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SYSTEMATIC REVIEW

Pharmacological Treatments of Temporomandibular Disorders: A Systematic Review Including a Network Meta-Analysis

Nikolaos Christidis[1] · Essam Ahmed Al-Moraissi[2] · Golnaz Barjandi[1] · Johanna Svedenlöf[1] · Hajer Jasim[1,3] · Maria Christidis[4,5] · Malin Collin[1]

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Abstract

Objective Temporomandibular disorders (TMD) comprise a cluster of conditions with a wide range of etiological factors that causes pain and discomfort in the masticatory muscles (TMD-M) and temporomandibular joints (TMD-J). More than 50% of the patients with TMD report regular usage of drugs. However, there is still no consensus, nor is there any evidence-based support for clinicians when choosing between different drugs. Therefore, this systematic review, including a network meta-analysis (NMA), aimed to evaluate the scientific evidence and discuss the pharmacological treatment options available to treat painful TMD.

Method An electronic search was undertaken to identify randomized controlled trials (RCTs) investigating pharmacological treatments for TMD-M and/or TMD-J, published until 6 April 2023. Since only 11 articles could be used for an NMA regarding TMD-M, a narrative synthesis was also performed for all 40 included RCTs. The quality of evidence was rated according to Cochrane's tool for assessing risk of bias, while the certainty of evidence was rated according to Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results When it comes to TMD-M, evidence arises for wet needling therapies with BTX-A, granisetron, and PRP as well as muscle relaxants. For TMD-J, evidence points toward pharmacological treatment approaches including non-steroidal antiinflammatory drugs (NSAIDs) and glucocorticosteriods (for inflammatory conditions) as well as hyaluronic acid and dextrose.

Conclusions The evidence clearly indicates that the pharmacological treatment approaches differ between TMD-M and TMD-J. Therefore, it is of great importance to first try to uncover each patient's individual and multifactorial etiology and then employ a multifaceted treatment strategy, including pharmacological treatment approaches.

Key Points

Evidence clearly indicates that the pharmacological treatment approaches differ between temporomandibular disorders of muscular and arthrogenous origin.

For temporomandibular disorders of muscular origin, evidence arises for wet needling therapies with BTX-A, granisetron, and PRP as well as muscle relaxants.

For temporomandibular disorders of arthrogenous origin, evidence arises for non-steroidal antiinflammatory drugs (NSAIDs) and glucocorticosteriods (for inflammatory conditions) as well as hyaluronic acid and dextrose.

✉ Nikolaos Christidis
nikolaos.christidis@ki.se

1 Division of Oral Diagnostics and Rehabilitation, Department of Dental Medicine, Karolinska Institutet, Box 4064, SE-14104 Huddinge, Sweden

2 Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Thamar University, Thamar, Yemen

3 Department of Orofacial Pain and Jaw Function, Public Dental Services, Folktandvården Stockholms län AB, SE-102 31 Eastmaninstitutet Stockholm, Sweden

4 The Institute of Health Sciences, The Swedish Red Cross University, SE-141 21 Huddinge, Sweden

5 Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, SE-14183 Huddinge, Sweden

1 Introduction

Temporomandibular disorders (TMD) comprise a cluster of conditions that causes pain and discomfort in the masticatory muscles, temporomandibular joints (TMJ), and surrounding structures [1, 2]. TMD encompasses a range of painful symptoms, such as ear and facial pain, headache in the temporal region, and tooth sensitivity, as well as non-painful symptoms such as clicking, popping, or crepitus of the TMJ, limited jaw-movements, and muscle fatigue or stiffness [2, 3].

TMD impacts approximately 10–15% of the adult population [4, 5] and seems to be three times more frequent in women [6]. Painful TMD of musculoskeletal origin, e.g., TMD-M, is the most common diagnosis with a frequency of 42–70% [7, 8]. It is often characterized as a persistent dull, mild-to-moderate muscle pain, which can be intensified into a sharper pain sensation and radiate to adjacent structures when provoked by jaw function [9]. Another typical sign of TMD-M is tenderness or pain on palpation of the masticatory muscles [2]. TMD-M has been shown to negatively affect quality of life [10] and is often associated with psychological distress such as depression and anxiety [11]. The underlying etiology is complex and likely to be both multifactorial and biopsychosocial [1, 12].

Painful TMD of arthrogenous origin, e.g., TMD-J, can manifest within a healthy TMJ or in a TMJ affected by inflammation, such as arthritis [2]. In a healthy TMJ, pain arises from nociceptors located in the surrounding soft tissue of the joint. This pain occurs mainly during mandibular movements and ceases as soon as the jaw returns to its natural resting position [13]. However, in an inflamed TMJ, pain also emerges from nociceptors in the subarticular bone, exposed by the inflammatory processes [13, 14]. In this case, pain is constantly throbbing and worsens with jaw function. TMJ arthritis can generally be categorized on the basis of its underlying causes as local arthritis or arthritis associated with systemic disease [15]. Examples of local arthritis include synovitis, traumatic arthritis, or capsulitis. While the etiology remains largely unknown, there are some reported contributing factors. Mechanical overload of the TMJ [16], a perforation of the TMJ disc [17], or a disc displacement in the TMJ [18–20] have been reported as potential contributing factors. Further, systemic arthritis stems from underlying systemic diseases such as rheumatoid arthritis, juvenile arthritis, and psoriatic arthritis, representing a localized manifestation of a broader systemic inflammatory process. As with local arthritis, the etiology remains largely unknown for systemic arthritis [21].

On the basis of the multifactorial etiology of painful TMD [22], and since painful TMD exhibit a range of intricate symptoms and underlying causes, it is advisable to employ a multifaceted treatment strategy [23–25]. This strategy encompasses a diverse range of therapeutic modalities, including occlusal splints [26], physiotherapy [27] and/or jaw exercises [28], behavioral medicine [24], TMJ surgery [29], and pharmacological interventions [30]. While reversible non-pharmacological interventions are often recommended as first-line treatments [24], pharmacological options can play a crucial role in pain management and enhancement of overall life quality in patients with painful TMD. Further, as many as 50% of patients with painful TMD have reported usage of drugs [31]. Numerous studies have investigated the efficacy of various pharmacological treatment in painful orofacial pain conditions, including TMD [32]. Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, anxiolytics, antidepressant, muscle relaxants, and anticonvulsants are the most frequently used pharmacological agents prescribed by clinicians [33]. Nonetheless, the best pharmacological treatment modality with predictable outcomes based on solid evidence is still largely unknown. Therefore, this systematic review, including a network meta-analysis (NMA), aimed to evaluate the scientific evidence and discuss the pharmacological treatment options available to treat painful TMD.

2 Materials and Methods

2.1 Protocol

This systematic review, including an NMA, followed the protocol that was registered a priori in PROSPERO (the International Prospective Register of Systematic Reviews, registration no. CRD42023406861). Further, the included NMA of randomized controlled trials (RCTs) was conducted according to the Preferred Reporting Items for the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (the PRISMA-P checklist) (Supplementary information 1) [34].

2.2 Selection Criteria

The following inclusion criteria were adopted on the basis of the PICOTS approach:

Population (P), Intervention (I), Comparator (C), Outcome (O), Time (T), Study (S)

The **population (P)** was adult patients having painful temporomandibular disorders. In the analysis they were subgrouped according to the location of pain to either ***(a)*** TMD-M; i.e., pain of myogenous origin, and ***(b)*** TMD-J; i.e., pain of arthrogenous origin. However, there were not

enough studies on TMD-J, so this is only presented in the narrative part of the results.

The **intervention (I)** was any type of pharmacological treatment for painful TMD.

The **comparators (C)** were other pharmacological treatments, no treatment, placebo, or on waiting list.

The primary **outcome (O)** was pain reduction using a visual analogue scale (VAS; 0–100) or a numeric rating scale (NRS; 0–10). For the analysis the NRS was transformed to a 0–100 scale. The secondary outcome was changes in maximum mouth opening (MMO). However, there too few studies to do an NMA, so this is only presented in the narrative part of the results.

The follow-up **time (T)** was either short term ≤ 3 months, intermediate term 3–5 months, or long term ≥ 6 months

The **study design (S)** was composed only of randomized controlled trials that reported the outcomes of interest.

The following exclusion criteria were used: (1) studies presented in languages other than English and Scandinavian languages; (2) editorials, letters, legal cases, interviews, case-series, duplicates, observational studies, cross-sectional studies and case-control studies, non-randomized clinical trials, cohort studies, and review articles; (3) publications using duplicated data; (4) studies not investigating pharmacological treatments for painful TMD; and an additional criterion for the NMA (5) studies with missing data required to perform a meta-analysis, such as the post-treatment mean and standard deviation for the outcomes of interest.

