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Trigger point injection therapies for chronic myofascial neck and back pain: A systematic review

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ABSTRACT

Objective: To assess the comparative effectiveness and harms of trigger point injections (TPI) for myofascial neck and back pain.

Methods: Electronic literature databases were searched to identify articles pertaining to TPI for chronic myofascial neck and back pain. Searches were done from database start dates up to April 2020. Inclusion criteria were randomized controlled trials, cohorts, and case control studies. Pain, functional outcomes, and harms were extracted. Outcome time points were divided into short term (7 days to <6 weeks), intermediate term (6 weeks to < 3 months), long term (3 months to < 6 months), and longest term (>6 months). Quality assessment was done using the Cochrane Back Review Group (CBRG) checklist for RCTs, and the Newcastle-Ottawa Quality Assessment Scale for cohort and case control studies.

Results: 14 studies met inclusion criteria. Six studies compared TPI of Botulinum toxin A (five with Onabutulinum toxin A, and one with Abobotulinum toxin A) with normal saline (NS). Two of the Onabotulinum toxin A studies showed greater pain improvement in the Onabotulinum toxin A group at short, intermediate, compared with NS. The Abobotulinum study showed pain improvement at short, intermediate, and long terms. Of note Onabotulinum toxin A was associated with improved anxiety and depression in two studies. Two studies compared Onabotulinum toxin A to local anesthetic, one to methylprednisolone, and one to dry needling (DN), all of which showed no difference. One study compared Ozone to Lidocaine and DN, and it showed no difference. Two studies compared sterile water to NS; they both found no difference in pain outcomes at the short term time point. However one of these two studies showed improved pain at intermediate, long, and longest terms in the sterile water group. Tropisetron showed no difference vs. NS. Adverse effects were mostly reported for Onabotulinum toxin A and Abobotulinum toxin A.

Conclusion: Given the mixed results, we are unable to conclude whether an injectate composition is superior to another, or make recommendations in that regard. Further studies will help elucidate the ideal injectate composition and parameters.

1. Introduction

Chronic pain, defined as pain that persists or recurs for more than 3 months, has been linked to numerous physical and mental conditions and contributes to high health care costs and lost productivity. Myofascial pain syndrome (MPS) has a high lifetime prevalence, estimated to be around 85%, and is a common reason for health-care visits and absenteeism [1,2]. The hallmark clinical sign of MPS is palpable myofascial trigger points (MTrP) [3,4], which are defined as hyper-irritable spots, usually within a taut band of skeletal muscle or in the muscle fascia which is painful on compression and can give rise to characteristic referred pain, motor dysfunction, and autonomic phenomena [5]. Treatment approaches in chronic MPS range from conservative approaches such as analgesics to various physical modalities to more invasive interventional techniques. Physical modalities include combined techniques (e.g. spray and stretch), manual techniques,

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transcutaneous electrical stimulation (TENS), frequency-modulated neural stimulation, ultrasound or massage, injections, acupuncture, and dry needling [6,7]. A more invasive but effective practice when conservative measures fail is injection of MTrPs [8]. Injections into MTrPs are an effective treatment, presumably due to mechanical disruption by the needle and termination of the dysfunctional activity of involved motor endplates [9]. MTrP injections show varying degrees of benefit, and employ dry needling and injections of various agents, including but not limited to normal saline, local anesthetics, steroids, Tropisetron, and Botulinum toxin A [10,11]. A recent systematic review and meta-analysis recommended dry needling to reduce pain in patients with MPS of the upper quarter [4]. Another systematic review published in 2009 concluded that there is no clear evidence of benefit or ineffectiveness of trigger point injections [12].

Through this systematic review we wished to investigate if there were any significant advances made in the search for the ideal injectate medication for trigger point injections in the treatment of myofascial pain. We used strict inclusion criteria to identify only studies that compared various injectate mixtures used for trigger point injections, while excluding studies that compared other conservative measures such as PT, stretching and ultrasound, to trigger point injections. With such strict inclusion criteria, we hoped to eliminate concurrent effects of other treatments that could potentially cloud the efficacy of the particular injectate mixtures.

1.1. Specific objectives

1) In patients with myofascial neck and back pain, what is the effectiveness of the following trigger point injection compositions on outcomes of pain relief and functional improvement?
   a. Local anesthetic
   b. Local anesthetic plus steroids
   c. Normal saline
   d. Botulinum toxin A
   e. Dry needling
2) What are the harms of trigger point injections?

2. Methods

2.1. Types of studies

This systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42020185867). We included randomized trials, cohort studies, and case-control studies. We defaulted the searches to start on each respective database inception year, up to April 2020. We included all languages in the searches and English translation assistance was first attempted by contacting the Cochrane Back Review Group [13], followed by seeking out a native speaker of the respective language. Studies for which we were unable to obtain English translation were excluded. Abstracts without full texts, case reports, case series, reviews, editorials, expert opinions, letters and protocols were also excluded.

2.2. Types of participants

Male and female patients at least 18 years of age, with myofascial neck and back pain for a duration of at least 3 months. Pediatric patients (<18-year-old) and patients with surgery or fracture within 6 weeks of injection therapy were excluded.

2.3. Types of interventions

We included studies that involved trigger point injections using dry needling, injectate administration, or a combination of dry needling and injectate. Studies that investigated treatment modalities for MPS not involving injections were excluded.

2.4. Effectiveness definition and types of outcome measures

Effectiveness of trigger point injection predefined as a $\geq$ 30% decrease from baseline score for the measures below, or by the following point reductions from baseline values [14,15]:

- Pain assessment
  - o NRS (Numerical Rating Scale): $\geq$ 2 points
  - o VAS (Visual Analog Scale): $\geq$ 15 points
- Physical functioning
  - o RMDQ (Rolland-Morris Disability Questionnaire): $\geq$ 5 points
  - o ODI (Oswestry Disability Index): $\geq$ 10 points
  - o BPI (Brief Pain Inventory): $\geq$ 2 points
  - o NDI (Neck Disability Index): $\geq$ 5 points
  - o MPI (Multidisciplinary Pain Inventory): $\geq$ 0.6 points
- Outcome measures not mentioned above but used in included studies were applied as stated in those studies.

For randomized studies, we considered studies where pain relief was a primary outcome and included a follow-up time point of 7 days or later. Studies with pain relief as not the primary outcome or follow up less than 7 days were excluded. Functional outcomes were considered as determined by respective studies. We classified reported outcome time points as follows:

- Short term: 7 days to <6 weeks
- Intermediate term: 6 weeks to <3 months
- Long term: 3 months to <6 months
- Longest term: > 6 months

In hopes of obtaining as much data as possible on harms of TPI, and given the rarity of their occurrence in small sample studies, we also included cohort and case control studies to find data on harms of TPI.

2.5. Search methods for identification

With the help of a biomedical research librarian and proper syntax codes for each database, literature searches were conducted in Ovid Medline, Embase, Cochrane Library, and Scopus. The search terms entered in each database are reported in Appendix A. Reference lists of relevant studies and systematic reviews were hand searched for the terms myofascial pain, muscle pain, myalgia, myositis, tender point, or trigger point injections. ClinicalTrials.gov was searched for unpublished studies.

2.6. Data collection and analysis

Fig. 1 shows the flowchart of the systematic review search strategy. Articles obtained from the searches were imported in Covidence, then deduplicated. Title and abstract screening, full-text review, data extraction, and risk of bias assessment were done by 2 independent authors. Conflicts were resolved by a separate independent author. None of the authors were involved in any of the selected studies.

