



# The hierarchy of different treatments for myogenous temporomandibular disorders: a systematic review and network meta-analysis of randomized clinical trials

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## Abstract

The best treatment modality for the management of painful temporomandibular disorders of muscular origin (M-TMD) with predictable outcomes based on solid evidence is still not well defined. Thus, the aim of this network meta-analysis (NMA) was to identify the best treatment for adult patients with M-TMD. An electronic search was undertaken from the inception of each database to August 2018, to identify randomized clinical trials (RCTs), which are comparing two or more of the following treatment modalities in patients with M-TMD: counseling therapy; occlusal appliances; manual therapy; laser therapy; dry needling; intramuscular injection of local anesthesia (LA) or botulinum toxin-A (BTX-A); muscle relaxants; hypnosis/relaxation therapy; oxidative ozone therapy; and placebo or no treatment. Primary outcome variables were the reduction of pain and mechanical sensitivity. The secondary outcome was the maximal mouth opening (MMO). The quality of evidence was rated according to Cochrane's tool for assessing risk of bias. Standardized mean difference was used to analyze via frequentist network meta-analysis (NMA), using STATA software. 52 RCTs were included in this NMA. At the most follow up moments, manual therapy, counseling therapy, occlusal splints therapy, and needling using BTX-A or LA as well as dry needling significantly decreased post-treatment pain intensity in M-TMDs, when compared to placebo. At short term ( $\leq 5$  months), the four highest-ranked treatments for post-treatment pain reduction were manual therapy (83.5%, low quality evidence), ozone therapy (75.7%, very low quality evidence), counseling therapy (71.2%, moderate quality), and occlusal appliances (71.7%, moderate quality evidence). When intermediate term ( $\geq 6$  months) was considered, BTX-A (85.8%, very low quality evidence), counseling therapy (80%, low quality evidence), occlusal appliances (62.8%, low quality evidence) and hypnosis (50.6%, very low quality evidence) were the four highest-ranked treatments. This NMA reveals that manual therapy can be considered the most effective treatment for M-TMD, followed by counseling treatment, intramuscular injection of LA, and occlusal appliances. However, considering the limitations of the studies included, and the scarce of strong evidence, the present findings should be interpreted cautiously.

**Keywords** Myogenous temporomandibular disorders · Network meta analysis · Counseling therapy · Occlusal splints · Manual therapy

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## Introduction

Temporomandibular disorders (TMDs) include conditions such as muscular and temporomandibular joint (TMJ) pain, impaired jaw function, and TMJ joint sounds [1, 2]. Next to chronic back pain, painful TMDs are the second most common musculoskeletal disorder [3, 4], affecting 5–25% of the adult population [5–7].

Painful TMD of muscular origin (i.e., TMD-myalgia [M-TMD]) is a musculoskeletal disorder of the masticatory system [8]. It is often described as a dull, pressing muscle pain of moderate intensity, which can become a more intense and sharper pain when provoked [9, 10]. M-TMD is often reported to occur while chewing, and to result in mouth opening difficulties as well as head pain; it has also been shown to be associated with depression and anxiety [11–13]. The involved masticatory muscles in M-TMD are usually associated with tender points and/or areas upon palpation [8]. Patients with M-TMD seek treatment to a greater extent than patients with painful TMJ pain [7], and these patients are mainly women aged 20–45 years old [14]. M-TMD has been shown to negatively affect quality of life [3] and, therefore, this chronic pain of moderate to severe intensity requires specific care and treatment [3, 15].

Several different treatments have been reported as successful for the treatment of M-TMD [7]. However, there is still no consensus regarding the most effective treatment for patients with this condition. Suggested treatments for M-TMD include behavioral-cognitive therapy or counseling [16]; physiotherapy or postural therapy [17, 18]; jaw exercises [19, 20]; behavioral medicine [22, 23]; manual or physical treatment such as acupuncture, dry needling, and wet needling therapies [24, 25]; transcutaneous electrical nerve stimulation (TENS) [26]; heat [27] and cold [28]; occlusal appliances [29, 30]; and pharmacological treatments [31], among others.

Many clinical studies have investigated the efficacy of various treatment modalities for the management of M-TMD. However, the best treatment modality with predictable outcomes based on solid evidence is still unknown. Conventional direct meta-analysis is designed to compare only head-to-head studies, which results in comparisons limited to these direct clinical trials [32]. Network meta-analysis (NMA) has emerged as a suitable tool to conduct a collective assessment of various interventions in a single study [33] and not only to compare two interventions that have not been compared directly in a head-to-head clinical trial [32]. An NMA of randomized controlled trials (RCTs) could, therefore, be appropriate to assess different treatments for M-TMD. The null hypothesis for this study was that there would

be no differences in pain reduction and maximal mouth opening between the different treatment options for M-TMD. The specific aims of this NMA were to challenge this hypothesis and to identify the best treatment for adult patients with M-TMD.

## Materials and methods

### Protocol and registration

A NMA of randomized controlled clinical 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) (Appendix A) [34]. This NMA was also registered in the International prospective register of systematic reviews (PROSPERO) with no. CRD42018103671 [35].

### Search strategy

Relevant RCTs, in any language and with any publication date, were retrieved by a systematic search from the inception of each database to August 2018 of the following major databases: MEDLINE, EMBASE, CINAHL, the Cochrane Central Registry of Controlled Trials (CENTRAL), and SCOPUS (Appendix B).

### Selection criteria

The following inclusion criteria were adopted based on the PICOTS process:

**(P) Patients:** (1) Adult patients with pain due to TMD of myogenous origin (Ia and Ib) based on the research diagnostic criteria for TMD protocol [36] or pain due to myalgia or myofascial pain based on the diagnostic criteria for TMD protocol [5]; (2) adult patients with a clear clinical diagnosis confirmed by the presence of signs and symptoms of TMD of muscular origin as follows: (a) patients with symptoms for at least three months; and (b) patients with two or more areas tender to palpation in the masticatory muscles on one side, namely, the temporalis, masseter, and/or pterygoid muscles.