2.3 Search Strategy

In collaboration with the librarians Lovisa Liljegren (LL) and Narcisa Hannerz (NH) at the Karolinska Institutet University Library, we designed a search strategy that identified randomized controlled studies reporting data on pharmacological treatments in a patient population with painful TMD. The electronic search was performed on 6 April 2023 and included all relevant RCTs, in any language and with any publication date, from the databases MEDLINE, EMBASE, CINAHL, the Cochrane Central Registry of Controlled Trials (CENTRAL), and Web of Science from the inception of each database to 6 April 2023.

The search strategy was developed in MEDLINE (Ovid) in collaboration LL and NH. The search strategies were peer-reviewed by NH before LL performed the search. For each search concept medical subject headings (MeSH-terms) and free-text terms were identified. The search was then translated, in part using Polyglot Search Translator [35], into the other databases. Finally, de-duplication was performed with the method presented by Bramer et al. in 2016 [36]. One final extra step was added to compare DOIs. Grey literature was not included. The complete search strategies for all databases are available in Supplementary information 2.

The Rayyan tool was used to assist with screening of titles and abstracts [37]. Two of the authors (MC and GB) independently and blinded screened the titles and the abstracts. When there was a conflict regarding potentially eligible articles for inclusion, a third author (NC) solved this disagreement by discussion, thus having the role of judge. All potentially eligible studies were then retrieved, and the full-text articles were reviewed by the same authors (MC and GB) to determine whether they met the inclusion criteria. Any disagreement was again resolved by discussion with the third author (NC).

2.4 Data Extraction

A data extraction form was developed for this review and pilot tested independently on two randomly selected studies by two of the authors (MC and GB) to ensure consistency in extraction. The extraction form was refined accordingly. Any disagreement in data extraction was resolved by discussion with a third author having the role of judge (NC). The extracted information included the characteristics of the studies and participants, i.e., authors, title, study design, subgroup diagnoses, diagnostic criteria used, age of patients, male–female ratio, treatment groups (number), duration of treatments/frequency, and outcome measures.

2.5 Assessment of Risk of Bias and Certainty of Evidence

Risk of bias was determined by two authors (MCh and JS) independently, using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB2) [38]. Any disagreement was resolved by discussion, with a third author having the role of judge (NC). The tool is structured into a fixed set of five domains of bias evaluating different aspects of the article including design, conduct, and reporting. Through an algorithm, judgment about the risk of bias is generated. The judgment can be that the article has either a low or a high risk of bias or that it can express some concerns.

Certainty of evidence was assessed (by EA) using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach of meta-analysis [39] GRADE was implemented to identify the certainty of effect estimates from the meta-analysis for the outcomes of interest, i.e., pain intensity, in the present NMA. The certainty of evidence for RCTs, as assessed by the GRADE system, includes four levels of quality of evidence: (1) high quality of evidence—i.e., the real effect is close to that of the estimated effect; (2) moderate quality evidence—i.e., the real effect is likely to be close to the estimated effect, but there is a possibility that there is a substantial difference; (3) low-quality evidence—i.e., the real effect may be significantly different from the estimated effect; and finally

(4) very low-quality evidence—i.e., the real effect is likely to be significantly different from the estimate of the effect. Thus, the certainty of evidence for RCTs, as assessed by the GRADE system, begins as high-quality evidence and is then down-rated due to limitations in study design (risk of bias), inconsistency, imprecision, indirectness, and publication bias.

2.6 Data synthesis

Before conducting the NMA in this review, a network plot was performed to present the network geometry. This was performed to assess whether the included RCTs were connected [40]. NMA was connected for the outcome of post-treatment pain intensity for TMD-M, while the other outcomes of post-treatment pain intensity for TMD-J as well as MMO with and without pain were not analyzed using NMA, but instead reported narratively.

As presented previously by our group [24, 41–43], the post-treatment pain intensity values, which were the outcome of interest, were used to calculate the standardized mean difference (SMD). For each possible pair of treatments, the results from the NMA are presented as a summary of relative effect sizes (SMD). The statistical unit used was number of patients.

The method used in this review follows our previous publications step by step and has been previously described by our group [24, 41–43]. Statistical models used in this NMA were according to multiple published statistics and assumptions [44–48].

To conduct the NMA, using the mvmeta command, the software STATA (StataCorp. 2011. Stata Statistical Software: Release 15. College Station, TX) was used [49–51]. To identify any local inconsistency, the loop-specific approach was performed separately in each closed loop of the network. The inconsistency factor was analyzed by analyzing the difference between direct and indirect estimates for a defined comparison in the loop of the network. The amount of the inconsistency factors and their 95% confidence intervals (CI) were used to infer the detection of inconsistency in each loop. In addition, a common heterogeneity estimate, within each loop, was assumed [47]. By using the ifplot command in STATA, the results of this approach were presented in a forest plot [46]. To control for the assumption of consistency in the entire network the design-by treatment model using STATA and the mvmeta command were performed, as described by Higgins and colleagues [52–54]. A meta-regression analysis of the mean of pain reduction based on VAS and follow-up time was used to assess whether the duration of follow-up influenced the post-treatment pain intensity. RCTs with a high risk of bias were excluded, and the analysis was then repeated to assess the robustness of the results. Ranking probabilities for all treatments at each possible rank for each intervention was then estimated. The treatment hierarchy was analyzed using the surface under the cumulative ranking (SUCRA) curve and mean ranks [54, 55]. SUCRA can also be presented as a percentage of treatment that can be ranked first without uncertainty [55].

3 Results

3.1 Literature Search Outcome

The full electronic search resulted in 4357 articles from all databases, but after removal of 1677 duplicates, a total of 2680 article titles and abstracts were screened. Out of the 2680 articles, 2527 were excluded after reading the titles and abstracts, resulting in 153 articles sought for retrieval. An additional ten were found from other sources. Finally, after reading the 163 full-text articles, 123 did not meet the inclusion criteria and were excluded, resulting in a total of 40 RCTs [56–95] included in this systematic review, out of which 11 were used in the NMA [56, 59, 69, 70, 72, 75, 76, 81, 83, 85, 93]. Figure 1 shows the PRISMA flow diagram with the process of evaluating RCTs for inclusion.

3.2 Presentation of Network Geometry

Nine interventions (botulinum toxin-A, clonazepam, morphine 5 mg, morphine 1.5 mg, magnesium sulfate, lidocaine, melatonin, cyclobenzaprine, and placebo) were included in the network diagrams for the outcome of post-treatment pain intensity via VAS, as shown in Fig. 2.

3.3 Study Characteristics, Individual Data, and Certainty of Evidence

The extracted study characteristics of the included RCTs are presented in Table 1. In total, 25 of the included studies showed a low risk of bias (green), 11 some concerns (orange), and 4 a high risk of bias (red), as presented with color and text in Table 2. For the NMA estimates, the certainty of evidence for all comparisons ranged from low (cyclobenzaprine) to very low (botulinum toxin-A, clonazepam, morphine 5 mg, morphine 1.5 mg, magnesium sulfate, lidocaine, melatonin, and placebo).

3.4 Results of Individual Studies

Individual results of every included RCT such as means, standard deviations, and sample size for overall post-treatment pain intensity, short to intermediate term (i.e., ranging from 2 days to ≤ 6 months) and long term (≥ 6 months), are reported in Supplementary information 3.