2.7. Data extraction and management

Data extraction variables were determined in our protocol, and the authors provided feedback on each variable, after which a final list of variables was organized. The following variables were extracted in excel sheet columns as follows:

- First author, publication type/year, study design, and body part injected
- Number of subjects
- Percentage of female patients
- Mean age
- Selection criteria

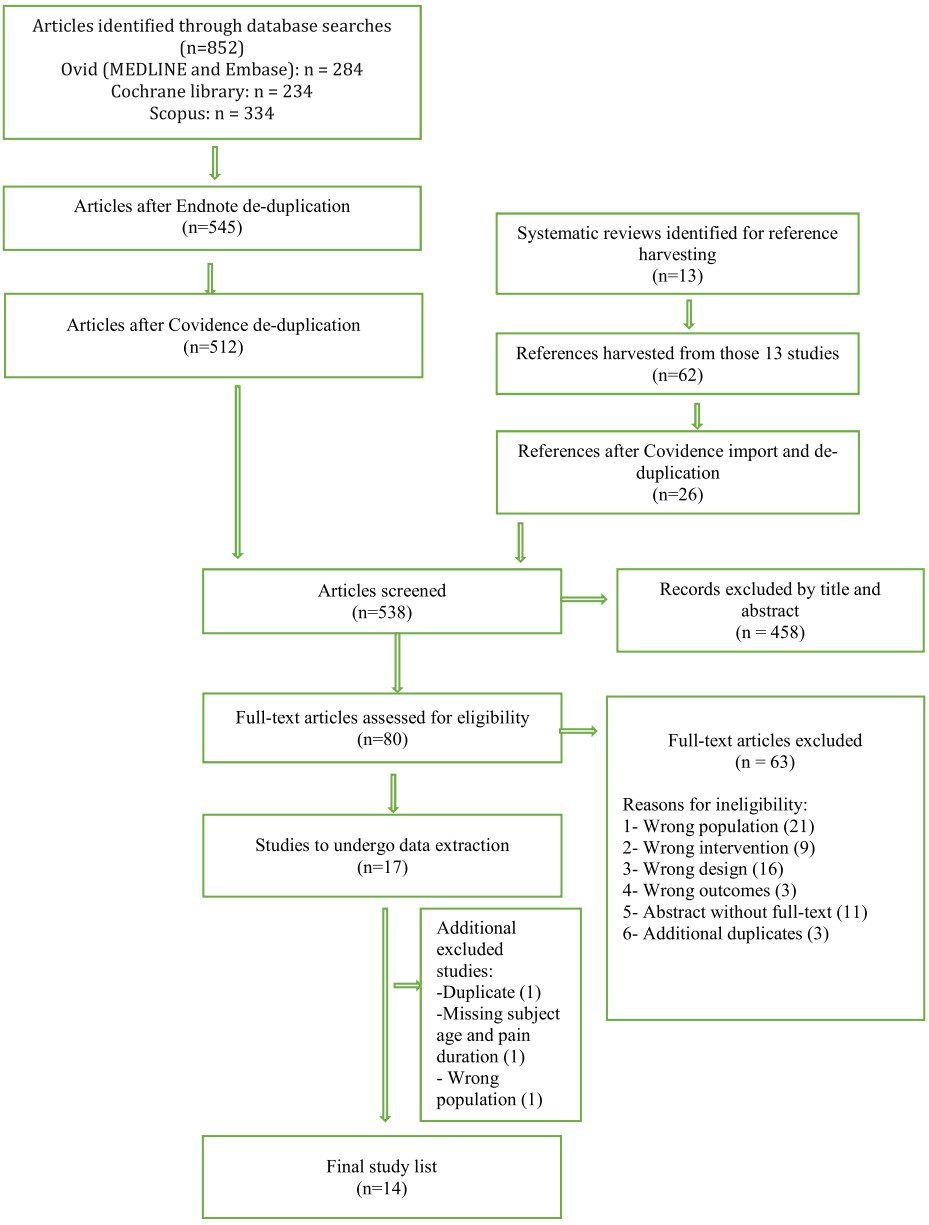

Fig. 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart for the search.

- Intervention/Injectate details
- Comparator/comparison (as stated in each respective study)
- Outcomes measured
- Pain outcomes
  - o 7days - <6wks (Short term)
  - o 6wks- <3months (Intermediate term)
  - o 3mo-<6mo (Long term)
  - o >6mo (Longest term)
- Harms (at any time point)
- Other outcomes
- Quality rating

2.8. Quality assessment and data synthesis

The risk of bias (ROB) of each included study was assessed using the Cochrane Back Review Group (CBRG) checklist, which includes 12 items (Table 2) [13,14,16]. That checklist evaluates the selection bias, performance bias, detection bias, attrition bias, and selective outcome reporting bias. Studies were rated as "High quality", "moderate quality", "low quality", or "unclear". "High quality" was defined as having low risk of bias in at least 8 out of 12 items. "Moderate quality" was defined as having low ROB in 4–7 items. "Low quality" was defined as having low ROB in less than 4 items. A study was defined as having unclear ROB if one or more of the criteria did not have enough information. Two authors independently assessed ROB in studies that passed full-text review. Quality assessment of observational studies was to be carried out using the Newcastle-Ottawa Quality Assessment Scale for cohort studies and case-control studies [17,18]. As per our protocol, we planned to carry out a meta-analysis if the full-text screening results yielded at least 3 randomized studies on myofascial pain for each body region (neck and low back), rated at least moderate quality and showing low or moderate heterogeneity.

3. Results

3.1. Methodological quality

As described in the PRISMA [19] flowchart (Fig. 1), we identified 852 articles from electronic databases and an additional 13 from related

systematic reviews, from which 62 references were harvested. After removal of duplicates, there were 538 articles that underwent title and abstract screening. From that list of studies, 80 articles underwent full-text review. 66 of these were excluded, leaving a final list of 14 studies which underwent data extraction.

3.2. Included studies

We included 14 studies, 13 of which were randomized controlled trials, from which a full data extraction was carried out. 2 studies were cohort studies, from which harms of TPIs were extracted, as specified in the protocol. From the included studies, there was a total of 759 participants (range 6–145 subjects). There were 13 randomized trials (references 20–32). The Jabbari article reported results of 2 separate studies: a randomized trial (Study #1), and a prospective cohort (Study #2). Another cohort study was done by Alo et al. (1997) [33]). As such, although we had a total of 14 articles, 13 of them were randomized and 2 of them were cohort studies. In accordance to input from the review team's statistician, the final list of included studies, especially the ones pertaining to Onabotulinum toxin A were different in design and outcomes measured, and tables reporting effect sizes were not consistently provided. Thus we were unable to group them for a meta-analysis, but a qualitative analysis of the outcomes was carried out.

With respect to how the authors of the included studies defined trigger points, 7 of the 13 included studies used Simon's criteria (references 20, 21, 24, 25, 26, 32, 30). The remaining 6 studies departed to varying degrees from these criteria. Specifically, in the study by Kwanchuay et al., myofascial pain and trigger point diagnoses were rendered at a Physical Medicine and Rehabilitation outpatient department, but specific diagnostic criteria were not provided. The studies by Gobel et al. and by Wheeler et al. (1998) did not specify how the diagnosis of trigger point pain was achieved. The studies by Byrn et al. and Jabbari did not specifically assess for trigger points. The study by Wreje included trigger points and tender points, though only a small percentage of subjects belonged to the latter group (9%). The age range of the subjects from all the studies combined was from 18 to 83 years old, and most subjects were of female gender in all of the studies, except in the randomized trial by Jabbari. As described in the methods section above, outcomes were labeled “short term” if they occurred between 7 days and 6 weeks, “intermediate term” if between 6 weeks and <3 months, “long term” if between 3 months and <6 months, and “longest term” if they occurred at time points greater than 6 months. The findings from each study are listed in Table 1. A legend for abbreviations used in Table 1 is listed before Table 1. The detailed quality assessment of each of the randomized studies is in Table 2. Harms are listed in Table 3 (see Table 4).