**(I) Intervention:** RCTs comparing two or more of the following treatment modalities for M-TMD: (1) counseling therapy (including cognitive-behavioral therapy, behavior therapy and education, and self-care and home exercises); (2) occlusal appliances (including full hard/soft flat maxillary or mandibular stabilization splints and an anterior midline stop device); (3) manual therapy (including joint mobilization, manipulation, or

treatment of the soft tissues and therapeutic exercises performed by a physiotherapist); (4) intramuscular injections of botulinum toxin-A (BTX-A) into the masticatory muscles regardless of type and dosage; (5) low-level laser therapy (LLT) (the application of soft laser with a wavelength ranging between 630 and 1300 nm on painful masticatory muscles); (6) dry needling (referring to direct needling with a thin monofilament needle without any chemical agent injected directly (superficially or deeply) into the masticatory muscles, provided that it does not conform to the principles of traditional Chinese medicine); (7) local anesthesia (including intramuscular injection of plain lidocaine); (8) muscle relaxants (including oral muscle relaxant regardless of dosage, such as benzodiazepines or cyclobenzaprine); (9) hypnosis/relaxation therapy; (10) oxidative ozone therapy (a gas mixture of medical oxygen and ozone that is produced from pure oxygen and that is passed through a high-voltage gradient (5–13 mV) in a medical generator).

**(C) Comparator:** Only RCTs with a placebo (such as a non-occluding splint, sham needling without any skin penetration, and sham laser therapy) or a control group (patients who did not receive any treatment or those on a waiting list for treatment) were included.

**(O) Outcomes:** Primary outcomes were pain reduction measured with a visual analogue scale (VAS) or pressure pain thresholds (PPT) (i.e., mechanical sensitivity) measured using an algometer. The secondary outcome was maximal mouth opening (MMO).

**(T) Time:** The follow-up time of the included studies was either short term ( $\leq 5$  months), or intermediate term ( $\geq 6$  months).

**(S) Study design:** Only RCTs that reported the outcomes of interest were included.

The following exclusion criteria were applied: (1) 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) RCTs that assessed articular or mixed TMDs; (3) non-randomized clinical trials, case series, and cohort studies; (4) review articles; and (5) publications using duplicated data.

## 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 (KA and AE) working independently to ensure consistency in extraction. The extraction form was refined accordingly. Data were extracted in duplicate. Any disagreement was resolved by discussion with a third author taking the role of judge

(EA). The extracted information included the characteristics of the studies and the participants, including the authors, study design, subgroup diagnosis/criteria used, age of patients, male-female ratio, number of treatments groups, duration/frequency of treatments, and outcome measures.

## Assessment of risk of bias and publication bias

The risk of bias of the included trials was assessed independently by two of the authors (AA and KA) using Cochrane's tool for assessing risk of bias [37, 38].

A comparison-adjusted funnel plot was conducted to assess network-wide publication bias [39, 40].

## Certainty of the evidence

To identify the certainty of meta-analysis effect estimates for all outcomes of interest, the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) approach to meta-analysis was used independently by two of the authors (AA and KA) [38, 41].

## Data synthesis

The network geometry was reported with a network plot, used to identify whether the different treatments were connected [42]. The post-treatment value of the outcomes of interest was used to calculate the mean difference (MD) or standardized mean difference (SMD). Results from the NMA were presented as a summary of relative effect sizes for each possible pair of treatments. The statistical unit was the number of patients. NMA was performed using STATA (StataCorp. 2011, Stata Statistical Software: release 14, College Station, TX, USA) [43], using the `mvmeta` command [44].

The loop-specific approach using the `ifplot` command in the Stata program and “design-by-treatment” model using the `mvmeta` command was taken to evaluate the assumption of consistency at local and global levels [41, 44, 45].

The ranking probabilities for all treatments at each possible rank were investigated using the surface under the cumulative ranking (SUCRA) curve and mean ranks [46]. A rank-heat plot was conducted to visualize and present the treatment hierarchy across the multiple outcomes of interest [46, 47].

To identify the possible sources of inconsistency, the patients were classified into the subgroup follow-up time (i.e., short term and long term). To assess whether the duration of follow-up influenced the outcomes of interest, a meta-regression analysis of the mean of pain reduction based on VAS and the increase of MMO and follow-up time was performed.

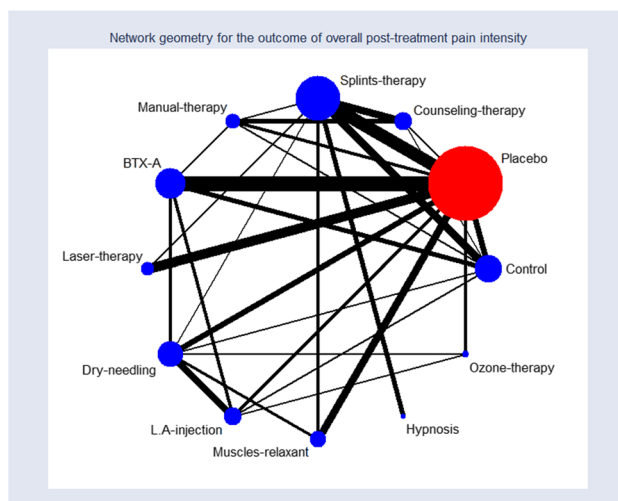
## Results

### Study selection

Figure 1 illustrates the PRISMA flow diagram, including the process of evaluating articles for inclusion in the review and NMA. The literature search in all databases resulted in a total of 1200 articles, while 20 additional articles were identified from other sources. Of the 1220 hits in the literature search, 580 articles were duplicates and were removed. Of the 640 remaining articles, 220 were excluded after reading the titles and abstracts. Finally, after reading the remaining 420 full-text articles, 368 were excluded since they did not meet the criteria, resulting in a total of 52 RCTs included and processed in this NMA [10, 40, 48–97].

### Presentation of network geometry

Twelve interventions (control, placebo, counseling therapy, occlusal appliances, manual therapy, BTX-A, laser therapy, dry needling, local anesthesia, muscle relaxant, hypnosis/relaxation therapy, and ozone therapy) were included in the network diagrams for the outcome of post-treatment pain intensity via VAS, as shown in Fig. 2. Ten interventions (control, placebo, counseling therapy, occlusal appliances, manual therapy, BTX-A, laser therapy, dry needling, local anesthesia, and ozone therapy) were included in the network diagrams for the outcome of mechanical sensitivity via PPT.