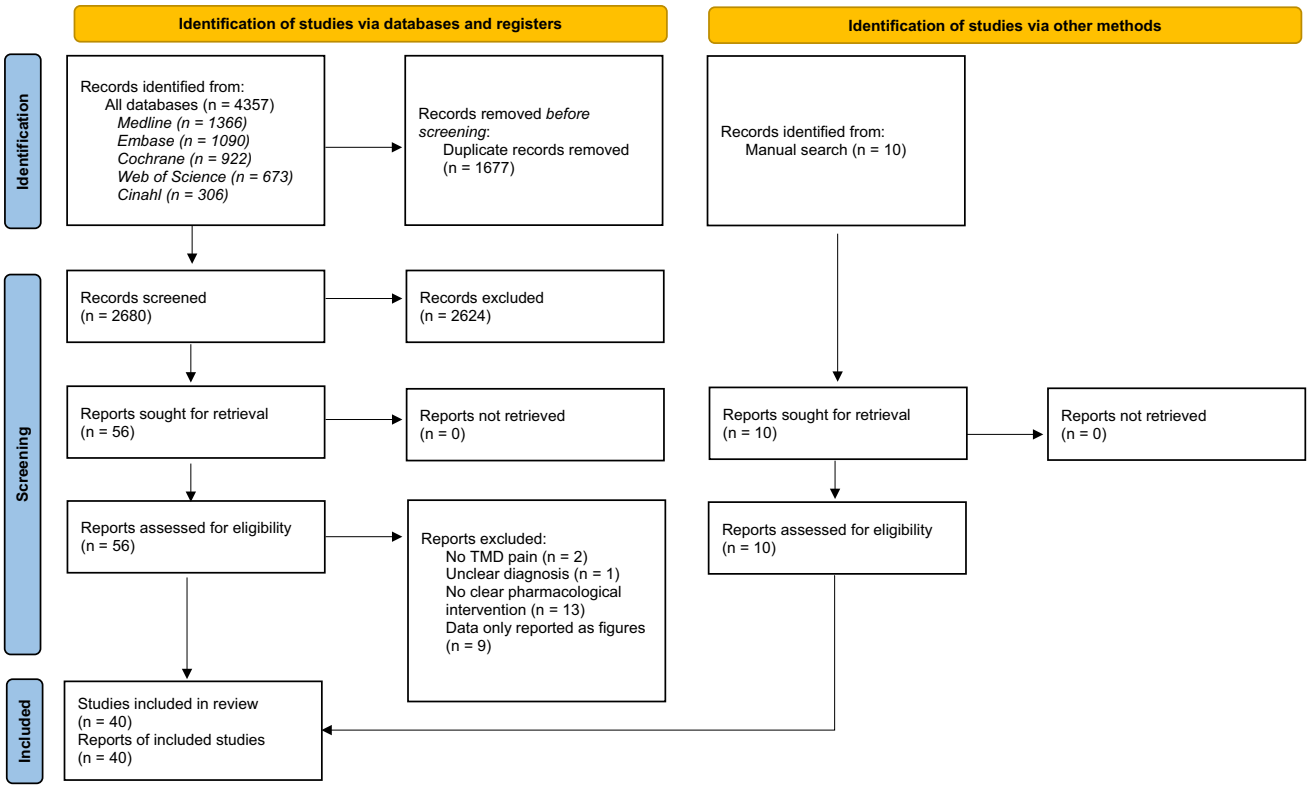

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the database search strategy. *TMD* temporomandibular disorders

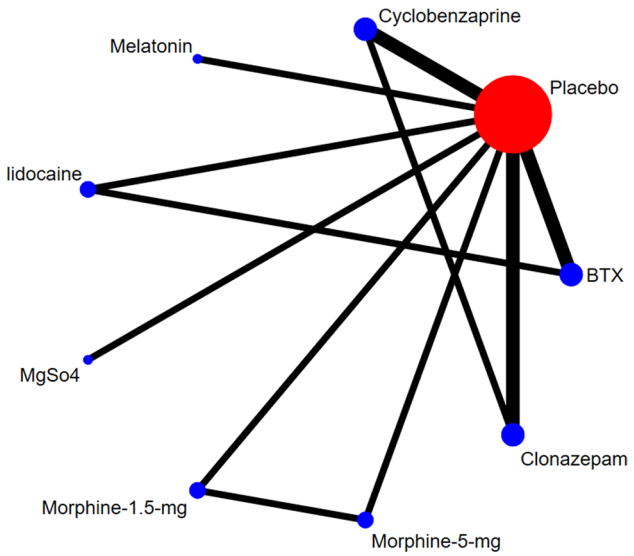

Fig. 2 Network geometry for the outcome of post-treatment pain intensity. *BTX* botulinum toxin-A, *MgSo4* magnesium sulphate

3.5 Narrative Synthesis of Pharmacological Treatment Outcomes for TMD of Muscular Origin

3.5.1 Non-steroidal Antiinflammatory Drugs

The electronic search revealed two RCT-studies that investigated the effect of naproxen as pharmacological treatment of TMD-M. On the basis of these studies, naproxen alone does not seem to have a pain-reducing effect. In the study by Cigerim and Kaplan (2023), treatment of TMD-M was more effective when naproxen was combined with codeine than when used alone or in combination with dexamethasone [60]. In the study by Khalighi et al. (2016), naproxen alone did not show any pain-reducing effect nor any increase in MMO [76].

3.5.2 Muscle Relaxants

When it comes to muscle relaxants, three RCT studies were found in the databases. These studies used skeletal muscle

Table 1 Extracted study characteristics of the 40 included RCTs

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Alencar et al. (2014) [56]	RCT	Myofascial jaw pain	AAOP	**G1:** 37 **G2:** 36.5 **G3:** 36.9	**G1:** 1:15 **G2:** 0:15 **G3:** 1:15	**G1:** placebo (15) **G2:** cyclobenzaprine (15) **G3:** tizanidine (15)	**G1:** every day for 3 weeks **G2:** every day for 3 weeks **G3:** every day for 3 weeks	Pain VAS	3 weeks	Low
Bhalla et al. (2019) [57]	RCT	Myofascial pain	Clinical examination	**G4:** NM **G5:** NM **G6:** NM	**G4:** NM **G5:** NM **G6:** NM	**G4:** ibuprofen + chlorzoxazone or carbamazepinen (10) **G5:** ibuprofen + chlorzoxazone or carbamazepine + holistic treatment (10) **G6:** holistic treatment (10)	**G4:** every day for 2 weeks **G5:** every day for 2 weeks, including 60 min of holistic treatment the first day **G6:** 60 min of holistic treatment the first day	Pain VAS	3 months	High
Cahlin et al. (2011) [58]	RCT	Osteoarthritis	RDC/TMD	**G1:** 54 **G7:** 61	**G1:** 1:10 **G7:** 1:6	**G1:** placebo (29) **G7:** glucosamine sulphate (30)	**G1:** every day for 6 weeks **G7:** every day for 6 weeks	Pain VAS MMO	6 weeks	Low
Christidis et al. (2015) [59]	RCT	Myofascial pain	DC/TMD	**G1:** 39.1 **G8:** 38.3	**G1:** 1:10 **G8:** 1:10	**G1:** placebo (20) **G8:** granisetron (20)	**G1:** once a week for 3 weeks **G8:** once a week for 3 weeks	Pain VAS MMO	6 months	Low
Cigerim and Kaplan (2020) [60]	RCT	Myofascial pain	DC/TMD	**G1:** 27.0 **G9:** 27.0 **G10:** 27.0 **G11:** 27.0	**G1:** 1:4 **G9:** 1:4 **G10:** 1:4 **G11:** 1:4	**G1:** placebo/control = paracetamol (47) **G9:** naproxen (42) **G10:** naproxen + codeine (40) **G11:** naproxen + single-dose dexamethasone (40)	**G1:** every day for 1 week **G9:** every day for 1 week **G10:** every day for 1 week **G11:** every day for 1 week	Pain VAS	4 weeks	Low
Cömert Kiliç (2016) [61]	RCT	Osteoarthritis	DC/TMD	**G12:** 32 **G13:** 28	**G12:** 1:8 **G13:** 1:3	**G12:** arthrocentesis + PRP injections (18) **G13:** arthrocentesis plus HA injection (13)	**G12:** arthrocentesis + 1 mL PRP injection initially, and then four consecutive 1 mL PRP injection in TMJ at monthly intervals **G13:** arthrocentesis + a single intraarticular injection of HA	Pain VAS	**G12:**11.6 months **G13:** 12.8 months	Some concerns
Da Silva Ramalho et al. (2023) [62]	RCT	Myofascial pain	Not specified	**G14:** 39 **G15:** 37	**G14:** 1:4 **G15:** 1:4	**G14:** BTX-A in masseter (10) **G15:** BTX-A in masseter and temporalis (10)	**G14:** single-session BTX-A injection in masseter, bilaterally (1 mL into every facial point, three points in each muscle) **G15:** single-session BTX-A injection in masseter and temporal muscles (1 mL into every facial point, three points in each masseter and two points in each temporal muscle)	Pain VAS	6 months	Some concerns

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
De la Torre Canales et al. (2021) [64]	RCT	Myofascial pain	RDC/TMD	**G1:** 31 **G16:** 30 **G17:** 35	0:54	**G1:** placebo ($n = 18$) **G16:** acupuncture ($n = 18$) **G17:** BTX-A low ($n = 18$)	**G1:** single-session bilateral injection in masseter and anterior temporalis NaCl 0.9% was bilaterally injected into the same muscles and sit **G16:** four sessions of traditional acupuncture, one 20-min session/week for 1 month **G17:** single-session bilateral injection in masseter and anterior temporalis using 30 U and 10 U of BoNT-A, distributed in five sites/muscles	Pain VAS	1 month	Low
De la Torre Canales et al. (2021) [65]	RCT	Myofascial pain	RDC/TMD	**G1:** 37 **G17:** 37 **G18:** 37 **G19:** 37 **G20:** 37	0:100	**G1:** placebo **G18:** OA ($n = 20$) **G17:** BTX-A low ($n = 20$) **G19:** BTX-A medium ($n = 20$) **G20:** BTX-A high ($n = 20$)	**G1:** single-session saline (0.9%) intramuscular injection (0.4 mL in m temporalis and 0.6 mL in masseter) **G18:** OA every night for 6 months **G17:** single-session intramuscular injection BTX-A low 10 U in m temporalis and 30 U in masseter **G19:** single-session intramuscular injection BTX-A medium 20 U in m temporalis and 50 U in masseter **G20:** single-session intramuscular injection BTX-A high 25 U in m temoralis and 75 U in masseter	Pain VAS	6 months	Low
De la Torre Canales et al. (2022) [63]	RCT	Myofascial pain	RDC/TMD	–	–	**G17:** BTX-A-low ($n = $ MD) **G19:** BTX-A-medium ($n = $ MD) **G20:** BTX-A-high ($n = $ MD)	**G17:** BTX-A-low (masseter 30 U, temporalis 10 U), **G19:** BTX-A-medium (temporalis 20 U, masseter 50 U) **G20:** BTX-A-high temporalis 25 U, masseter 75 U)	Pain VAS	6 years	Some concerns
De la Torre Canales et al. (2022) [66]	RCT	Myofascial pain	RDC/TMD	**G1:** 18–45 **G17:** 18–45 **G19:** 18–45 G**20:** 18–45	0:80	**G1:** placebo ($n = 20$) **G17:** BTX-A low ($n = 20$) **G19:** BTX-A medium ($n = 20$) **G20:** BTX-A high ($n = 20$)	**G1:** saline solution 0.9%. 1–4: bilateral injection **G17:** 10 U in each temporalis and 30 U in each masseter **G19:** 20 U in each temporalis and 50 U in each masseter **G20:** 25 U in each temporalis and 75 U in each masseter	Pain VAS MMO	6 months	Low