3.3. Quality assessment

As specified in Table 2 below, the quality rating for the included randomized studies is compiled in Table 2. Six studies were rated high quality, and seven were rated moderate quality. None of the included studies were rated low quality.

3.4. Comparative effectiveness of trigger point injection therapies

Of the thirteen randomized trials used for this systematic review (Table 1), five pertained to the effectiveness of Onabotulinum toxin A for trigger point injections compared to normal saline, one compared Abobotulinum toxin A to normal saline, one of them compared Onabotulinum toxin A with bupivacaine and dry needling, 1 compared Onabotulinum toxin A with normal saline and a local anesthetic (bupivacaine), one of them compared Onabotulinum toxin A with steroids (methylprednisolone), one of them compared ozone to local anesthetic (lidocaine) and dry needling, two pertained to sterile water vs normal saline, and one pertained to Tropisetron (compared to normal saline). In many instances, due to the heterogenous populations studied in the data sets, comparisons for pain scores and functional improvement were not performed. Hence, a descriptive discussion of the data was deemed most appropriate for data analysis, a decision that was corroborated by the review team's statistician.

3.5. Statistical findings for pain outcomes in included studies

In the study by Raiessadat et al., upper trapezius VAS pain scores were assessed at baseline and 4 weeks. Statistically significant reductions in VAS scores were achieved for Ozone, Lidocaine, and dry needling groups ($p = 0.001$ for each group). In Kwanchuay et al's study, no statistically significant VAS improvement of upper trapezius pain was observed in Onabotulinum toxin A versus normal saline groups across study time points (weeks 0, 3 and 6). The study by De Andres et al. [20] used fluoroscopy-guided, iliopsoas or quadratus lumborum, injections of Onabotulinum toxin Ain their experimental group, and Bupivacaine or normal saline (NS) as controls, and looked at the following time points in days: 0, 15, 30, and 90. VAS scores for pain within the Botulinum toxin type A group were improved in a statistically significant fashion at all time points compared to baseline ($p = 0.006$ for day 15, $p = 0.002$ for day 30, $p = 0.002$ for day 90). However no statistically significant VAS difference was observed between Onabotulinum toxin A and Bupivacaine or NS. Jabbari's study assessed the percentage of back pain patients who achieved 50% reduction in VAS at 3 weeks and 8 weeks. This outcome was observed in 73% of the Onabotulinum toxin A subjects, as opposed to 25% of the NS subjects ($p = 0.012$). In the study by Gobel et al., investigators injected the 10 most painful trigger points in the cervical and/or shoulder muscles in each subject with 40U of Abobotulinum toxin A (Dysport), for a total of 400U per patient, and results were measured weekly over 12 weeks. The primary outcome was the proportion of patients who had mild or no pain at week 5 on a self-rating scale of 1–4, with 4 being the most severe pain. 51% of Abobotulinum toxin A subjects reported mild or no pain at week 5 ($p = 0.002$), 29% at week 6 ($p = 0.004$), and 20% at week 11 ($p = 0.04$). Kamanli et al. compared cervical and parascapular pain scores comparing Lidocaine, Onabotulinum toxin A, and dry needling. Two pain outcomes were used, namely the Pain score form (PS) and VAS for pain (referred to as VAS-pain), and they were measured at 0 and 4 weeks. Greater pain improvement was noted for the lidocaine group compared to Onabotulinum toxin A or dry needling groups at 4 weeks ($p = 0.00$ for all groups). Statistical significance was achieved for PS score in all groups, but only for lidocaine and Onabotulinum toxin A for VAS-pain. Muller et al.‘s study [32] did not demonstrate statistically significant VAS change in neck pain between Tropisetron and Prilocaine groups. Wheeler et al. (2001) assessed subjects with neck and upper back pain. The investigators used the NPAD (Neck Pain and Disability) score as the pain outcome measure, at time points of 0, 4, 8, 12, and 16 weeks. Onabotulinum toxin A was compared with NS. NPAD declined across all time points in a statistically significant manner ($p < 0.01$) for both groups. Porta et al. assessed pain in the scalenus anterior, piriformis, and iliopsoas using CT-guided injections of Onabotulinum toxin A mixed with bupivacaine or methylprednisolone mixed with bupivacaine. VAS change was recorded at 30 and 60 days. No significant VAS reduction was noted at 30 days between the two groups ($p = 0.06$), but a statistically significant greater VAS reduction was observed at 60 days in the Onabotulinum toxin A group vs the methylprednisolone group ($P < 0.0001$). The study by Wheeler et al. (1998) compared 2 doses of Onabotulinum toxin A (50U, 100U) and NS and recorded NPAD scores in neck pain subjects. No intergroup difference was noted, but intra-group differences were observed, meaning each group showed significant NPAD reduction across time points ($p = 0.0001$). Wreje et al. investigators performed subcutaneous injections of sterile water vs NS in subjects, and assess VAS-pain at baseline, 10 min and 14 days post-injection. No significant differences in pain reduction was observed. Cheshire et al. study compared injections of Onabotulinum toxin A to NS, and measured VAS at baseline, 2, 4 and 8 weeks. The Onabotulinum toxin A group had statistically significant VAS decreases

Table 1
Details of randomized trials on the efficacy of trigger point injections.