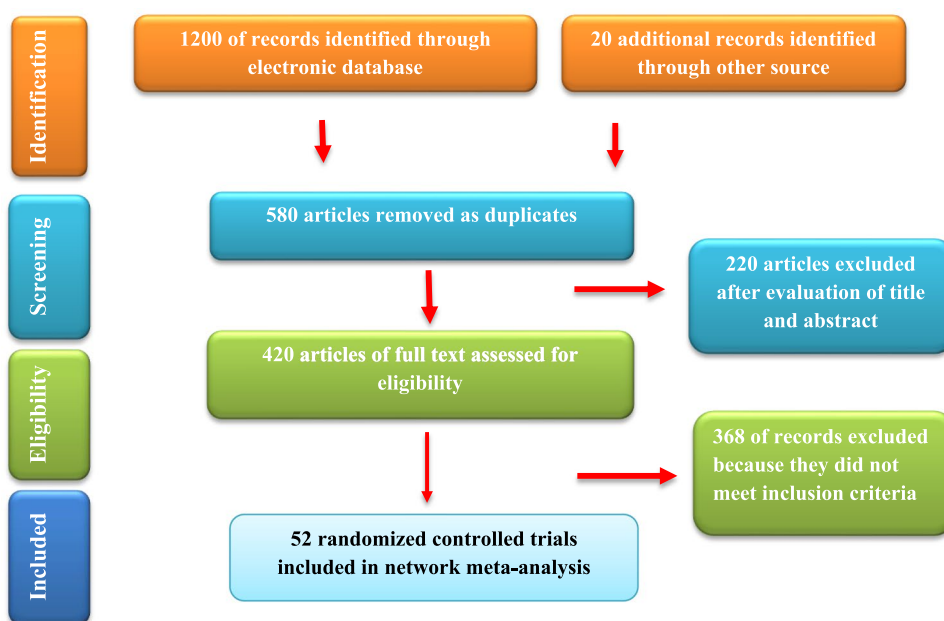


**Fig. 2** Presentation of the network geometry. This figure shows the network geometry for the outcome of overall post-treatment pain intensity regarding the twelve included interventions: control, placebo, counseling therapy, occlusal appliances, manual therapy, BTX-A, laser, dry needling, local anesthesia, muscle relaxant, hypnosis/relaxation therapy, and oxidative ozone therapy

### Study characteristics, individual data, and confidence of evidence

The characteristics of the included RCTs are summarized in Appendix C. Twenty-five of the included studies showed a low risk of bias, thirteen an unclear risk of bias, and fourteen a high risk of bias, as shown in Appendix D. The quality of evidence of direct, indirect, and NMA estimates for all comparisons ranged from high to very low.

**Fig. 1** PRISMA flow diagram. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram illustrates the literature search outcome, resulting in 52 included RCTs



In various comparisons, the evidence was downgraded because of study limitations, imprecision, or incoherence. More details about the quality of evidence for all outcomes based on the GRADE system are indicated in the figures by different colors on the bar indicating the confidence interval.

**Results of individual studies**

The individual results of every included RCT, including means, standard deviations, and sample size for overall post-treatment pain intensity, short-term ( $\leq 5$  months), intermediate term ( $\geq 6$  months), MMO, and PPT, are reported in the five tables in Appendix E.

**Synthesis of results**

**Overall pain reduction via VAS**

Forty-two RCTs ( $n = 1989$  participants) reported pain reduction using the VAS after treatment of patients with myogenous TMDs with twelve different interventions (Appendix E1). The follow-up times ranged from two weeks to 12 months post-treatment.

This NMA revealed a significant decrease in pain following the use of occlusal appliances (moderate-quality evidence) and counseling therapy (low-quality evidence) when compared with the control or no treatment.

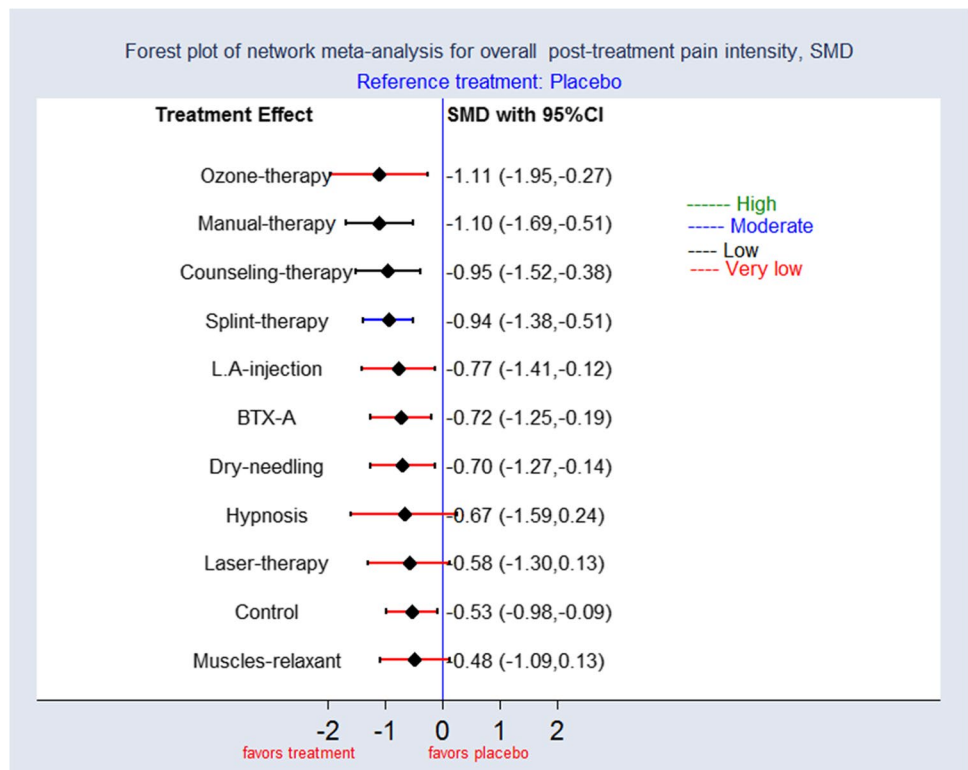
Further, this NMA showed a significant reduction in pain after the use of occlusal appliances (moderate-quality evidence), counseling (low-quality evidence), manual therapy (low-quality evidence), BTX-A (very low-quality evidence), dry needling (very low-quality evidence), local anesthesia (very low-quality evidence), ozone therapy (very low-quality evidence), or control (very low-quality evidence) when compared with a placebo, as shown in Fig. 3.

However, there were no statistically significant differences between the following modalities: occlusal appliances, counseling therapy, manual therapy, BTX-A, dry needling, local anesthesia, and ozone therapy as well as control and placebo when compared with laser treatment, muscle relaxants, and hypnosis.

**Overall mechanical sensitivity of masticatory muscles via PPT**

Twenty RCTs ( $n = 828$  participants) reported the degree of mechanical sensitivity of the masticatory muscles using algometer-assessed PPT for ten different interventions, as shown in Appendix E2. The follow-up times ranged from two weeks to 6.5 months following treatment. Since treatment RCTs using muscle relaxants and/or hypnosis did not report PPT figures, these two groups were excluded from the network analysis for this variable.