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Ernberg et al. (2011) [67]	RCT	Myofascial pain	RDC/TMD	**G1:** 38 **G14:** 38	**G1:** 1:10 **G14:** 1:10	**G1:** placebo ($n = 21$) **G14:** BTX-A intramuscular (masseter) ($n = 21$)	**G1:** single-session intramuscular isotonic saline masseter injection **G14:** single-session intramuscular BTX-a (50 U) injection	Pain VAS MMO	7 months	Low
Gencer et al. (2014) [68]	RCT	Internal derangement of the TMJ	Wilke's classification **G1:** Control groups selected from early-stage (I) patients **G21–G23:** Late-intermediate (IV) and late-stage (V) patients included in the study groups	**G1** 40 **G21:** 36 **G22:** 38 **G23:** 40	**G1:** 12/13 **G21:** 11/14 **G22:** 11/14 **G23:**11/14	**G1:** intraarticular injection saline solution ($n = 25$) **G21:** HA intraarticular injection ($n = 25$) **G22:** betamethasone intraarticular injection ($n = 25$) **G23:** tenoxicam intraarticular injection ($n = 25$)	**G1** intraarticular injection saline solution **G21:** HA **G22:** betamethasone **G23:** tenoxicam	Pain VAS	6 weeks	Low
Guarda-Nardini et al. (2008) [69]	RCT	Myofascial pain	RDC/TMD	**G1:** 25–45 **G24:** 25–45	1:1	**G1:** placebo ($n = 10$) **G24**: BTX-A ($n = 10$)	**G1:** single-session intramuscular injection **G24**: single-session with 4 BTX-A intramuscular injections (masseter 30 U, temporalis anterior 20 U)	Pain VAS MMO	6 months	Some concerns
Guarda-Nardini et al. (2012) [70]	RCT	Myofascial pain	RDC/TMD	**G25:** 48 **G26:** 43	1:3	**G25:** BTX-A masseter and temporalis muscle ($n = 15$) **G26**: three sessions with fascial manipulation treatment ($n = 15$)	**G25:** single session of multiple botulin toxin injections in the temporalis and masseter muscles (150 U) **G26:** 3× (±1) 50-min sessions on a weekly basis, for a total of 150 (±50) min over a 2–4-week span	Pain VAS MMO	3 months	Some concerns

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Haghighat et al. (2013) [71]	RCT	Symptomatic osteoarthrosis	RDC/TMD	**G27:** 27 **G28:** 27	1:3 1:3	**G27:** ibuprofen 400 mg ($n = 30$) **G28:** glucosamine sulphate 1500 mg ($n = 30$).	**G27:** twice a day for 3 months **G28:** once a day for 3 months	Pain VAS MMO	3 months	High
Herman et al. (2002) [72]	RCT	Myofascial pain	RDC/TMD	**G1:** 30 **G29:** 27 **G30:** 24	**G1:** 1:2 **G29:** 1:5 **G30:**: 1:8	**G1:** placebo ($n = 15$) **G29:** clonazepam ($n = 13$) **G30:** cyclobenzaprine ($n = 13$)	**G1:** placebo capsule **G29:** capsule 1 h before bedtime for 3 weeks **G30:** capsule 1 h before bedtime for 3 weeks	Pain VAS	3 weeks	High
Isacsson et al. (2019) [73]	RCT	Unilateral TMJ arthralgia	DC/TMD	**G1:** 56 **G31:** 48	**G1:** 1:3 **G31:** 1:6	**G1:** placebo ($n = 27$) **G31:** methylprednisolone ($n = 27$)	**G1:** single-session intraarticular injection **G31:** single-session intraarticular injection	Pain VAS MMO	6 weeks	Low
Jayachandran et al. (2017) [74]	RCT	TMJ osteoarthritis	Clinical examination	**G32:** 49 **G33:** 49 **G34:** 49	**G32:** 13:17 **G33:** 13:17 **G34:** 13:17	**G32:** diclofenac sodium 50 mg ($n = 10$) **G33:** diclofenac sodium + oral enzymes [bromelain, trypsin, rutoside trihydrate] ($n = 10$) **G34:** oral enzyme ([romelain, trypsin, rutoside trihydrate] ($n = 10$)	**G32:** twice a day for 10 days **G33:** twice a day for 10 days **G34:** twice a day for 10 days	Pain VAS	10 days	High
Kang et al. (2018) [75]	RCT	Myalgia	DC/TMD	**G1:** M: 30, F: 29 **G35:** M: 30, F: 29 **G36:** M: 30, F: 29 **G37:** M: 30, F: 29 **G38:** M: 30, F: 29	**G1:** 6:5 **G35:** 8:5 **G36:** 5:6 **G37:** 6:5 **G38:** 2:3	**G1:** saline in masseter ($n = 11$) **G35:** morphine 1.5 mg in masseter ($n = 13$) **G36:** morphine 5 mg masseter ($n = 11$) **G37:** lidocaine masseter ($n = 11$) **G38:** morphine 5 mg trapezius ($n = 5$)	**G1:** single bolus intramuscular injection **G35:** single bolus intramuscular injection **G36:** single bolus intramuscular injection **G37:** single bolus intramuscular injection **G38:** single bolus intramuscular injection	Pain VAS	48 h	Low
Khalighi et al. (2016) [76]	RCT	Myofascial pain	RDC/TMD	**G39:** 36 **G40:** 36	1:3	**G39:** naproxen 500 mg + placebo laser sessions ($n = 20$) **G40:** active laser (diode 810 nm CW) as treatment + placebo drug ($n = 20$)	**G39:** naproxen daily for 3 weeks + 12 placebo laser sessions **G40:** 12 active low-level laser sessions + daily placebo drug for 3 weeks	Pain VAS MMO	2 months	Low

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Kopp et al. (1985) [76]	RCT	Arthralgia	Clinical examination	**G1:** 46 **G41:** 46	**G1:** 1:7 **G41:** 1:7	**G1:** intraarticular injection of 0.5 mL sodium hyaluronate (10 mg/mL) ($n = 18$) **G41:** intraarticular injection of 0.5 mL of corticosteroid betamethasone ($n = 15$)	**G1:** single intraarticular injection **G41:** single intraarticular injection	Helkimos index	4 weeks	Low
Louw et al. (2019) [78]	RCT	TMJ arthralgia	RDC/TMD	**G42:** 44 **G43:** 50	**G42:** 1:3 **G43:** 1:23	**G42:** intraarticular injections 20% dextrose + 0.2% lidocaine ($n = 30$) **G43:** intraarticular injections 0.2% lidocaine ($n = 24$)	**G42:** intraarticular injections at 0, 1, and 2 months **G43:** 0.2% lidocaine; intraarticular injections at 0, 1, and 2 months At 3-month follow-up, allocation groups were revealed; participants in both groups were offered open-label injection of 20% dextrose/0.2% lidocaine monthly on a by-request basis	Pain VAS MMO	1 year	Low
Marini et al. (2012) [79]	RCT	TMJ osteoarthritis or arthralgia	RDC/TMD	**G44:** 14–54 **G45:** 14–54	**G44:** 1:2 **G45:** 1:2	**G44:** palmitoylethanolamide ($n = 12$) **G45:** ibuprofen ($n = 12$)	**G44:** palmitoylethanolamide 300 mg (morning) + 600 mg (evening) for 7 days and then 300 mg twice a day for an additional 7 days **G45:** ibuprofen 600 mg	Pain VAS MMO	2 weeks	Low
Mejersjö and Wenneberg (2008) [80]	RCT	TMJ osteoarthritis	RDC/TMD	**G18 :** 62 **G32:** 62	**G18:** 1:14 **G32:** 1:14	**G18:** OA ($n = 15$) **G32:** diclofenac 50 mg ($n = 14$)	**G18:** OA every night for 3 months **G32:** 2–3 times a day for 3 months	Pain VAS MMO	1 year	Some concerns
Montes-Carmona et al. (2020) [81]	RCT	Localized myalgia, myofascial pain, referred pain	DC/TMD	**G1:** 43 **G37:** 45 **G46:** 42	**G1:** 6:1 **G37:** 4:1 **G46:** 4:1	**G1:** placebo ($n = 20$) **G37:** lidocaine ($n = 20$) **G46:** BTX-A ($n = 20$)	**G1:** single-session injection of 0.9% saline solution in masseter and temporalis mucles **G37:** single-session injection of 2% lidocaine with vasoconstrictor in masseter and temporalis mucles **G46:** single-session injection of onabotulinumtoxin A	Pain VAS MMO	6 months	Some concerns

