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*Review*

# A Mixed Comparison of Non-surgical Interventions for Pain Caused by Temporomandibular Disorders: Systematic Review and Network Meta-analysis

**KOMNIVOC THARMO[1] and SB Feng[1,*]**

1. Faculty of Sports Science, Ningbo University, 315211, Ningbo, China
* Correspondence: 2201040006@nbu.edu.cn

**Abstract:** *Background*: Pain management is one of the main parts of treatments for Temporomandibular Disorders (TMDs). However, there is still a lack of high-quality evidence that compare the overall effects of these non-surgical treatments. The objective of this systematic review is to identify the most potential treatment protocol in dealing with pain caused by TMDs through a mixed comparison of interventions based on network meta-analysis. *Methods*: A systematic review and network meta-analysis of studies identified by searching PubMed, Embase, Medline, Ovid, and CINAHL. All the included studies should have characteristics that: (1) participants with TMDs of any age; (2) non-surgical treatments; (3) score of Visual Analog Scale (VAS) as the outcome measure; (4) randomized controlled trials. The Cochrane Bias Assessment Toll was used to assess the bias, the CINeMA website was applied to rate the confidence of evidence, and ADDIS software was used to conduct the network meta-analysis. *Results*: 46 studies were included in this review. The agreement between authors reached a kappa value of 0.78. The results of the network meta-analysis showed that wearable therapy devices are more likely to be the best choice for reducing the pain of patients with myogenic TMDs, whereas a combination of platelet-rich plasma injection and wearable therapy devices is more likely to be the best choice for reducing the pain in a long term after treatment for patients with mix-type TMDs. Moreover, the application of therapy equipment has the most potential in reducing pain in a long term after treatment for patients with articular TMDs. *Discussion*: Wearable devices have a great potential for pain syndrome caused by TMDs, the mechanism might come from a biomechanical perspective. However, the overall confidence rating of evidence is low. Studies with high quality are still needed in the future. *Other:* The PROSPERO Registration Number of this systematic review is CRD42021253442.

**Keywords:** TMDs; temporomandibular; TMJ; network meta-analysis; systematic review

## 1. Introduction

Temporomandibular disorders (TMDs) are commonly encountered and have been classified in several different ways [1]. Previously, TMDs are attributed solely to alterations in dental occlusion that affected maxillomandibular position and function. However, although there is a structural component to TMDs, there are also multiple contributing and comorbid factors, including biological, behavioral, environmental, and cognitive, which could contribute to the development of TMDs [2, 3]. Symptoms of TMDs are characterized by acute or chronic pain and may include pain and dysfunction of the temporomandibular joint (TMJ), headache, and earache. The anatomic source of the pain could originate from the joint itself or the muscles of mastication. In a retrospective study including over 4523 patients with TMDs, the most common presenting signs and symptoms were pain (96%) [4]. The pain syndrome includes facial pain [4], ear pain [5], frontal-temporal-occipital headache [6-12], neck pain [13-15], orbital pain [16-18], and pain in the shoulders and upper back [18]. The acute or chronic pain caused by TMDs would eventually make patients over-reacted in response and develop an avoidance of behaviors [19]. Therefore, pain syndrome and its history provide important diagnostic information for TMDs, while a better effect on relief pain is one of the treatment goals of TMDs and the main sources of patient satisfaction.

There is, however, a lack of high-quality data evaluating the overall efficacy of the treatments for pain syndrome caused by TMDs with a methodologic limitation [5, 20-29]. Current clinical guidelines recommend the use of a combination of non-pharmacological and pharmacological therapies, which sometimes could include bio-behavioral therapies, muscle splint fixations, and intraarticular injections [30, 31]. For patients, who have structural anatomic pathology on imaging and persistent jaw locking severe enough to interfere with activities of daily living despite three to six months of nonsurgical management, it would be suggested to have surgical treatment[31-36].