**Fig. 3** Forest plot of network meta-analysis. This forest plot shows the overall post-treatment pain intensity, in myogenous temporomandibular disorders. The quality of evidence for all outcomes based on the GRADE system is illustrated by different colors on the bar indicating the confidence interval. Green indicates high quality of evidence, blue moderate quality of evidence, black low high quality of evidence, and red very low quality of evidence. SMD, standardized mean difference; CI, confidence interval; BTX-A, botulinum toxin-A; LA, local anesthesia



The NMA showed that there were no statistically significant differences between any of the ten different treatments or placebo (all very low-quality evidence), as illustrated in Fig. 4.

### Overall change in maximum mouth opening (MMO)

Twenty-one RCTs ( $n = 807$  participants) reported changes in MMO for twelve different interventions, as shown in Appendix E3. The follow-up times ranged from two weeks to 12 months post-treatment.

There was a significant increase in MMO after treatment with manual therapy (low-quality evidence) and local anesthesia (very low-quality evidence) when compared with a control group. Manual therapy also showed a significantly greater increase in MMO when compared with counseling therapy, occlusal appliances, dry needling, control, and/or muscle relaxants (all low-quality evidence). Further, manual therapy, counseling therapy, and hypnosis resulted in a significant greater MMO than occlusal appliances (all low-quality evidence). This NMA could show that the increase in MMO was significantly higher after treatment with muscle relaxants than counseling therapy (moderate-quality evidence), occlusal appliances (low-quality evidence), dry needling (low-quality evidence), and/or BTX-A and laser (both low-quality evidence), as shown in Fig. 5.

Instead, there was a significant decrease in MMO after dry needling when compared with counseling therapy, hypnosis, manual therapy, and/or local anesthesia (all very

low-quality evidence). There was also a significant decrease in MMO after dry needling and muscle relaxants when compared with local anesthesia (all very low-quality evidence). Finally, there was a significant decrease after hypnosis when compared with occlusal appliances, muscle relaxants, and dry needling (all very low-quality evidence). No statistically significant differences between ozone therapy and other treatments were found.

### Results of additional analyses

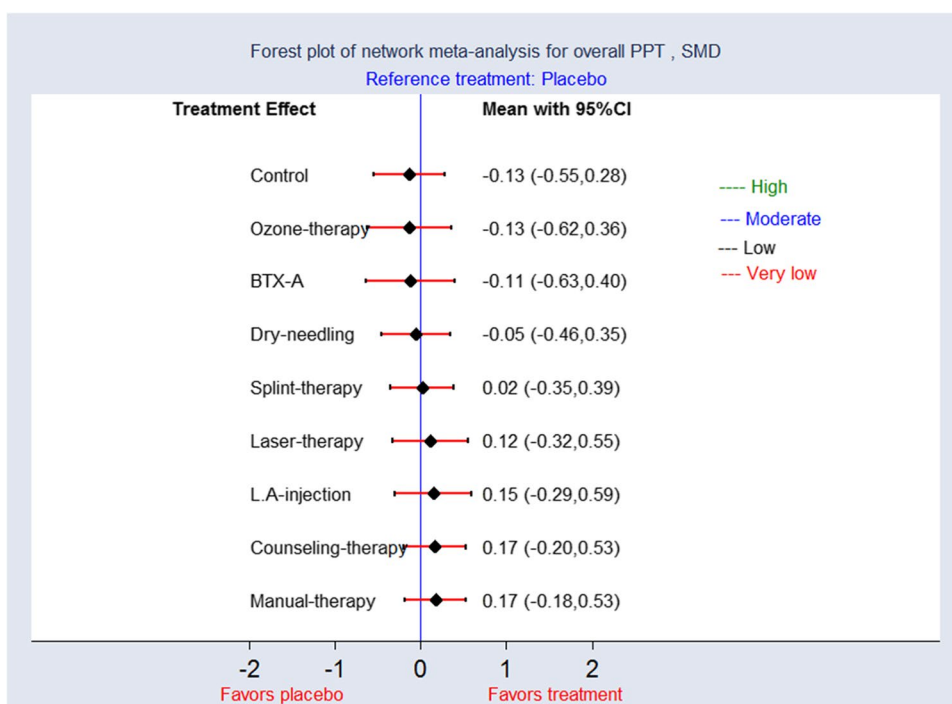
This NMA conducted two subgroup analyses based on the duration of the follow-up time, one short-term and one intermediate term.

#### RCTs with short-term ( $\leq 5$ months) follow-up on pain intensity via VAS

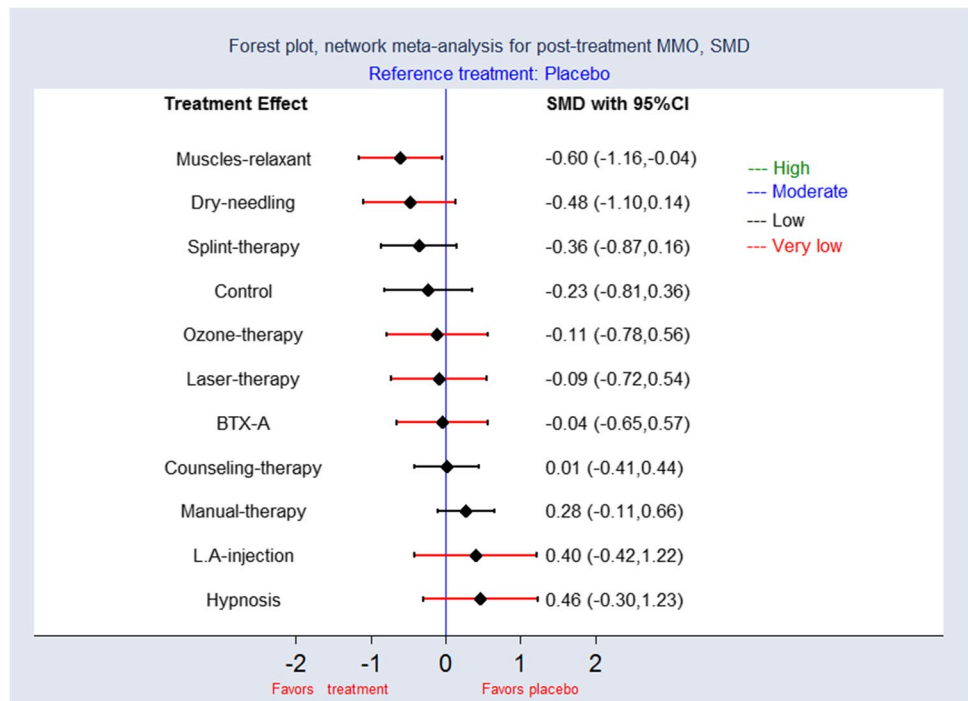
Forty-two RCTs ( $n = 1525$  participants) reported pain intensity via VAS after twelve different interventions, as shown in Appendix E4. The follow-up times ranged from two weeks to three months post-treatment.