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Mustafa et al. (2018) [82]	RCT	TMJ hypermobility	Patient history and clinical examination	**G47:** 25 **G48:** 24 **G49:** 27 **G50:** 25	**G47:** 4:5 **G48:** 1:2 **G49:** 1:8 **G50:** 1:2	**G47:** saline solution + lidocaine ($n = 9$) **G48:** 10% dextrose ($n = 10$) **G49:** 20% dextrose ($n = 9$) **G50:** 30% dextrose ($n = 9$)	**G47:** injections into four different areas of each TMJ in four sessions at monthly intervals **G48:** injections into four different areas of each TMJ in four sessions at monthly intervals **G49:** injections into four different areas of each TMJ in four sessions at monthly intervals **G50:** injections into four different areas of each TMJ in four sessions at monthly intervals	Pain VAS MMO	4 months	Some concerns
Nitecka-Buchta et al. (2018) [83]	RCT	Myalgia	DC/TMD	**G1:** 40 **G51:** 37 **G52:** 43	**G1:** 7:8 **G51:** 1:2 **G52:** 5:8	**G1:** placebo/saline ($n = 15$) **G51:** collagen injections (MD Muscle [Guna]) ($n = 15$) **G52:** 2% lidocaine without a vasoconstrictor injection ($n = 13$)	**G1:** masseter triggerpoint injections at day 0 and day 7 **G51:** masseter triggerpoint injections at day 0 and day 7 **G52:** masseter triggerpoint injections at day 0 and day 7	Pain VAS MMO	14 days	Some concerns
Priyadarshini et al. (2021) [84]	RCT	TMJ internal derangement	Wilkes stages II or III	**G18:** 28 **G53:** 32	**G18:** 1:2 **G53:** 1:2	**G18:** OA ($n = 17$) **G53:** prolotherapy 50% dextrose ($n = 17$)	**G18:** 12 hours/day for 3 months **G53:** four sessions of intraarticular injection: day 1, day 14, day 42, and day 82	Pain VAS MMO	1 year	Some concerns
Refahee et al. (2022) [85]	RCT	Myofascial pain	DC/TMD	**G1:** 31 **G54:** 36	**G1:** 1:5 **G54:** 1:5	**G1:** saline master trigger point injection ($n = 90$) **G54:** MgSo4 masseter trigger point injection ($n = 90$)	**G1:** single intramuscular injection **G54:** single intramuscular injection	Pain VAS MMO	6 months	Low
Refai et al. (2011) [86]	RCT	Painful TMJ subluxation or dislocation	Patient history and clinical examination	**G55:** 30 **G56:** 23	**G55:** 1:2 **G56:** 0:6	**G55:** saline solution + 2% mepivacaine ($n = 6$) **G56:** dextrose 10% + 2% mepivacaine ($n = 6$)	**G55:** four intraarticular injections each 6 weeks apart **G56:** four intraarticular injections each 6 weeks apart	MMO	8 months	Some concerns

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Rezazadeh et al. (2022) [87]	RCT	Painful TMJ clicking and tender lateral pterygoid muscle	RDC/TMD	**G1:** 25 **G57:** 28	**G1, G57:** 17:19	**G1:** placebo/saline ($n = 18$) **G57:** BTX-A 300 U ($n = 18$)	**G1:** single-session intramuscular injection m pterygoidies lateralis **G57:** single-session intramuscular injection m pterygoidies lateralis	MMO Helkimos index	3 months	Low
Sakalys et al. (2020) [88]	RCT	Masseter myofascial pain	Simons D, Travell J, Simons L. Travell and Simons' Myofascial Pain	**G43:** 47 **G58:** 49	**G43:** 3:22 **G58:** 6:19	**G43:** lidocaine masseter injection ($n = 25$) **G58:** PRP injection ($n = 25$)	**G43:** single-session intramuscular injection m masseter **G58:** single-session intramuscular injection m masseter	Pain VAS	4 weeks	Low
Sousa et al. (2020) [89]	RCT	Arthralgia	DC/TMD	**G18:** 41 **G59:** 41 **G60:** 37 **G61:** 37	**G18:** 1:4 **G59:** 1:4 **G60:** 1:4 **G61:** 1:4	**G18:** OA ($n = 20$) **G59:** OA + intraarticular betamethasone ($n = 20$) **G60:** OA + intraarticular sodium hyaluronate ($n = 20$) **G61:** OA + intraarticular PRP ($n = 20$)	**G18:** OA every night for 6 months **G59:** OA every night for 6 months + single-session intraarticular injection **G60:** OA every night for 6 months + single-session intraarticular injection **G61:** OA every night for 6 months + single-session intraarticular injection	Pain VAS MMO	6 months	Low
Tchivileva et al. (2020) [90]	RCT	Myalgia	DC/TMD	**G1:** 34 **G62:** 34	**G1:** 1:4 **G62:** 1:2	**G1:** placebo ($n = 99$) **G62:** extended-release propranolol hydrochloride [60 mg, twice a day] ($n = 100$)	**G1:** Twice a day for 10 weeks **G62:** Twice a day for 10 weeks	MMO	10 weeks	Low
Thie et al. (2001) [91]	RCT	Osteoarthritis	Confirmed on computed tomography	**G27:** 39 **G28:** 37	**G27:** 1:8 **G28:** 1:8	**G27:** ibuprofen ($n = 28$) **G28:** glucosamine sulphate ($n = 21$)	**G27:** once a day for 90 days **G28:** once a day for 90 days	MMO	90 days	Low

Table 1 (continued)

Authors, year	Study design	Subgroup diagnosis	Criteria used	Age of patients (years)	Male:female ratio	Treatment groups (no. of participants)	Duration of treatments/frequency	Outcomes measure	Follow-up time	Risk of bias
Tjakkes et al. (2007) [92]	RCT	Arthralgia, osteoarthrosis, and osteoarthritis	RDC/TMD	**G1:** 33 **G63:** 33	**G1:** 1:18 **G63:** 1:18	**G1:** placebo ($n = 19$) **G63:** ultracain ($n = 19$)	**G1:** single-session intraarticular injection **G63:** single-session intraarticular injection	Pain VAS	3 weeks	Low
Vidor et al. (2013) [93]	RCT	Myofascial pain	RDC/TMD	**G1:** 30 **G64:** 32	**G1:** 0:32 **G64:** 0:32	**G1:** placebo ($n = 16$) **G64:** melatonin ($n = 16$)	**G1:** at bedtime for 28 days **G64:** at bedtime for 28 days	Pain VAS	28 days	Low
Winocur et al. (2000) [94]	RCT	Unilateral TMJ pain	Patient history and clinical examination	**G1:** 38 **G65:** 36	**G1:** 1:3 **G65:** 1:5	**G1:** Placebo ($n = 13$) **G65:** 0.025% capcacin cream ($n = 17$)	**G1:** vehicle cream applied to the painful area four times/day **G65:** capcacin cream applied to the painful area four times/day	MMO	4 weeks	Low
Zarate et al. (2020) [95]	RCT	Arthralgia	RDC/TMD	**G42:** 45 **G43:** 50	**G42:** 1:5 **G43:** 1:5	**G42:** dextrose prolotherapy (20% dextrose/0.2% lidocaine) **G43:** 0.2% lidocaine ($n = 15$)	**G42:** intraarticular injection at 0, 1, and 2 months ($n = 14$) **G43:** intraarticular injection at 0, 1, and 2 months ($n = 15$)	MMO	3 months	Low