Study/Methods/ Pain region(s)	Participants	Intervention(s)	Outcome (s)	Result (s)	Conclusion (s)	Quality rating
Raeissadat et al. (2018) Randomized, single-blind trial Upper trapezius	72 patients (77.4% female); age range 25–60yo (mean age 39.4 ± 7.9), with upper trapezius pain for >3 month	Three equal injection groups: - 8 cc of 15ug/ml Oxygen/ozone mix (OI) N = 20 - 2 cc of 2% lidocaine (LI) N = 20 - Dry needling (DN) N = 22 Injections done weekly over 3 consecutive weeks. Needle size: 22G, 1.25inch *Note:* N total reduced from 72 to 62, as 10 subjects exited the study due to various reasons such as unwillingness to continue physiotherapy and personal problems	Time points: baseline, 4 weeks after final treatment. Outcome measures: VAS, pain pressure threshold, ROM in neck lateral flexion, neck disability index (NDI)	Mean differences (MD) VAS -OI: -3.8 ± 1.8, p = 0.001 -LI: -3.7 ± 1.5, P = 0.001 -DN: -3.1 ± 0.8, P = 0.001 NDI -OI:-12.8 ± 11.1, p = 0.001 -LI: 11.1 ± 7.5, p = 0.001 -DN: 5.5 ± 3.8, p = 0.001 PPT -OI: 8.5 ± 6.1, p = 0.001 -LI: 7.8 ± 4.3, p = 0.001 -DN: 5.1 ± 4.1, p = 0.001 ROM -OI: 2.0 ± 5.7, p = 0.104 -LI: 3.7 ± 5.2, p = 0.01 -DN: 1.1 ± 3.9, p = 0.909	TP injections of the upper trapezius with ozone, 2% lidocaine, and DN all provided significant improvement in pain, PPT, and NDI in the short-term. There was no significant improvement in neck lateral flexion, except in the lidocaine group.	High quality (8/12)
Kwanchuay et al. (2015) Randomized, double-blind trial Upper trapezius	33 patients, (83% female in Onabotulinum toxin A group, 91.7% in NS group), age range 18–70 (mean age 39.8 in Onabotulinum toxin A group, 38.8 in NS group), with upper trapezius myofascial pain for >3 months *Note:* 18 subjects had unilateral (UL) pain, 15 subjects had bilateral (BL) pain	*Note:* A total of 48 TPs were injected among the 33 subjects. Exp: Single inj. of 20U Onabotulinum toxin A (0.2 cc) at most painful TP in upper trapezius N = 16 subjects, 24 TPs Ctrl: NS (0.2 cc) N = 17 subjects, 24 TPs *Note:* 8 subjects with UL pain received Onaboutulinum toxin A only (10 with UL had NS only). 4 with BL pain received Onabotulinum toxin A only (3 with BL pain had NS only). 8 with BL pain received Onabotulinum toxin A on one side and NS on the other side. Subjects were advised to perform stretching or upper trapezius after injections, and only Paracetamol intake was allowed post-injection Needle size: 27G Inj depth: 1inch Inj. vol: 0.2 mL	Time points: 0, 3, 6 weeks Outcomes: -VAS -Pressure pain threshold (PPT)	Mean differences (MD) between Onabotulinum toxin A and NS groups (95% CI) VAS: 3 weeks: 0.25 (−1.2, 1.7), p = 0.725 6 weeks: 1.3 (−0.3, 3.0), p = 0.112 PPT: 3 weeks: −0.2 (−0.5, 0.2), p = 0.344 -Paracetamol use: - 3 patients (12.5%) in Onabotulinum toxin A group took 2 tablets, while only 2 patients (8.3%) in 0.9% NaCl control group took the same amount (p = 1.000) At 6 weeks: −0.5 (−0.9, −0.1), p = 0.036	No difference in trapezius pain relief at short and intermediate terms in Onabotulinum toxin A vs placebo. PPT was increased at intermediate term in the Onabotulinum toxin A group compared to placebo. No difference of paracetamol intake among both groups.	High quality (12/12)
De Andres et al. (2010) Randomized, double-blind trial Low back (Iliopsoas and quadratus lumborum)	28 patients (71.4% female), age range 20–70 yo (mean age 51 ± 12), with at least 6 months of bilateral low back pain, namely in iliopsoas (IP) or quadratus lumborum (QL) muscles.	Experimental: 50U Onabotulinum toxin A injected in the IP or QL. N = 27 Ctrl: NS or 0.25% Bupi N = 27 Each of the 27 patients received a bilateral, fluoroscopically guided injection in the affected muscle(s) to randomly deliver Onabotulinum toxin A in one side of the low back and a control drug (randomly constituted by NaCl 0.9% or bupivacaine 0.25%) in the opposite side Needle size: 22G, 3.5inch Inj vol per site: 5 mL	Time points: 0,15,30,90 days Outcomes: Primary: VAS score Secondary: ADLs and psychological status as per: -Hospital Anxiety and Depression scale [HAD-A, HAD-D] -Spielberger State-Trait Anxiety Index (STAI) -Lattinen -Oswestry scale	*Primary* No inter-group difference in VAS change between Onabotulinum toxin A and NS or Bupi - Sig. intra-group difference in Onabotulinum toxin A group from baseline, but not in Bupi or NS groups - 20% VAS reduction at 15 d (95% CI, 0.46–2.43; P = 0.006) - 20% VAS reduction at 30 days (95% CI, 0.58–2.24; P = 0.002) - 22% VAS reduction at 90d (95% CI, 0.67–2.52, P = 0.002) *Secondary* At 90 days - STAI reduction by 11%, P = 0.022	Fluoroscopy-guided Onabotulinum toxin A injection in IP and QL did not provide significantly more pain relief than Bupi or NS. Activities of daily life and psychological status did not significantly improve with Onabotulinum toxin A compared with Bupi and NS. TP with Onabotulinum toxin A provided short-term, intermediate, and long-term pain relief. Onabotulinum toxin A was associated with less anxiety at long term per STAI anxiety index, but no stat sig improvement in anxiety per HAD-A scale.	High (7/12)

(*continued on next page*)

Table 1 (*continued*)

Study/Methods/ Pain region(s)	Participants	Intervention(s)	Outcome (s)	Result (s)	Conclusion (s)	Quality rating
				No significant reduction of: - HAD-A (P = 0.673) - HAD-D (p = 0.484) - Lattinen (P = 0.078) - Oswestry (p = 0.085)		
Jabbari (2007) RCT Low back pain	31 subjects (% female NR), age range 20–73yo (mean age 46.7), unilateral low back pain for >6months, MRI of lumbosacral area within past 2 years	Exp: 40U Onabutulinum toxin A injected in 5 erector spinae sites (200U total) N = 15 Ctrl: NS N = 16 Needle size: 27G Injection vol: 0.4 cc	Time points: 0,3,8 weeks Outcomes: -% subjects with >50% VAS reduction -% subjects with improved scores in Oswestry low back pain questionnaire (OLBPQ)	*% patients with >50% VAS decrease* At 3 weeks - Onabutulinum toxin A: 73% -NS: 25% (p = 0.012) At 8 weeks: - Onabutulinum toxin A: 60% -NS: 12.5% (p = 0.009) *% patients with improved OLBPQ* At 8 weeks: Onabutulinum toxin A: 66.7% NS: 18.8% (P = 0.011)	Onabutulinum toxin A, compared with NS, improves pain in the short term and intermediate term. Onabutulinum toxin A injection is associated with improvement in function at intermediate term, compared with NS	High (11/12)
Gobel et al. (2006) Randomized, double-blind, placebo-controlled trial Cervical and/or shoulder muscles	145 patients (80% female), age range 18–70yo (mean age 45), with upper back pain of at least 6 duration	Exp: 10 most painful TPs were injected with Abobotulinum toxin A, ie Dysport) (40U per injection site - total 400U per patient) N = 75 Ctrl: NS N = 70 Needle size: 27G, 40 mm (1.57inch) Inj depth: 1–3 cm. Inj vol: 2.5 mL	Time points: weekly follow-up for 12 weeks. Primary: Proportion of patients with mild or no pain at week 5 on self-rating pain scale (1–4; 1 being no pain; 4 being severe pain) Secondary: - changes in pain intensity, duration of pain, number of pain free days/week, duration of sleep, number and pain intensity of TPs and time to pain improvement.	Primary: At 5 weeks, 51% Abobotulinum toxin A patients had mild or no pain, vs 26% in placebo (P = 0.002). At 6 weeks, 53% Abobotulinum toxin A pts had no/mild pain, vs 29% in placebo (p = 0.004). At week 11 - More 36% Abobotulinum toxin A group pts had mild/no pain, vs 20% in placebo (P = 0.04) Secondary: Abobotulinum toxin A group: more pain-free days/week (P = 0.036) -More days/week w no or mild pain (p = 0.023) -Mean pain intensity for all TPs sig. less w Abobotulinum toxin A than placebo at wk 4 (p = 0.001). and wk 12 (p = 0.002) -No group difference in duration of daily pain nor duration of sleep Physician global assessment of patient's condition favored Abobotulinum toxin A at week 4 (p = 0.004), week 8 (p < 0.001), and week 12 (p = 0.003) Patient's global assessment of their condition favored Abobotulinum toxin A over placebo at week 4 (p = 0.03), week 8 (p = 0.002), and week 12 (p = 0.001) More Abobotulinum toxin A patients in the recommended a repeat treatment (82%) compared to placebo (60%), p = 0.007. More physicians treating patients that received Abobotulinum toxin A	More patients treated with Abobotulinum toxin A reported mild or no pain in the cervical and/or shoulder muscles, compared with NS in the short-term, intermediate term, and long term. Compared with NS, Abobotulinum toxin A patients reported more pain-free days, lower pain intensity of their TPs in the short and long term, but no difference in quality of life. Both patients and physicians' global assessment of the patient's condition favored Abobotulinum toxin A over NS. Patients who received Abobotulinum toxin A, as well as their treating physicians, were more likely to recommend Abobotulinum toxin A than NS.	High (10/12)