There was a significant decrease in pain intensity after all treatments except for hypnosis when compared with a placebo. Further, there was a significant decrease in pain intensity after treatment with manual therapy when compared with the control group (low-quality evidence). Instead, there was a significant increase in pain intensity in the control group when compared with a placebo (very low-quality evidence). Finally, the decrease in pain

**Fig. 4** Forest plot of network meta-analysis. This forest plot shows the overall change in mechanical sensitization (PPT), in myogenous temporomandibular disorders. The quality of evidence for all outcomes based on the GRADE system is illustrated by different colors on the bar indicating the confidence interval. Green indicates high quality of evidence, blue moderate quality of evidence, black low high quality of evidence, and red very low quality of evidence. SMD, standardized mean difference; CI, confidence interval; PPT, pressure pain threshold; BTX-A, botulinum toxin-A; LA, local anesthesia



**Fig. 5** Forest plot of network meta-analysis. This forest plot shows the post-treatment maximum mouth opening (MMO), in myogenous temporomandibular disorders. The quality of evidence for all outcomes based on the GRADE system is illustrated by different colors on the bar indicating the confidence interval. Green indicates high quality of evidence, blue moderate quality of evidence, black low high quality of evidence, and red very low quality of evidence. SMD, standardized mean difference; CI, confidence interval; BTX-A, botulinum toxin-A; LA, local anesthesia

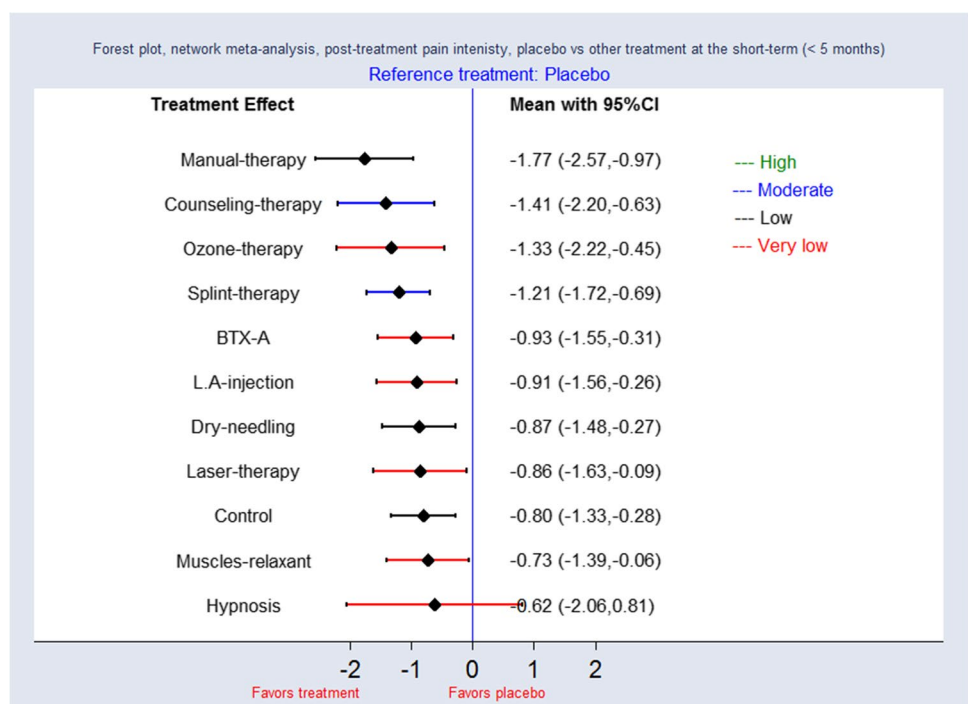


intensity was significantly greater after treatment with manual therapy when compared with a placebo (moderate-quality evidence), control (moderate-quality evidence), BTX-A, muscle relaxants, dry needling, and/or laser therapy (all low-quality evidence), as shown in Fig. 6.

**RCTs with intermediate-term (≥ 6 months) follow-up on pain intensity via VAS**

Nine RCTs (*n* = 897 participants) reported pain intensity via VAS after seven different interventions, as shown in Appendix E5. The follow-up times ranged from 6 to 12 months after treatment. Since the RCTs on laser therapy,

**Fig. 6** Forest plot of network meta-analysis. This forest plot shows the overall post-treatment pain intensity in the short term (≤ 5 months), in myogenous temporomandibular disorders. The quality of evidence for all outcomes based on the GRADE system is illustrated by different colors on the bar indicating the confidence interval. Green indicates high quality of evidence, blue moderate quality of evidence, black low high quality of evidence, and red very low quality of evidence. SMD, standardized mean difference; CI, confidence interval; BTX-A, botulinum toxin-A; LA, local anesthesia



ozone therapy, local anesthesia, and muscle relaxants did not report the presence of pain at the intermediate-term follow-up, these groups were excluded from the network analysis.

There was a significant decrease in pain intensity scores after manual therapy, occlusal appliances, and counseling therapy when compared with a placebo (all low-quality evidence). Further, BTX-A showed a significant decrease in pain intensity when compared with manual therapy (very low-quality evidence). Also, pain intensity was significantly lower after manual therapy when compared with counseling therapy and occlusal appliances (all very low-quality evidence), as seen in Fig. 7.

### Treatment rankings

#### Overall pain reduction via VAS

The most effective option to reduce pain intensity in the overall follow-up of patients with myogenous TMD was manual therapy (83%, low quality evidence), followed by ozone therapy (79.8%, very low quality evidence), occlusal appliances (73%, moderate quality evidence), counseling therapy (71.2%, low quality evidence), local anesthesia (54.1%), BTX-A (51.5%), dry needling (48%), hypnosis (48%), control (28.7%), muscle relaxants (27.7%), and placebo (2%) (all very low quality evidence), as illustrated in Fig. 8 and Appendix F.