G1: placebo, G2: cyclobenzaprine, G3: tizanidine, G4: ibuprofen + chlorzoxazone or carbamazepine, G5: ibuprofen + chlorzoxazone or carbamazepine + holistic treatment, G6: holistic treatment, G7: glucosamine sulfate, G8: granisetron, G9: naproxen, G10: naproxen + codeine, G11: naproxen + single-dose dexamethasone, G12 arthrocentesis + PRP injections, G13: arthrocentesis plus HA injection, G14: BTX-A in masseter, G15: BTX-A in masseter and temporalis, G16: acupuncture, G17: BTX-A Low, G18: OA, G19: BTX-A medium, G20: BTX-A high, G21: HA intraarticular injection, G22: betamethasone intraarticular injection, G23: tenoxicam intraarticular injection, G24: Botox in masseter and temporalis, G25: BTX-A injections in masseter and temporalis muscle, G26: three sessions with fascial manipulation treatment, G27: ibuprofen, G28: glucosamine, G29: clonazepam, G30: cyclobenzaprine, G31: intraarticular injection of methylprednisolone, G32: diclofenac sodium, G33: diclofenac sodium + oral enzymes (bromelain, trypsin, rutoside trihydrate), G34: oral enzyme (bromelain, trypsin, rutoside trihydrate), G35: morphine 1.5 mg masseter, G36: morphine 5 mg masseter, G37: lidocaine masseter, G38: morphine 5 mg trapezius, G39: naproxen + 12 placebo laser sessions, G40: low-level laser treatment + placebo drug, G41: intraarticular injection corticosteroid betamethasone, G42: intraarticular injections 20% dextrose + 0.2% lidocaine, G43: intraarticular injections 0.2% lidocaine, G46: BTX-A, G47: intraarticular injection saline solution + lidocaine, G48: intraarticular injection 10% dextrose, G49: intraarticular injection 20% dextrose, G50: intraarticular injection 30% dextrose, G51: collagen muscle injections, G52: 2% lidocaine without vasoconstrictor muscle injections, G53 intraarticular injection 50% dextrose, G54: magnesium sulfate masseter trigger point injection, G55: intraarticular saline + 2% mepivacaine, G56: intraarticular dextrose 10% + 2% mepivacaine, G57: BTX-A single-session intramuscular (m pterygoideus lateralis) injection, G58: PRP intramuscular injection, G59: OA + intraarticular betamethasone, G60: OA + intraarticular sodium hyaluronate, G61: OA + intraarticular PRP, G62: extended-release propranolol hydrochloride, G63: intraarticular ultracain, G64: melatonin, G65: 0.025% capcacin cream

AAOP American Academy of Orofacial Pain, *BTX-A* botulinum toxin-A, *CW* continuous wave, *DC/TMD* diagnostic criteria for temporomandibular disorders, *HA* hyaluronic acid, *MgSo4* magnesium sulfate, *MD* missing data, *DMMO* maximal mouth opening, *NM* not mentioned, *OA* occlusal appliance, *PRP* platelet-rich plasma, *RCT* randomized controlled trial, *RDC/TMD* Research Diagnostic Criteria for Temporomandibular Disorders, *TMJ* temporomandibular joint, *VAS* visual analogue scale

relaxants in addition to self-care management. However, there were diverging results concerning the treatment outcome regarding reduction in TMD-M pain. For example, cyclobenzaprine, a serotonin type 2 (5-HT_2) receptor antagonist, was shown to have a significantly better pain-reducing effect when compared with the benzodiazepine clonazepam and with placebo [72]. On the contrary, when tizanidine, an alpha-2 adrenergic receptor agonist, was compared with placebo, no significant pain-reducing effect was found and there were no differences between substances [56]. Finally, in the third study, 10 weeks of treatment with propranolol, a nonselective beta-adrenergic receptor antagonist, reduced TMD-M to a slightly higher degree than placebo. However, in this study, propranolol was more prone to adverse effects [90].

3.5.3 Melatonin

Only one RCT study was found investigating the pain-reducing effect of melatonin on TMD-M. This study showed that melatonin reduces pain scores in a significantly higher degree than placebo and that this effect was independent of the effect on sleep quality [93].

3.5.4 Wet Needling Therapies

There are several different types of wet needling therapies for TMD-M, and the focus seems to be on botulinum toxin-A (BTX-A) [62–67, 69, 81], but other wet needling therapies such as lidocaine [75, 81, 83], magnesium sulfate [85], granisetron (5-HT_3 receptor antagonist) [59], platelet-rich plasma (PRP) [88], and morphine [75] have been investigated in RCTs as well.

Several studies investigating which effect BTX-A has on pain intensity in patients with TMD-M were found. BTX-A has been shown to be more effective than placebo in reducing local pain of muscular origin in bruxers and patients with TMD-M [62, 63, 69, 81]. Two studies also reported a long-lasting pain-reducing effect of BTX-A in patients with localized TMD-M [63, 81]. The pain-reducing effect in patients with localized TMD-M does not seem to depend on dosage [63]. Further, it does not depend on whether only the masseter muscle is treated or both the temporal and masseter muscles are treated [62]. However, when it comes to the patient group with persistent TMD-M, it was shown in a study by Ernberg et al. (2011) that BTX-A had no effect on pain and that the number needed to treat (NNT) at the 1-month follow-up was 11 [67]. When BTX-A has been compared with other non-pharmacological treatments, it has been shown that the pain-reducing effect was equivalent to physiotherapy [70], acupuncture [64], and occlusal appliances [65]. Similar findings have been shown when it comes to MMO. BTX-A has been shown to improve MMO in a greater extent when compared with placebo in bruxers [69] and patients with localized TMD-M [81], regardless of dosage [66].

When it comes to other wet needling therapies, there are several one-of-a-kind studies showing promising results included in this review. First, in a study by Christidis et al. (2015), the 5-HT_3 receptor antagonist granisetron was shown to have a 30–50% pain-reducing effect, which also was significantly higher than placebo, lasting for more than 6 months, with a NNT of 4. Further, granisetron also increased the MMO significantly [59]. Second, in a study by Kang et al. (2018), a single dose of morphine had an analgesic effect for 48 h and was significantly more effective than placebo. The same study also indicated that a higher dose, 5 mg, is more effective than a dose of 1.5 mg [75]. The third study by Refahee et al. (2022) indicates that a single injection with magnesium sulfate significantly reduced pain and increased MMO up to 3 months in patients with TMD-M [85]. In the fourth study, Nitecka-Buchta et al. (2018) showed that repeated intramuscular injections with collagen were significantly more efficient in pain reduction than injections with lidocaine [83]. In the fifth study by Sakalys et al. (2020), a single injection with PRP resulted in a significantly greater pain reduction after 4 weeks than a single injection with lidocaine [88]. In the sixth and final study on wet needling therapies (except for BTX-A), four different treatment strategies for painful TMD-M were compared. The treatments were either an occlusal splint alone or in combination with either betamethasone, sodium hyaluronate, or PRP. Even though all four treatment approaches were effective, the one with the combination of occlusal splint and PRP was the only that achieved long-term success [89].

3.6 Network Meta-analysis and Treatment Ranking of Pharmacological Treatment Outcomes for TMD of Muscular Origin, Post-treatment Pain Intensity, Other Comparisons versus Placebo, SMD

Altogether, 11 RCTs with a total of 457 patients were identified [56, 59, 69, 70, 72, 75, 76, 81, 83, 85, 93]. All these reported pain reductions using the VAS after pharmacological treatment of TMD-M. The post-treatment pain intensity compared post-treatment pain intensity in eight comparisons versus placebo. The eight comparisons included intramuscular injections of BTX-A [69, 70, 81], intramuscular injection of lidocaine [81], cyclobenzaprine [56, 72], melatonin [93], magnesium sulfate [85], morphine 1.5 mg [75], morphine 5 mg [75], and clonazepam [72, 83].

Table 2 Summary of risk of bias assessed by the revised Cochrane risk-of-bias tool for randomized trials (RoB2)

Authors	Randomization process	Deviation from intended intervention	Missing outcome data	Measurement of the outcome	Selection of reported results	Judgment
Alencar et al., 2014	Low	Low	Low	Low	Low	Low
Bhalla et al., 2019	Some concerns	Low	Low	High	High	High
Cahlin et al., 2011	Low	Low	Low	Low	Low	Low
Christidis et al., 2015	Low	Low	Low	Low	Low	Low
Cigerim & Kaplan, 2020	Low	Low	Low	Low	Low	Low
Cömert Kiliç, 2016	Some concerns	Low	Low	Low	Low	Some concerns
da Silva Ramalho et al., 2023	Low	Low	Low	Some concerns	Low	Some concerns
De la Torre Canales et al., 2021	Low	Low	Low	Low	Low	Low
De la Torre Canales et. al., 2021	Low	Low	Low	Low	Low	Low
De la Torre Canales et. al., 2022	Low	Low	Some concerns	Low	Low	Some concerns
De la Torre Canales et. al., 2022	Low	Low	Low	Low	Low	Low
Ernberg et. al., 2011	Low	Low	Low	Low	Low	Low
Gencer et al., 2014	Low	Low	Low	Low	Low	Low
Guarda-Nardini et al., 2008	Some concerns	Low	Low	Low	Low	Some concerns
Guarda-Nardini et al., 2012	Some concerns	Low	Low	Low	Low	Some concerns
Haghighat et al., 2013	High	Some concerns	Low	Low	High	High
Herman al., 2002	High	Some concerns	Low	Low	Low	High
Isacsson et al., 2019	Low	Low	Low	Low	Low	Low
Jayachandran et al., 2017	High	Low	Low	Low	Low	High
Kang et al., 2018	Low	Low	Low	Low	Low	Low
Khalighi et al., 2016	Low	Low	Low	Low	Low	Low
Kopp et al., 1985	Low	Low	Low	Low	Low	Low
Louw et al., 2019	Low	Low	Low	Low	Low	Low
Marini et al., 2012	Low	Low	Low	Low	Low	Low
Mejersjö & Wenneberg, 2008	Some concerns	Low	Low	Low	Low	Some concerns
Montes-Carmona et al., 2020	Some concerns	Low	Low	Low	Low	Some concerns
Mustafa et al., 2018	Some concerns	Low	Low	Low	Low	Some concerns
Nitecka-Buchta et al., 2018	Low	Some concerns	Low	Low	Low	Some concerns
Priyadarshini et al., 2021	Low	Some concerns	Low	Low	Low	Some concerns
Refahee et al., 2022	Low	Low	Low	Low	Low	Low
Refai et al., 2011	Some concerns	Some concerns	Low	Low	Low	Some concerns
Rezazadeh et al., 2022	Low	Low	Low	Low	Low	Low
Sakalys et al., 2020	Low	Low	Low	Low	Low	Low
Sousa et al., 2020	Low	Low	Low	Low	Low	Low
Tchivileva et al., 2020	Low	Low	Low	Low	Low	Low
Thie et al., 2001	Low	Low	Low	Low	Low	Low
Tjakkes et al., 2007	Low	Low	Low	Low	Low	Low
Vidor et al., 2013	Low	Low	Low	Low	Low	Low
Winocur et al., 2000	Low	Low	Low	Low	Low	Low
Zarate et al., 2020	Low	Low	Low	Low	Low	Low