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Table 1 (*continued*)

Study/Methods/ Pain region(s)	Participants	Intervention(s)	Outcome (s)	Result (s)	Conclusion (s)	Quality rating
				recommended a repeated treatment compared with those treating patients with placebo (68%), p = 0.004		
Kamanli et al. (2005) RCT Cervical and parascapular pain	29 subjects (79% female), age range 25–54yo (mean age 37), with at least one TP in cervical, upper back or shoulder muscles for at least 6 months	3 groups: −0.5% Lidocaine (1 mL); n = 10 −10-20IU Onabotulinum toxin A (1–2 mL); n = 10 -DN; n = 9 Needle size: 25G, 1.25in Injection vol: 1–2 cc	Time points: 0, 1 month Outcomes: -PS (pain score form) pain (0–3) -VAS (0–10, namely VAS-pain, VAS-fatigue, VAS-work disability) -PPT -Hamilton depression rating -Hamilton anxiety rating -Nottingham health profile (NHP)	*Value change from 0 to 4 weeks* PS pain Li:-1.19, p = 0.00 Onabotulinum toxin A: -0.78, p = 0.00 DN: -0.52, p = 0.00 VAS-pain Li: -4.95, p = 0.005 Onabotulinum toxin A:-3.41, p = 0.01 DN:-1.91, p = 0.083 VAS-fatigue Li:-3.02, p = 0.005 Onabotulinum toxin A:-2.11, p = 0.021 DN: 0.81, p = 0.44 VAS-work disability Li:-3.1, p = 0.012 Onabotulinum toxin A:-2.96, p = 0.011 DN:-1.71,p = 0.059 Trigger point PPT Li:1.16, p = 0.000 Onabotulinum toxin A: 0.76, p = 0.001 DN: 0.71, p = 0.000 NHP Li: -12.1, p = 0.005 Onabotulinum toxin A:-6.44, p = 0.021 DN: -2, p = 0.293 Ham. Depression Li: -2.2, 0.234 Onabotulinum toxin A: -4.12, p = 0.027 DN: 0.5, p = 0.722 Ham. anxiety Li: -0.9, p = 0.474 Onabotulinum toxin A: -4.62, p = 0.028 DN: 0.2, p = 0.777 Cervical ROM Li: improved, p < 0.05 Onabotulinum toxin A: p < 0.05 DN: p < 0.05	*Differences between groups:* Sig. cervical/parascapular PS decrease in lidocaine group vs Onabotulinum toxin A or DN at short term. More VAS pain improvement in Lidocaine and Onabotulinum toxin A vs DN at short term. Less fatigue in lidocaine group vs DN at short term. *Differences within groups:* Lidocaine group had stat. sig. improvement in VAS-pain, VAS-fatigue, VAS-work disability, and NHP reduction, and cervical range of motion at short term. No sig difference in PPT, Hamilton depression and anxiety scales at short term. Onabotulinum toxin A group had sig decreases in PS, VAS-pain, VAS-fatigue, VAS-work disability, NHP, and cervical ROM at short term. PPT was increased at short term. Hamilton depression and anxiety scores showed sig reduction at short term. Dry needling group showed sig increase in PPT and cervical ROM, and sig reduction in PS. No sig change in VAS-pain, VAS-fatigue, VAS-work disability.	Moderate (7/12)
Muller et al. (2005) Randomized, double blind Neck and shoulder pain	33 subjects (79% female), age range 43–64yo (mean age 56.5), myofascial pain neck and shoulder of at least 3 months	Exp: 5 mg Tropisetron (5 cc) N = 17 Ctrl: 0.5% Prilocaine (10 cc) N = 16 Needle size: NR	Time points: Outcomes: -VAS day 7 -Global Pain assessment of improved pain (GPA)	*VAS change at day 7* -Trop: -3.17 -Prilo: -1.04 No stat sig. among groups *% subjects reporting improved pain in GPA at 7 days* -Trop: 53% -Prilo: 12% (P = 0.02551) *Note:* Two patients who reported no VAS reduction recorded improvement on GPA. Except those 2 patients, trial was discontinued in Trop without VAS response	No significance in neck pain improvement at short term in Trop vs prilocaine groups. No conclusion on GPA of improved pain due to trial discontinuation in Trop subjects without pain relief	Moderate (6/12)
Wheeler et al. (2001) RCT	50 subjects (76% female), age range 21–70yo (mean age 43.6 ± 10), chronic pain in	Exp: Onabotulinum toxin A: N = 25; mean dose 231 units, divided among TPs	Time points: 0,4,8,12, and 16th week Outcomes: NPAD, SF-36 health	Reduced NPAD and disability in both groups P < 0.01 No sig change over time	No sig difference between Onabotulinum toxin A and NS, as both were associated with improved	High (9/12)

(*continued on next page*)

Table 1 (*continued*)