#### Overall mechanical sensitivity of masticatory muscles via PPT

The most effective technique to reduce the mechanical sensitivity of the masticatory muscles in the overall follow-up of

patients with myogenous TMD was manual therapy (74.9%), counseling therapy (73%), local anesthesia (72.8%), laser (69.3%), occlusal appliances (49.8%), placebo (44.9%), dry needling (37.1%), BTX-A (29.6%), ozone therapy (26.3%), and control (22.3%) (all very low quality evidence), as shown in Fig. 8 and Appendix F.

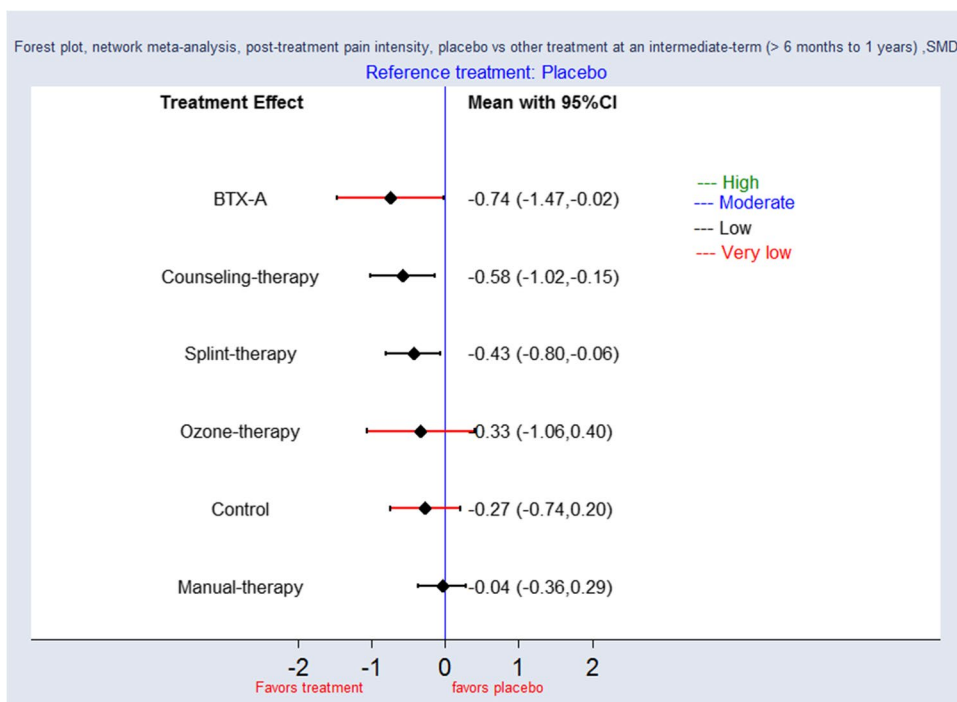
#### Overall change in MMO

According to the SCURA value, the most effective treatments to increase the MMO for patients with myogenous TMD at follow-up times ranging from 1 to 12 months were hypnosis (88%, very low quality evidence), followed by local anesthesia (85%, very low quality evidence), manual therapy (84%, low quality evidence), counseling (58%, low quality evidence), BTX-A (55%), low laser therapy (50%), ozone therapy (47%), control (33.5%), occlusal appliances (22%), dry needling (13.1%), and muscle relaxants (5%) (all very low quality evidence), as shown in Fig. 8 and Appendix F.

#### RCTs with short-term (≤ 5 months) follow-up on pain intensity via VAS

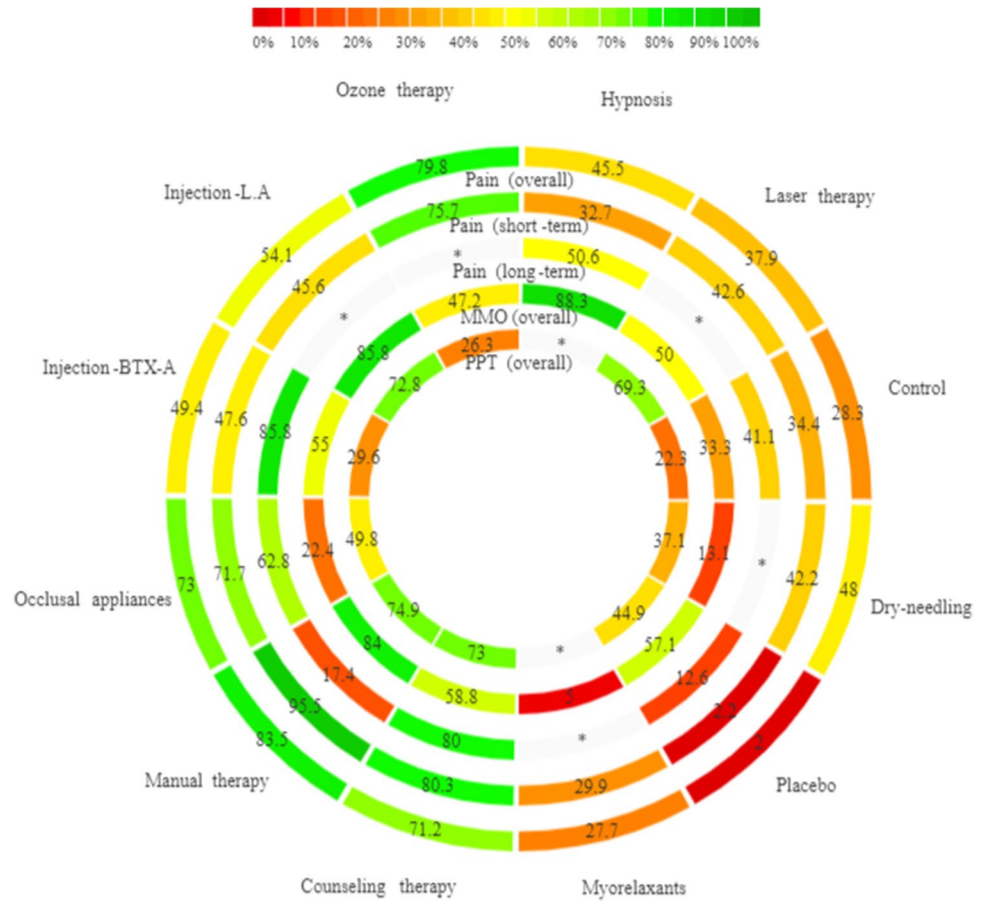
The most effective treatments to reduce pain intensity in the short term for patients with myogenous TMD were manual therapy (95.5%, low quality evidence), followed by counseling (95.5%, moderate quality evidence), ozone therapy (75.7%, very low quality evidence), occlusal appliances (71.2%, moderate quality evidence), BTX-A (47.6%), local