The follow-up times ranged from 2 days [75], 2 weeks [83], 3 weeks [56, 72], 4 weeks [93], 3 months [70], and 6 months [69, 81, 85].

The NMA revealed a significant pain reduction after pharmacological treatment with magnesium sulfate when compared with placebo (SMD = −5.81; CI −10.09 to −1.53; very low-quality evidence). However, there were no statistically significant differences between the other comparisons and placebo as shown in Fig. 3.

3.7 Treatment Ranking

The most effective pharmacological treatment option in reducing TMD-M pain at follow-up times ranging from 2 days to 6 months was magnesium sulfate (96.9%; very low-quality evidence), which was followed by BTX-A (64%; very low-quality evidence), cyclobenzaprine (53.6%; low-quality evidence), clonazepam (52.6%; very low-quality evidence), melatonin (50.9%; very low-quality evidence), morphine 5 mg (42%; very low-quality evidence), placebo (34.4%; very low-quality evidence), morphine 1.5 mg (33.7%; very low-quality evidence), and lastly, lidocaine (22%; very low-quality evidence), as illustrated in Fig. 4 and Table 3.

3.8 Narrative Synthesis of Pharmacological Treatment Outcomes for TMD of Arthrogenous Origin

3.8.1 Non-steroidal Antiinflammatory Drugs

The electronic search revealed four RCT studies investigating the effect of NSAIDs as pharmacological treatment for TMD-J. In one study investigating patients with TMD-J, diclofenac sodium was shown to have a significant pain-reducing effect, but that the effect is even better if it is combined with bromelain, rutoside, trihydrate, and trypsin [74]. In another study, ibuprofen was compared with the endocannabinoid-like lipid mediator palmitoylethanolamide (PEA). Even though ibuprofen was shown to have a significant pain-reducing effect and increased MMO, PEA was more effective [79]. Two studies comparing the effect of ibuprofen and glucosamine sulfate showed that ibuprofen resulted in similar or less pain reduction than glucosamine [71, 91].

3.8.2 Glucosamine Sulfate

When it comes to glucosamine sulfate, the findings are diverging. One study could not show any difference between treatment with glucose amine sulfate and placebo, neither regarding pain intensity nor MMO in patients with TMD-J [58]. However, when glucosamine sulfate was compared with ibuprofen it showed similar [91] and better [71] effects on both TMD-J pain and MMO. In the case with similar effect immediately after 90-day treatment, there was a long-term difference after 120 days where glucosamine sulfate was superior to ibuprofen [91].

3.8.3 Topical Treatment—Capsaicin

One study investigating topical treatment of painful TMD-J fulfilled the inclusion criteria. That study showed that both placebo and capsaicin cream resulted in a significant

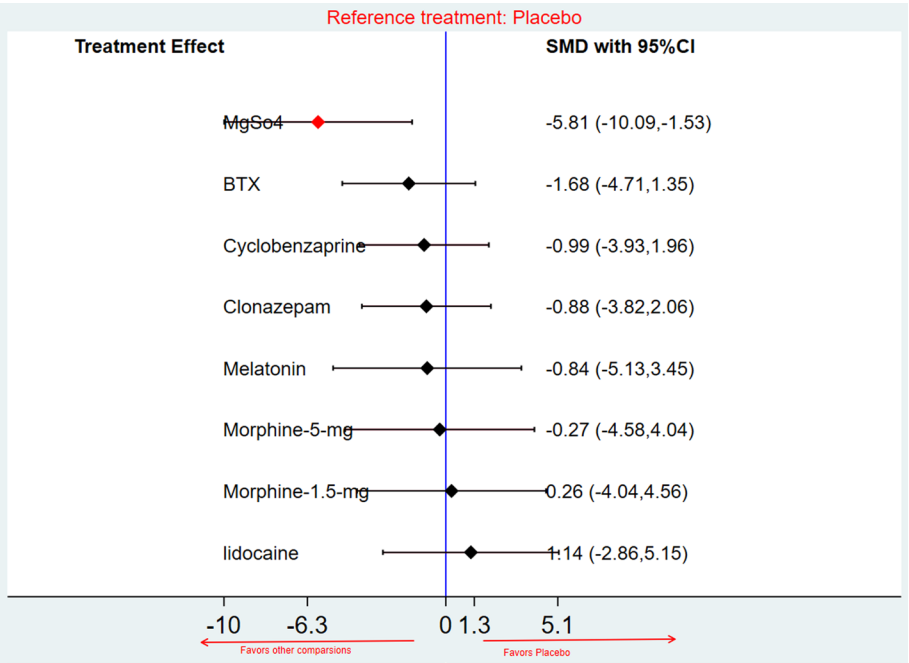

Fig. 3 Forest plot, network meta-analysis, post-treatment pain intensity and placebo versus other pharmacological treatments. *BTX* botulinum toxin-A, *CI* confidence interval, *MgSo4* magnesium sulphate, *SMD* standardized mean difference

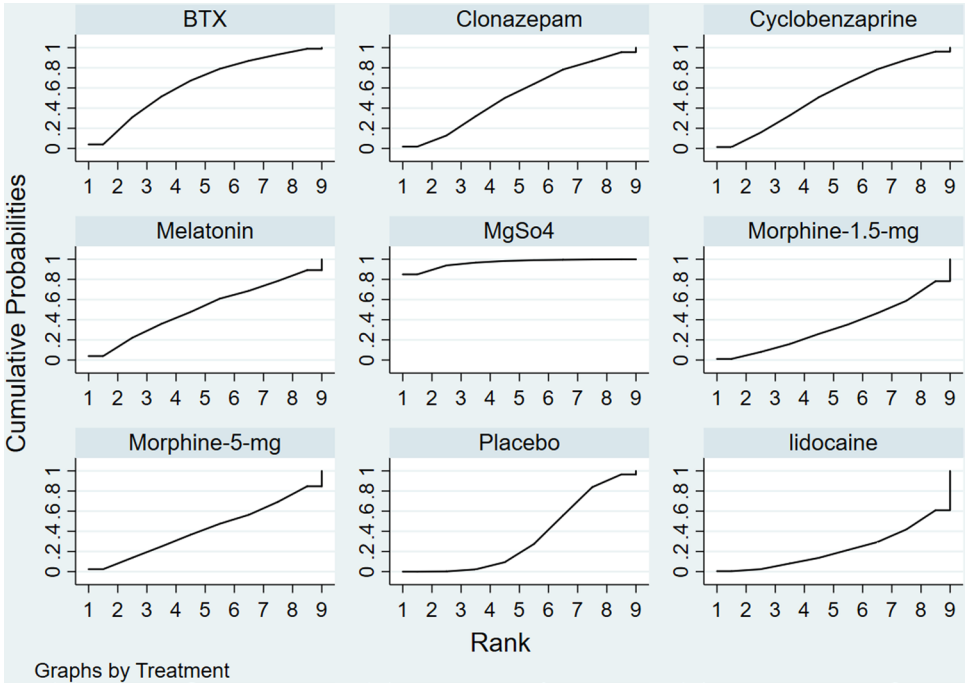

Fig. 4 Surface under the cumulative ranking curve, overall and subgroup analyses based on pharmacological treatment types. *BTX* botulinum toxin-A, *MgSo4* magnesium sulfate

improvement of unilateral TMD-J. There was, however, no statistically significant difference in either pain intensity or MMO when capsaicin was compared with placebo [94].

3.8.4 Wet Needling Therapies

There are several different types of wet needling therapies for TMD-J, some are antiinflammatory [68, 73] since TMD-J can be a painful condition assumed to be associated with local inflammation, and others focus on pain reduction with local anesthetics [78, 92, 95].