Study/Methods/ Pain region(s)	Participants	Intervention(s)	Outcome (s)	Result (s)	Conclusion (s)	Quality rating
Neck/upper back pain	upper, mid, and lower trapezius, and thoracic region for at least 3 months	Ctrl: NS Needle size: NR	survey, Beck depression inventory	in BDI and SF-36 mental and physical scores	neck and upper back pain and disability. There was no change in depression and SF-36 scores.	
Porta et al. (2000) Randomized, single-blind Neck and low back	40 subjects (67.5% female), age range 18–75yo (mean age 47.7), TPs at scalenus anterior, piriformis, and iliopsoas	CT-guided injections of Onabotulinum toxin A + bupi (n = 20) and MP + bupi (n = 20) .scalenus ant: 80U Onabotulinum toxin A+ 4 cc 0.25% Bupi .Piriformis: 6cc 0.25% Bupi+ 100U Onabotulinum toxin A .Iliopsoas: 6cc 0.25% Bupi + 150U Onabotulinum toxin A Ctrl: .scalenus ant: 80 mg MP +4 cc 0.25% Bupi .Piriformis: 80 mg MP +6 mL 0.25% Bupi .Iliopsoas: 80 mg MP +6 mL 0.25% Bupi Intensive physiotherapy after injections Needle size: 20G (Lutz or blunt)	Time points: 0, 30, 60 days Outcome: -VAS (0–10)	*VAS change at 30 days:* Onabotulinum toxin A: -3.9 MP: -3.5 p = 0.06 *VAS change at 60 days:* Onabotulinum toxin A: -5.5 MP: -2.5 P < 0.0001 More compliance to PT noted in Onabotulinum toxin A group	No sig. VAS reduction of neck pain between Onabotulinum toxin A and MP groups at 30 days Sig. greater VAS decrease at 60 days in Onabotulinum toxin A group vs MP	Moderate (4/12)
Wheeler et al. (1998) RCT, double-blind, prospective pilot study Neck pain	33 subjects (% female not listed), age >21 (mean age 38.1 ± 9.0 (NS), 40.7 ± 11.1 (50U Onabotulinum toxin A), 43.4 ± 8.0 (100U Onabotulinum toxin A) *See next column for treatment group details* Unilateral neck pain for >3 months	3 groups (n per group unclear) −50U Onabotulinum toxin A in 2 cc PF NS −100U Onabotulinum toxin A in 2 cc NS −2 cc of NS *Note 1:* a second injection of 100U Onabotulinum toxin A+2 cc NS was given to 11 subjects in same site as prior injection in that group, and in 2 subjects at different site. In the latter case, those 2 subjects had developed adjacent TPs after pain resolution from the initial injection *Note 2:* MVC-related injuries were more prevalent in Onabotulinum toxin A group, whereas work-related injury was more prevalent in NS group Needle size: NR	Time points: 0, 1wk, 3wk, 6wk, 9wk, 3mo, 4mo Outcomes -PPT -NPAD score -Neck Pain and Disability Scale	No significance between NS vs Onabotulinum toxin A groups, but ↓ pain intensity per NPAD and PPT in each group. P = 0.0001 for NPAD and PPT	No difference in NPAD and PPT improvement between Onabotulinum toxin A (50U), Onabotulinum toxin A(100U), and NS groups, but sig. difference within each of these groups group in terms of NPAD and PPT	Moderate (6/12)
Wreje et al. (1995) RCT, multicenter Upper quadrants of body	117 subjects (77.7% female), aged >25yo (mean age NR), myofascial pain for > 3months, in one or both upper quadrants of the body. 9% of subjects had fibromyalgia, 16% had post-traumatic myofascial pain, and 75% had local pain syndromes of different localizations	Exp: 0.5 cc of sterile water (subcutaneously, and intracutaneously at needle withdrawal) N = 55 Ctrl: 0.5 cc NS N = 61 (1 patient lost at follow-up due to no permanent address) Mean of 10 TPs injected Needle size: NR	Time points: pre-injection, 10min post-inj, 14 days Outcomes: -VAS-current pain -VAS-Treatment intensity (during injection) -Questionnaire on pain interference (QPI) with physical functioning, sleep, leisure activities, and general well-being. -Treatment non-compliance	*VAS-pain change from baseline to 14d* SW: -1.6 NS: -1.6 *VAS-Treatment intensity change* SW: 16.2 NS: 8.2 *QPI* SW subjects reported less pain when touching their chin (p < 0.05) *Non-compliance due to injection pain:* SW: 12% NS: 1% P < 0.01	No sig. difference in pain reduction between SW and NS. SW caused more injection site pain than NS, which caused more patients in the SW group to discontinue treatment before injection completion.	Moderate (6/12)
Cheshire et al. (1994) RCT, double-	6 patients (67% female), age 34-55yo (mean age 43.8), with cervical	Experimental: 50U Onabotulinum toxin A divided among 2–3 sites, n	Time points: 0, 2, 3, 4 and 8 weeks Outcomes	Mean VAS (Onabotulinum toxin A vs ctrl): 0wk: 70 vs 65;	Onabotulinum toxin A group had stat sig improvement of VAS and	Moderate (7/12)

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Table 1 (*continued*)

Study/Methods/ Pain region(s)	Participants	Intervention(s)	Outcome (s)	Result (s)	Conclusion (s)	Quality rating
blind, crossover, placebo Cervical paraspinal and shoulder girdle muscles	paraspinal and shoulder girdle muscle pain of mean duration of 3 years	= 6 Ctrl: 0.9% NaCl, n = 6 Needle size: NR Inj. depth: NR Inj. vol: 4 mL	-VAS -PPT	2wks: 44 vs 60, p = 0.04; 3wks: 40 vs 60, p = 0.01; 4 weeks: 58 vs 70, p = 0.001 8wks: 70 vs 60, p = 0.06 PPT 2wks: (Onabotulinum toxin A vs ctrl) 2.8 vs 2.3, p = 0.03; 4wks: 2.9 vs 2.5, p = 0.02	PPT in the cervical paraspinal and shoulder girdle muscles in the short term. Note: preliminary data	
Byrn et al. (1993) Randomized, non-blinded Neck and shoulder pain	40 patients (52.5% female), age range 24–73yo (mean age 47). Pain for 4–6 years after whiplash syndrome secondary to motor vehicle accident	Exp: 0.3–0.5 cc sterile water (SW) per TP N = 20 Ctrl: same vol NS N = 20 Needle size: 27G Injection depth: 2–3 mm *Note 1:* Number of injected TPs ranged from 5 to 80. Up to 3 treatments were given during the 1st two months. *Note 2:* At end of procedure patient rested supine for 5 min, then stood and moved head and arms a few times. If pain then reported in a certain area, that area was palpated a 2nd time and injected during same session.	Time points: 0, 1, 3 and 8 months Outcomes: .Mean VAS(0–10) .Mean cervical spine mobility (in degrees, sum of neck rotation, flexion/ extension, and lateral rotation) .Patient general assessment of pain (PGA), Psychometric exams (for depression (Beck depression inventory), anxiety (Spielberger anxiety test), and personality traits (NEO personality inventory), and mood adjective	*VAS change at* 1mo SW:-1.9 NS: -0.2 p > 0.05 *VAS change at* 3mo SW: -1.7 NS: 0.4 P < 0.01 *VAS change at* 8mo SW: 1.6 NS: 1.1 P < 0.001 *Mean total cervical spine mobility at* 1 month SW: +36 ° NS: +5 ° p > 0.05 *Mean total cervical spine mobility at* 3 months SW: +39 ° NS: +6 ° P < 0.05 *Mean total cervical spine mobility at* 8 months SW: +20 ° NS: -11 P < 0.05 *Patients' assessments at* 3months *rating pain at least improved* SW: 19/20 (90%) NS: 6/20 (30%) P < 0.0002 *Patients' assessments at* 8months *rating pain at least improved* SW: 11/20 (65%) NS: 8/20 (40%) P > 0.05	In the short term, there was no sig difference in pain relief and neck mobility between sterile water and NS In intermediate, long and longest terms, sterile water was associated with greater neck pain relief and neck mobility, compared with NS. Patients' general self-assessments of pain improvement was higher for sterile water than NS at in the long term, but that no sig difference at longest term time point.	Moderate (5/12)

- Dysport = Abobotulinum toxin A.
- Bupi: bupivacaine.
- Ctrl: control group.
- DN: dry needling.
- Exp: experimental group.
- Inj: injection.
- IP: iliopsoas.
- MP: methylprednisolone.
- NHP: Nottingham health profile (quality of life assessment scale).
- NPAD: neck pain and disability scale.
- NR: not reported.
- NS: 0.9% normal saline.
- PF: preservative-free.
- Prilo: prilocaine.
- PS: Pain score measurement.
- RCT: randomized controlled trial.
- Sig: significant.
- Stat: statistically.
- TP: trigger point.
- VAS: visual analog scale.
- Vol: volume.
- Wk: week.

Table 2
Quality assessment - cochrane back review group (CBRG) scoring sheet for randomized studies.

Quality indicators (randomized studies)	De Andres, 2010	Raeissadat, 2018	Gobel, 2006	Kwanchuay, 2015	Cheshire, 1994	Wheeler, 1998	Wheeler 2001	Kamanli, 2005	Porta, 1999	Byrn, 1993	Wreje, 1995	Jabbari, 2007	Muller, 2005
1- Was the method of randomization adequate?*	Y	Y	Y	Y	U	N	Y	U	U	U	Y	Y	U
2- Was the treatment allocation concealed?	Y	Y	Y	Y	U	Y	Y	U	N	N	U	Y	U
3-Was the patient blinded to the intervention?	Y	Y	Y	Y	Y	Y	Y	U	Y	N	U	Y	Y
4- Was the care provider blinded to the intervention?	Y	N	Y	Y	Y	Y	Y	Y	N	N	U	Y	Y
5- Was the outcome assessor blinded to intervention? *Or,* were incomplete outcome data adequately addressed?	Y	U	Y	Y	U	U	U	U	N	U	U	Y	U
6- Was subject dropout rate acceptable ($\leq$ 20%)?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7- Were all randomized participants analyzed in the group to which they were allocated (intention-to-treat)?	U	U	U	Y	U	Y	Y	U	U	Y	Y	Y	U
8- Are reports of the study free of suggestion of selective outcome reporting?	U	N	U	Y	U	U	U	U	U	U	U	U	N
9- Were the groups similar at baseline?	U	Y	Y	Y	N	N	N	Y	U	Y	Y	Y	U
10- Were co-interventions in each group avoided or similar?	Y	Y	Y	Y	Y	N	Y	Y	Y	N	Y	Y	Y
11-Was the compliance acceptable in all groups?	U	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y
12- Was the timing of the outcome assessment similar in all groups?	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	Y
TOTAL (# of Y/12)	7/12	8/12	10/12	12/12	7/12	6/12	9/12	7/12	5/12	5/12	6/12	11/12	6/12
QUALITY RATING (H, M, L)	M	H	H	H	M	M	H	M	M	M	M	H	M

- "Y" means a "Yes" answer.
- "N" means a "No" answer.
- "U" means unclear or unknown answer.