**Fig. 7** Forest plot of network meta-analysis. This forest plot shows the overall post-treatment pain intensity in the intermediate term (≥ 6 months), in myogenous temporomandibular disorders. The quality of evidence for all outcomes based on the GRADE system is illustrated by different colors on the bar indicating the confidence interval. Green indicates high quality of evidence, blue moderate quality of evidence, black low high quality of evidence, and red very low quality of evidence. SMD, standardized mean difference; CI, confidence interval; BTX-A, botulinum toxin-A; LA, local anesthesia





**Fig. 8** Rank-heat plot. This rank-heat plot shows the hierarchy of the twelve included treatments regarding the overall post-treatment pain intensity as well as the short-term ( $\leq 5$  months) and intermediate-term ( $\geq 6$  months) post-treatment pain intensities, the maximum mouth opening (MMO), and the mechanical sensitization (PPT), in myogenous temporomandibular disorders. BTX-A, botulinum toxin-A; PPT, pressure pain threshold



anesthesia (45.6%), laser therapy (42.6%), dry needling (42.2%), control (34.4%), hypnosis (32%), muscle relaxants (29.9%), and placebo (34.4%) (all very low quality evidence), as shown in Fig. 8 and Appendix F.

**RCTs with intermediate-term ( $\geq 6$  months) follow-up on pain intensity via VAS**

The most effective treatments to reduce pain intensity in the intermediate term were BTX-A (85.5%), followed by counseling (80%), occlusal appliances (62.8%), hypnosis (50.6%), control (41.1%), manual therapy (17.4%), and placebo (12.6%), as shown in Fig. 8 and Appendix F.

**Additional analysis**

**Meta-regression analysis between follow-up time and pain**

Meta-regression analysis showed that there was a negative, not statistically significant relationship between

pooled means of post-treatment pain intensity and follow-up time in the included studies (coefficient =  $-0.35$ , CI:  $-0.13, 0.11$ ,  $P = 0.870$ ).

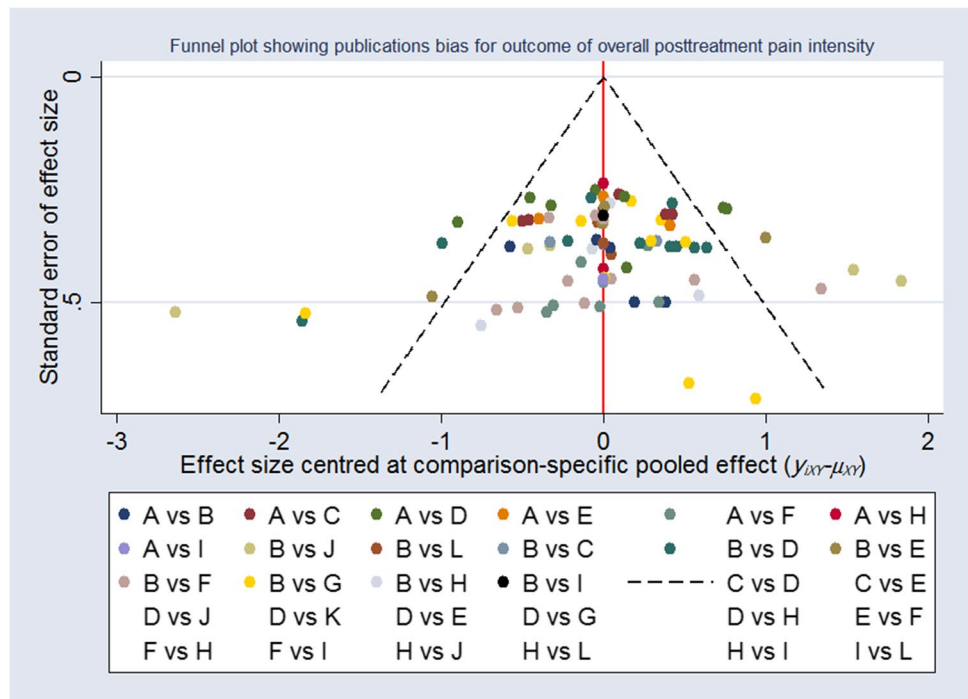
**Funnel plot and publication bias**

The funnel plot for outcomes of overall pain intensity is shown in (Fig. 9). Scatters in the funnel plot were relatively symmetrical, indicating the absence of small-size effect and publication bias.

**Exploration for inconsistency**

For the outcome of overall pain, loop-specific tests to assess local inconsistency did not detect any statistical inconsistency between direct and indirect evidence. All confidence intervals were truncated from zero. There were small inconsistencies (they did not reach statistical significance) in the loops: control – manual-BTX-A therapy; control – placebo

**Fig. 9** Funnel plot, publication bias, and overall post-treatment pain intensity. A, control; B, placebo; C, counseling therapy; D, occlusal appliances; E, manual therapy; F, BTX-A; G, laser; I, dry needling; J, local anesthesia; K, muscle relaxant; L, hypnosis/relaxation therapy; M, oxidative ozone therapy



– manual therapy; and placebo – occlusal appliances – manual therapy. These insignificant statistical inconsistencies were due to variations in follow-up times. Thus, after subgroup analysis based on follow-up time, the number of formed triangular loops was decreased significantly.

Based on the design-by-treatment interaction model, used to test a global inconsistency in the network, no significant inconsistency between direct and indirect evidence was identified within the evidence network as a whole ( $I = 23.14$ ;  $P = 0.39$ ). Therefore, both inconsistency and consistency models were fitted for all analysis (overall pain intensity via VAS, mechanical sensitization of the muscles via PPT, MMO, and the subgroup analyses based on follow-up time) according to global, local, and node-splitting models. The ifplots for all outcomes and subgroup analyses are presented in Appendix G.

## Discussion

Currently, there is no consensus regarding the most effective treatment strategies for M-TMD, although several treatments have been presented as successful in the management of TMD [7], which makes it very hard to provide clear therapeutic recommendations. With this in mind, the results from this NMA can help to increase knowledge regarding treatment modalities of M-TMD by providing data regarding both treatment outcomes and treatment rankings.

The main findings of this NMA regarding pain reduction indicate that manual therapy, counseling therapy, occlusal appliances, and BTX-A have a superior treatment effect,

both in the short term and intermediate term. This NMA also highlights that local anesthetics and ozone therapy have a superior effect when compared to dry needling, hypnosis, laser therapy, and muscle relaxants in the short term. With regard to maximum mouth opening capacity, manual therapy, local anesthesia, hypnosis, counseling therapy, and BTX-A were superior to the other treatments. Finally, with regard to mechanical sensitivity, no differences in pressure pain threshold were detected, but in terms of treatment rankings, manual therapy, counseling therapy, local anesthesia, laser therapy, and occlusal appliances were superior to the other five treatment modalities.

