *Methodology*: A. Alito and B. Di Matteo. *Validation*: S. Portaro, S. Respizzi, G. Massazza. *Data curation*: A. Alito, B. Di Matteo, S. Respizzi. *Data extraction*: E. Kon and G. Leonardi. *Writing original draft preparation*: A. Alito and G. Leonardi. *Review and editing*: S. Portaro, S. Respizzi, C. Sconza and G. Massazza *Supervision*: C. Sconza, B. Di Matteo and G. Massazza. All authors read and approved the content of the final version of the manuscript to be published.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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