Scoring and Quality Rating.

- If total number of Yes answers is $\geq$ 8, study is rated "H," meaning "High quality".
- If total number of Yes answers is 4-7, study is rated "M," meaning "Moderate quality".
- If total number of Yes answers is $<$ 4, study is rated "L," meaning "Low quality".

Table 3
Harms associated with trigger point injections reported in studies.

Study	Harm(s)	Timing and treatment
De Andres et al. (2010)	5 flu like symptoms, 4 muscle weakness and 2 local edema at injection site	Transient and resolved without treatment
Raeissadat et al. (2018)	Flare reaction - one in OI and one in DN group	Transient and resolved without treatment
Gobel et al. (2006)	Adverse effects (AE) in 31/64 pts in Dysport (Abobotulinum toxin A) gp (48.4%), vs 11/56 pts in placebo (19.6%), p = 0.001. 75% of AE were mild-moderate. Most common AE was muscle soreness (59% in Abobotulinum toxin A group, vs 37% of AE in placebo).	Most AEs in Abobotulinum toxin A group were first noted 7days after treatment, peaked at week 4 (87%, p < 0.001). They resolved by week 8 (p = 0.565), continuing until week 12 (p = 0.719). Marginal hypotension in Abobotulinum toxin A group was significant at week 12 (p = 0.04)
Kwanchuay et al. (2015)	No statistically significant difference between adverse effects in Onabotulinum toxin A vs NaCl 45.8% of patients in Onabotulinum toxin A group had non-severe effects (skin redness, stiffness), 41.7% of NS group had non-severe effects. (p = 0.771)	They resolved within 1 week
Cheshire et al. (1994)	None	
Wheeler et al. (2001)	More adverse events in the Onabotulinum toxin A group. Most frequent events reported were excessive weakness of the injected muscle, pain or soreness of the injection site and flu-like symptoms.	
Wheeler et al. (1998)	Two Onabotulinum toxin A subjects had ipsilateral arm heaviness and numbness; 2 reported injection site pain; 2 reported pain shifted to contralateral side, and 1 reported pain shifter to the midline.	Arm heaviness and numbness resolved within 1 week
Kamanli et al. (2005)	Lidocaine: 30% subjects had coldness sensation and 30% had paresthesia, 20% had discomfort at time of injection. Onabotulinum toxin A: 55.6% subjects had fatigue, 33.3% had muscle pain, and 10% had headache. Dry needling: 80% subjects had discomfort at time of injection	Side effects in all groups did not last more than a few days.
Porta et al. (2000)	Mild dysphonia in 5% subjects who had scalenus anterior injections	
Byrn et al. (1993)	Pain during sterile water injections	
Wreje et al. (1995)	None reported	
Jabbari (2007), low back pain RCT	None	
Jabbari (2007), prospective cohort	4% of Onabotulinum toxin A subjects had mild, flu-like reactions. Injections	Lasted 2–5 days

Table 3 (*continued*)

Study	Harm(s)	Timing and treatment
study (14-month follow-up)	were done at 5 sites along erector spinae (40–50U Onabotulinum toxin A in each site, total dose ranging 200–500U)	
Muller et al. (2005)	Tropisetron group had burning pain	It lasted less than 30sec
Alo et al. (1997). Onabotulinum toxin A injections of 10–300U/ treatment in head, neck, lumbar paraspinals, quadratus lumborum, and piriformis. Injections were done at 1 month, 3 months, and 6 months.	Flu-like side effects in: −62% of pts after 1st treatment −13% after 2nd tx −2% after 3rd tx. Each treatment was 4 weeks apart	Symptoms resolved within 1 week

- AE: adverse effects.
- Gp: group.
- OI: ozone injection
- LI: Lidocaine.
- NaCl: sodium chloride.
- Tx: therapy.

at 2 and 4 weeks, but not at 8 weeks. The study by Byrn et al. assessed injections of sterile water vs NS, with the number of injected trigger points varying from 5 to 80. In addition to baseline, time points of 1, 3 and 8 months were assessed. The sterile water injection group had greater pain improvement at 3 and 8 months ($p < 0.01$, $p < 0.001$ respectively), but not at 1 month ($p > 0.05$).

3.6. Botulinum toxin A vs normal saline

Gobel et al.'s study showed Abobotulinum toxin A (Dysport) provides pain relief at short, intermediate, and long term ([22]). Dysport is a highly purified form of Botulinum toxin A. More patients in the Abobotulinum toxin A group reported mild or no pain, they reported more pain free days, and Abobotulinum toxin A was favored by both physician's and patient's global assessments.

Cheshire et al.'s study found that Onabotulinum toxin A patients had improved cervical paraspinal and shoulder girdle muscle pain, as well as pain pressure threshold (PPT), at short term [24]. Jabbari reported that Onabotulinum toxin A significantly improved pain and disability at short and intermediate terms [31].

Two studies revealed no difference in neck pain relief between Onabotulinum toxin A and saline groups (Kwanchuay [23], Wheeler [29], and Wheeler [30]). However, Kwanchuay revealed increased PPT in the Onabotulinum toxin A group. Functional outcomes such as depression and SF-36 scores revealed no difference between Onabotulinum toxin A and saline [30]. Paracetamol use was no different between Onabotulinum toxin A and saline groups [23].

Kamanli's study ([25]) compared Onabotulinum toxin A with lidocaine and dry needling. Both Onabotulinum toxin A and lidocaine group had greater pain relief than DN, as well as improved PPT, fatigue, work-related disability, and NHP scores. It is noteworthy that Onabotulinum toxin A subjects had improvement in depression and anxiety at short term, which was not found in lidocaine and dry needling groups.

3.7. Botulinum toxin A vs steroids

Porta et al. study looked at the effectiveness of Onabotulinum toxin A vs methylprednisolone in chronic neck pain [26]. Those injections were

Table 4
Injection Technicalities (Needle dimensions, volume, and imaging use).