Altogether, this NMA shows manual therapy to be the most effective treatment for M-TMD, followed by counseling treatment, local anesthesia, and occlusal appliances. These results are not surprising and agree with previous studies. Manual therapy obtains positive results not just in the orofacial region [86, 87] but also in other parts of the body [98, 99]. With regard to counseling therapy, previous studies [10, 100, 101] as well as the Swedish national guidelines for dentistry have stressed the importance of always including or even starting the treatment of TMD with this modality [16]. The superiority of local anesthesia when compared to other needling therapies, as shown in this NMA, was also reported in a recently published NMA showing that local anesthesia is superior to treatment with BTX-A or dry needling, both in the short term and intermediate term [25]. Finally, it is not surprising that the use of occlusal appliances appears in the top-ranked treatments for M-TMD as several studies have reported good treatment outcomes with this modality [48,

102–106]. In addition, a recent NMA reported that occlusal appliances had a real pain-reducing effect at follow-ups, beyond the placebo effect [107].

Except for mechanical sensitivity, placebo was ranked the lowest among all the treatment modalities, indicating that the effect of the included treatment modalities in this NMA is real, beyond the placebo effect only. From one perspective, this could be considered an unexpected finding, since previous studies have detected a significant placebo effect in at least half of the participants in clinical studies [108]. Moreover, this positive placebo effect is even greater in studies investigating pain-reducing treatment modalities where the control group is treated with a placebo [109]. The different results for reported pain (VAS) and mechanical sensitivity (PPT) are expected. The patients' experience and perception of improvement is usually the first and most sensitive parameter to be noted. Alterations in the PPT, expressed by local changes (peripheral sensitization) and central factors such as central sensitization and impaired inhibitory modulation, seem to need more time to occur and to be expressed in the algometry. Less surprising was the fact that untreated controls were ranked in the lower third of the treatment modalities, oscillating between the third or fourth position from the end. The superiority of untreated controls compared to some of the included treatment modalities, such as muscle relaxants and hypnosis, and the superiority of MMO over occlusal appliances and dry needling may have several different explanations. One is that M-TMD symptoms are usually mild to moderate, fluctuating and self-limiting, and tend not to be progressive [110]; therefore, the passage of time usually has a beneficial outcome on pain outcomes regardless of the treatment strategy. Another explanation is that most outcomes are related only to pain reduction on a single-dimension scale (for this NMA, the VAS), which has the shortcoming of not assessing and identifying all treatment-related changes, such as such satisfaction with the treatment, behavioral improvements, and improved quality of life, among others. It has also been shown that treatment success in M-TMD is poorly correlated with reduction in pain intensity [111, 112]. Hence, by using other variables (in this NMA, the MMO, e.g., physical functioning), more dimensions of the patients' experiences are taken into consideration. The use of a single-dimension scale can therefore explain why treatment modalities such as occlusal appliances and dry needling were ranked among the top five treatments in this NMA but ranked lower than the untreated controls in relation to physical functioning. Therefore, future studies not only should include changes in pain intensity as a single variable but should also consider pain as a multidimensional experience [113]. This would result in the inclusion of several outcome variables, such as physical functioning (including jaw function), psychosocial and behavioral aspects, and emotional status (stress, depression,

anxiety, somatization, pain catastrophizing, etc.) [111, 112, 114–116]. Improvements in psychological variables as such anxiety and depression were reported in patients after counseling and the use of occlusal appliances, while decreased pain catastrophizing levels were detected in those receiving only counseling [81]. These findings highlight the urgent need to expand the parameters of judging treatment efficacy beyond the single pain report, which is usually done usually in a biased fashion with the use of single-dimension scales.

The current NMA has the following limitations: (1) since all the included RCTs used different criteria in the recruitment of patients with respect to the severity and chronicity of M-TMD at baseline, selection bias may be present in the original RCTs. Thus, a minimum of three months of signs and symptom of M-TMD was used in the present study as an inclusion criteria; (2) heterogeneity was also present in the treatment modalities with regard to medication dosage, number of treatment sessions/injections, etc., which may also have affected the outcomes.

The present study has the following strengths: (1) to the best of the authors' knowledge, this is the first NMA including 52 RCTs that assesses the hierarchy of twelve different treatment modalities versus placebo for patients with M-TMD; (2) only RCTs that assessed M-TMD were included; (3) the GRADE system to assess the certainty of the evidence for all outcomes was used to avoid under- and overestimation of the effect size measure; (4) subgroup analyses were conducted based on follow-up times (e.g., short term and intermediate term) to identify the impact of effect modifiers such as the follow-up time; (5) all evidence and analyses were derived from consistency assumptions, since the presence of transitivity and the absence of incoherence were checked using global, local, and node split statistical tests, which all indicate insignificant inconsistencies; (6) transitivity and consistency assumptions were upheld in the current study since it showed an insignificant correlation between the follow-up times and the changes in post-treatment pain intensity; and (7) the reference group (common comparator) was the placebo group. Although these results are not surprising and reflect those of previous studies, it is interesting to note that all reversible treatments considered in the actual NMA showed some degree of pain and MMO improvement over time. The time effect (short term or intermediate term) and the variables considered did not strongly affect these favorable outcomes. Even the placebo and control groups showed improvements at a certain level, which reinforces the benign progression of M-TMD. Therefore, there is a need to expand the way the response of patients to treatments is judged. The actual findings suggest the inclusion of other psychological and behavioral outcomes in future studies designed to investigate the efficacy of different treatment modalities not only for M-TMD but, ideally, for all clinical studies dealing with a complex phenomenon

such as pain, especially in chronic conditions. These complementary outcome variables could be patient satisfaction or global improvement; physical functioning, including jaw function; psychosocial and behavioral measurements; and emotional status, including stress, depression, anxiety, and somatization.

In conclusion, this NMA showed that manual therapy is the most effective treatment for M-TMD, followed by counseling, local anesthesia, and occlusal appliances. However, considering the limitations of the studies included, and the scarce of strong evidence, the present findings should be interpreted cautiously. For future studies, the authors suggest the inclusion of behavioral and psychosocial variables when judging the efficacy of pain therapies.

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## Declarations

**Ethical approval** Not required.

**Informed consent** Not required.

**Conflict of interest** The authors declare no competing interests.

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