Table 3 Pharmacological treatment of patients with temporomandibular disorders of a muscular origin ranked using the SUCRA

Treatment	SUCRA	PrBest	Mean rank
Botulinum toxin-A	64.0	4.0	3.9
Placebo	34.4	0.0	6.2
Cyclobenzaprine	53.6	1.4	4.7
Melatonin	50.9	3.9	4.9
Lidocaine	22.3	0.4	7.2
Magnesium sulfate	96.5	85.0	1.3
Morphine 1.5 mg	33.7	1.1	6.3
Morphine 5 mg	42.0	2.4	5.6
Clonazepam	52.6	1.8	4.8

PRBest probability of being the best, *SUCRA* surface under the cumulative ranking curve

When it comes to antiinflammatory needling therapies, no difference in TMD-J pain was found after a single dose of methylprednisolone when compared with placebo (saline), however, the adverse effects were twice as common after treatment with methylprednisolone [73]. Similar findings were also reported in another study with the unselective NSAIDs betamethasone and tenoxicam, which were found to have less pain-reducing effect when compared with hyaluronic acid. However, all three pharmacological treatments were significantly superior when compared with placebo [68].

Further, for anesthetics, a combination of dextrose and lidocaine is superior to just lidocaine for reducing TMD-J pain intensity and increasing MMO [78, 95]. Likewise, the local anesthetic ultracain shows a short-term reduction in pain intensity, but no effect on MMO [92].

In regard to internal derangements of the TMJ with pain, dextrose prolotherapy has been found to have a significant long-term pain relief [82, 84, 95] and improved MMO [80, 83, 86, 95].

3.8.5 Pharmacological Treatment in Combination with Arthrocentesis

Pharmacological treatment can be used in combination with surgical procedures such as arthrocentesis of TMJs in patients with osteoarthritis and/or osteoarthrosis to alleviate joint pain. Only one study was found to have investigated this matter. When comparing the effect of postoperative injections with either hyaluronic acid or PRP, there were no differences in pain reduction or MMO [61].

3.9 Network Meta-analysis and Treatment Ranking of Pharmacological Treatment Outcomes for TMD of Arthrogenous Origin

There were not enough studies included to be able perform an NMA for this patient group.

4 Discussion

Currently there is no consensus regarding pharmacological treatments for painful TMD. The main findings of this systematic review provide some support for pharmacological treatment approaches for TMD of both muscular and arthrogenous origin. However, due to the small number of present and included RCTs on pharmacological treatments, in combination with the results presented in the narrative synthesis, one cannot generalize nor rank the pharmacological treatment options. Thus, there must be an individual assessment considering the multifactorial etiology of painful TMD with a range of intricate symptoms and causes. Thus, it is advisable to employ a multifaceted treatment strategy, including pharmacological treatment approaches [22–25].

For the large patient group with TMD-M [5], i.e., the TMD-M group, the NMA could only show a significant pain-reducing effect by the use of magnesium sulfate when compared with placebo, however, with very low-quality evidence. When the treatment alternatives were ranked, magnesium sulfate was placed first, followed by BTX-A, cyclobenzaprine, and clonazepam. Surprisingly, local anesthetics were ranked last, after placebo. On the basis of the narrative synthesis of this review, muscle relaxants, BTX-A, and some other wet needling agents such as granisetron, morphine, and PRP seem to be promising both when it comes to reduction of TMD-M pain and the increasing of MMO. These findings were not surprising and are in consistency with a previous NMA that also suggested that there might be a possible pain-reducing effect by BTX-A, and the muscle relaxant cyclobenzaprine could be a promising pharmacological treatment approach although lacking long-term follow-ups [32]. Further, two other NMAs also concluded that BTX-A, granisetron, and muscle relaxants could have a possible pain-reducing effect, thus ranking them high [24, 41]. When considering treatment with muscle relaxants, the reported side effects (drowsiness, dizziness, weakness, and ataxia) limits the usability [96] . In contrast to this NMA, the local anesthetic lidocaine was ranked among the highest in those NMAs [24, 41]. When it comes to non-opioid analgesic drugs, this systematic review could not provide any scientific evidence. However, they can be considered as a good complement to other treatment modalities for painful TMD-M. This and other studies suggest that non-opioid analgesic drugs can be recommended for patients with mild-to-moderate TMD-M pain, mainly as a complement to other treatment approaches [97, 98].

For the patient group with TMD-J, no NMA could be performed. Therefore, the discussion is based on the narrative synthesis of this review. The results from the synthesis of the included RCTs support pharmacological treatments of TMD-J with NSAIDs, glucocorticosteroids, and hyaluronic acid, which is in accordance with the findings from previous systematic reviews [25, 32, 99]. However, this review also indicates that the effect of prolotherapy with dextrose is promising, showing long-term pain-relieving effects and increased MMO. However, more studies are necessary to draw any conclusions. As for TMD-M, local anesthetics do not seem to provide any significant pain-reducing effects. Just like TMD-M, painful conditions arising from TMJ can be mechanical, inflammatory, due to mechanical overload, systemic diseases, etc., i.e., having a divergent, multifactorial etiology and individualized treatment plans including pharmacological treatment approaches [25, 32, 99].

4.1 Study Strengths and Limitations

The strengths of the present review encompass the following key aspects: (1) this research marks the inaugural publication of a network meta-analysis (NMA) that systematically compares the effectiveness of 39 distinct pharmacotherapeutic treatment options for TMD of muscular origin, according to the authors' knowledge; (2) by exclusively incorporating RCTs within the NMA, the researchers ensured the presence of high-quality evidence while mitigating potential biases stemming from selection and performance factors; and (3) the integration of the GRADE-system into the analytical process effectively assigned accurate grades to all findings, preventing both overestimation and underestimation of outcomes.

Nevertheless, there exist several limitations associated with this study that warrant consideration: (1) owing to unavailable data, NMA was not executed for every comparison group, and not for TMD of articular origin either; (2) certain NMA-groups were characterized by a restricted number of RCTs and participants, highlighting the imperative need for additional RCTs with larger sample sizes to comprehensively assess effectiveness before arriving at definitive conclusions; (3) variations in follow-up durations across RCTs and inadequate follow-up periods in specific instances exerted additional influence on the analysis. Moreover, the absence of essential mean and standard deviation information hindered the execution of subgroup analyses; (4) limited

data availability precluded statistical analysis of outcomes such as MMO with and without pain, necessitating a narrative presentation of results. Finally, most evidence acquired exhibited notably low quality. It is also important to note that certain included RCTs had limited sample sizes for patients with disc displacement, potentially compromising the reliability and robustness of the conclusions drawn. Therefore, a cautious approach is recommended when interpreting these findings.

4.2 Conclusions

This systematic review presents the current knowledge and evidence regarding pharmacological treatment approaches for painful temporomandibular disorders. Although a limited number of RCTs were included, there is some evidence, though not sufficient, to generalize the results. The evidence clearly indicates that the pharmacological treatment approaches differ between TMD-M and TMD-J. Therefore, it is of great importance to first try to uncover each patient's individual and multifactorial etiology and then employ a multifaceted treatment strategy, including pharmacological treatment. When it comes to TMD-M evidence, an increasing body of evidence points toward wet needling therapies with BTX-A, granisetron, and PRP as well as muscle relaxants. For TMD-J, the evidence points toward pharmacological treatment approaches including NSAIDs and glucocorticosteriods (for inflammatory conditions) as well as hyaluronic acid and dextrose.

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Declarations

Author Contributions Nikolaos Christidis had the main idea for the article. However, all authors contributed to the study conception and design. Nikolaos Christidis, Malin Collin, and Essam Ahmed Al-Moraissi performed the literature search with help from the university library at Karolinska Institutet. Selection of papers was performed by Malin Collin and Golnaz Barjandi. Analysis of risk of bias was performed by Johanna Svedenlöf and Maria Christidis. Maria Christidis is a senior lecturer and responsible for the course "Scientific theory and methods" and teaches specifically about the different methods existing for risk of bias and certainty of evidence. Further, both Nikolaos Christidis and Essam Al-Moraissi are very experienced in carrying out systematic reviews and have, together with Maria Christidis, double checked all parts of the assessment of risk of bias and certainty of evidence. Data were analyzed by Essam Al-Moraissi. Nikolaos Christidis, Maria Christidis, Malin Collin, and Hajer Jasim drafted the first manuscript that was critically revised by all authors, who commented on previous versions of the manuscript. All authors read and approved the final version manuscript.

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Conflict of Interest Authors Nikolaos Christidis, Essam Ahmed Al-Moraissi, Golnaz Barjandi, Johanna Svedenlöf, Hajer Jasim, Maria Christidis, and Malin Collin declare that they have no conflicts of interest that might be relevant to the contents of this manuscript.

Ethics Approval Not applicable.

Consent (participation & publication) Not applicable.

Code Availability Not applicable.

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