	Pain location	Needle diameter (Gauge)	Needle length (inch)	Injection depth	Injection volume	Image-guided?
De Andres (2010)	Piriformis, quadratus lumborum)	22 G	3.5inch	NR (not reported)	5 cc	Fluoroscopy
Raeissadat (2018)	Upper trapezius	22 G	1.25inch	NR	2 cc	No
Gobel (2006)	Cervical and/or shoulder muscles	27 G	1.57	1–3 cm	2.5 cc	No
Kwanchuay (2015)	Upper trapezius	27 G	NR	2.5 cm	0.2 cc	No
Cheshire (1994)	Cervical paraspinal and shoulder girdle muscle	NR	NR	NR	4 cc	No
Wheeler (1998)	Neck	NR	NR	NR	2 cc	No
Wheeler (2001)	Upper, mid, and lower trapezius, and thoracic region	NR	NR	NR	NR	No
Kamanli (2005)	Cervical, upper back or shoulder muscles	25 G	1.25 in	NR	1–2 cc	No
Porta (2000)	Scalenus anterior, piriformis, and iliopsoas	20 G	NR	NR	6 cc	CT
Byrn (1993)	Neck and shoulder	27 G		2–3 mm	0.3–0.5 cc	No
Wreje (1995)	Upper quadrants of body	NR	NR	NR	0.5 cc	No
Jabbari (2007)	Low back (erector spinae)	27 G	NR	NR	0.4 cc	No
Muller (2007)	Neck and shoulder	NR	NR	NR	5 cc	No

Cc: cubic centimeters.
Cm: centimeters.
CT: computed tomography.
G: gauge.
In: inch.
Mm: millimeters.
NR: not reported.

done with CT guidance. No significant difference was noted at short term, but there was a statistically significant difference favoring Onabotulinum toxin A at intermediate term.

3.8. Onabotulinum toxin A vs local anesthetic

De Andres investigated fluoroscopy guided injections for bilateral iliopsoas and quadratus lumborum pain. For each study subject, in a random fashion, one painful side of the body was injected with Onabotulinum toxin A, and the other side with either 0.25% Bupivacaine or normal saline. No inter-group difference was found between Onabotulinum toxin A and bupivacaine or normal saline injections in terms of pain relief, activity of daily life, and psychological status. However, within the Onabotulinum toxin A group, pain relief was noted at short, intermediate and long terms. Similarly to the Kamanli et al. article, this study found that, compared with NaCl and Bupivacaine, Onabotulinum toxin A was associated with less anxiety at long term.

3.9. Ozone vs local anesthetic vs dry needling

Raeissadat et al. compared 3 groups: ozone, 2% lidocaine and dry needling ([21]). All 3 agents provided short term pain relief. Though no statistically significant difference was noted between the groups, from an intra-group standpoint, the reduction of pain scores was greater for Ozone and lidocaine than for dry needling. No difference in cervical range of motion was found between the groups.

3.10. Sterile water vs normal saline

Byrn et al. investigated sterile water injections for neck pain and shoulder pain compared with saline ([27]). In the short term, there was no difference in pain relief and neck mobility between sterile water and saline. However, at intermediate, long, and longest terms, sterile water was associated with greater neck pain relief and neck mobility, compared with NS. Moreover, patients' general self-assessments of pain improvement was higher for sterile water than NS, but that was only observed at the long term.

Wreje et al. investigated sterile water injection compared to normal saline for upper quadrant pain ([28]). He found no difference in pain reduction at short term, which is similar to Byrn et al.'s findings, in terms of that specific time point. That study did not assess later time points (intermediate, long, and longest terms). It is noteworthy that in this study sterile water caused more pain during injection than normal saline.

3.11. Tropisetron vs local anesthetic (prilocaine)

Muller et al. investigated Tropisetron injection for chronic neck pain. No significant improvement was noted in Tropisetron compared to prilocaine groups at short term. Of note that trial was discontinued in Tropisetron patients who did not obtain relief, and thus the authors made no conclusion on the outcome of global patient assessments of improved pain.

4. Discussion

This systematic review sought to find evidence on the comparative effectiveness and the safety of trigger point injections for chronic neck and low back pain. A systematic review on trigger point injections for musculoskeletal pain by Scott et al. concluded that there was no clear evidence of benefit or ineffectiveness of TPIs, irrespective of the injectate used. As Scott's study included data up to July 2006, we undertook this review to add trigger point injection studies since that date. A noteworthy aspect of the included studies is the difficulty of diagnosing trigger points. As stated in page 31 of Travell and Simons' landmark book, The Trigger Point Manual, "The lack of general agreement as to appropriate diagnostic criteria for examining trigger points has been an increasingly serious impediment to more widespread recognition of myofascial trigger points …" [34] Furthermore, marginal interrater reliability compounds the issue. Spot tenderness and pain recognition have the least difficulty in terms of examining for trigger points, but one of the essential diagnostic criteria for identifying a latent or active trigger point, namely eliciting a palpable taut band, is difficult to perform. Lastly, the local twitch response, a confirmatory observation for trigger points, has the highest difficulty to perform (Simons et al., 1999).

Most studies point to the efficacy of trigger point injections, regardless of the injectate used. In recent times, Botulinum toxin has attracted the interest of researchers the most with it being the most prevalent injectate in our studies. We found five studies that compared the efficacy of Onabotulinum toxin A to normal saline, two of which showed Onabotulinum toxin A was more effective for pain relief. One study

comparing Abobotulinum toxin A to normal saline showed greater effectiveness of the former versus the latter. All of those three studies showed effectiveness at short term, two showed intermediate term benefit, and one showed long term pain relief (the Onabotulinum toxin A study). One of these studies showed improved disability in the Onabotulinum toxin A group at short and intermediate terms. Onabotulinum toxin A was no different than saline in the other three studies. The other studies we found compared Onabotulinum toxin A to local anesthetic, steroid or dry needling, and no difference in effectiveness was found. In terms of sterile water injection for myofascial neck and upper back pain, one of the two studies that we found showed significant pain improvement at intermediate and long term, compared to normal saline. No difference was noted at short term between sterile water and normal saline groups. Novel injectates such as Ozone and Tropisetron also ignited the interest of researchers. However, limited evidence has similarly failed to show significant improvement over more standard injectates such as local anesthetic.

4.1. Safety of injection therapies

The harms reported for trigger point injections are listed in Table 3. Onabotulinum toxin A injection was associated with transient, flu-like symptoms (Jabbari et al., Alo et al., De Andres et al.), local muscle weakness (De Andres at al, Wheeler et al. (2001), Wheeler et al. (1998)). Overall, with the exception of the Gobel et al. study, the harms reported were short-lasting (less than 1 week). In Gobel et al.'s study, muscle soreness were noted in 59% of subjects treated with Abobotulinum toxin A. The incidence of these side effects appeared to have been dose-dependent. Injection soreness occurred for all injectate modalities, though least frequently with local anesthetic injections (20% in Kamanli et al.'s study). The highest occurrence of injection discomfort was reported with dry needling (80% in Kamanli et al.'s study), followed by Abobotulinum toxin A and normal saline (59% and 37%, respectively, per Gobel et al.'s study). Kwanchuay et al. reported 45% incidence of non-severe skin redness in Onabotulinum toxin A groups. About a third of subjects in Kamanli et al.'s study reported injection pain in Lidocaine and Onabotulinum toxin A groups, but 80% of subjects reported that discomfort in the dry needling group. Porta et al. reports 5% incidence of mild dysphonia in subjects who received Onabotulinum toxin A in the scalenus anterior. Byrn et al.'s study found that sterile water injection was associated with procedural pain.

5. Limitations

None of our studies compared local anesthetics with steroids, which are commonly used in clinical practice. Even though two of the studies used imaging (one used fluoroscopy and one used CT), since experimental and control groups used imaging guidance in both studies, we are unable to make recommendations on whether imaging use may affect injection outcomes.

6. Conclusion

On the basis of the findings of this systematic review, we are unable to recommend a particular injectate composition. Moreover we did not find a consensus in terms of needle size, injectate doses, and volumes. Larger high-quality studies will hopefully shed more light on the ideal injectate parameters for chronic myofascial pain resulting from trigger points.

Declaration of competing interest

The authors declare no conflict of interest and received no funding or other support pertaining to this systematic review project.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inpm.2022.100076.

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