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Non-surgical treatments are usually chosen at first and are commonly preferred in managing pain syndrome caused by TMDs. There are many non-surgical treatments with potential effects such as trigger point muscle injections, botulinum toxin injections, intraarticular injections [37, 38], and alternative and complementary therapies which include herbal medicine, acupuncture, moxibustion, dry needling, and manipulative therapy [39, 40]. In clinical practice, a great deal of information about non-surgical treatment has already been accumulated. For example, therapy equipment such as ultrasound [41], low-level laser [42], and transcutaneous electrical nerve stimulation [43]. In addition, manual therapy [44] and physical exercises [45] are increasingly being used to manage this condition due to their favorable effects [46-48] and claiming that they could improve function by restoring the quantity and the quality of mandibular movements and reducing pain used alone or as an adjunct treatment. Evidence suggests that manual therapy is a proper treatment for pain syndrome caused by TMDs and a mixed therapy involving manual therapy techniques as well as exercises improves patient outcomes[49]. Physical exercise is widely utilized for pain syndrome caused by TMDs, although the potential mechanisms of action are not fully clear. Physical exercise is prescribed to improve craniomandibular function and improve muscular coordination, relax tense muscles, increase range of motion, and increase muscular strength [45, 50, 51]. Although the evidence supporting the use of manual therapy and therapeutic exercise for pain syndrome caused by TMDs has been historically limited, in the last few years, several systematic reviews in the area have been published. All of the systematic reviews published [44, 52, 53] provide further evidence in support of postural exercises and active and passive oral exercises in reducing pain and improving mouth opening in people with pain syndrome caused by TMDs. At the same time, evidence strongly advocates the use of acupuncture for headaches. This may be related to differences in technique, clinical reasoning, patient populations, diagnostic criteria, and the training received by the clinician applying the technique, among other reasons. An interesting meta-analysis found evidence suggesting that acupuncture applied by physical therapists was superior to no treatment or sham treatment, but was as equally effective as other physical therapy treatments for short- and mid-term follow-ups for functional outcomes in patients with musculoskeletal pain [54]. Several studies have demonstrated that real acupuncture of the masticatory muscles was more effective than medication or sham needling in patients with pain syndrome caused by TMDs [55-57] or bruxism-related pain [58]. Moreover, the orofacial region is the area where more studies are comparing the effectiveness of acupuncture versus other injection therapies. For example, two studies reported no significant differences between botulinum toxin injections, lidocaine injections, and acupuncture in patients with headaches and orofacial pain [59, 60]. Another study observed no significant differences between injections with saline or anesthetic and acupuncture in individuals with temporalis muscle pain [61]. A meta-analysis found no significant differences between acupuncture and lidocaine injection at short and mid-term follow-up periods confirming that the therapeutic effect is related to the needle and not to any substance [62].

The controversy that occurs in clinical trials could be found in a higher level of evidence. For example, in 2019, a network meta-analysis reported that complementary therapy seemed to be slightly more effective than remaining treatment modalities for pain reduction in TMDs patients with masticatory muscle pain. However, this network meta-analysis only compared 19 different therapies by further categorizing them into 9 treatment modalities [63]. Moreover, in 2020, a network meta-analysis of 48 randomized controlled trials was performed to assess the effectiveness of various types of occlusal splints in the management of pain syndrome caused by TMDs, finding that there was moderate to very low-quality evidence confirming the effectiveness of occlusal splint therapy in the treatment of pain syndrome caused by TMDs [64]. In the same year, another network meta-analysis compared the treatment outcome of dry needling, acupuncture, or wet needling using local anesthesia, botulinum toxin-A, granisetron, platelet-rich plasma, passive placebo versus real active placebo in patients with TMDs, demonstrated that the effectiveness of needling therapy did not depend on needling type (dry or wet) or needling substance, and local anesthesia, botulinum toxin-A, granisetron, platelet-rich plasma holds some promise as injection therapies. Considering the controversy within existing evidence, it is necessary to make a new systematic review to update the existing evidence for pain management in the treatment of TMDs.

To sum up, at present, it is still unclear which non-surgical intervention is the best choice in dealing with the pain caused by TMDs due to the low level of evidence and the limited number of interventions in each comparison [64]. The purpose of this systematic review is to identify the most potential treatment protocol for dealing with pain caused by TMDs through a mixed comparison of interventions based on a network meta-analysis.

## 2. Method

### 2.1. Eligibility Criteria

#### 2.1.1. Participants

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This systematic review included studies with participants: (1) reported pain symptoms caused by TMDs; (2) more than 18 years old. The diagnostic criteria of the TMDs were according to Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) [65].

According to the guidelines of the RDC/TMD, the diagnoses could be divided into Group I (Muscle diagnoses), Group II (Disc displacements), and Group III (Arthralgia, arthritis, arthrosis), all participants would be reclassified into 6 subgroups according to the types of TMDs, which were caused by muscle disorders (Group I in RDC/TMD), articular disorders (at least one diagnosis from Group II or one diagnosis from Group III in RDC/TMD) or mixed mechanism, and the duration of their pain syndrome, which were acute (duration < 1 month) or chronic (duration > 1 month).

Therefore, the subgroups of participants were: (1) Chronic pain & articular TMDs; (2) Acute pain & articular TMDs; (3) Chronic pain & Myogenic TMDs; (4) Acute pain & Myogenic TMDs; (5) Chronic pain & mix-type TMDs; (6) Acute pain & mix-type TMDs.

#### 2.1.2. Interventions

All studies whose interventions were non-surgical treatments would be included in this review. Each non-surgical treatment was further categorized according to its characteristics. The categories were: (1) Acupuncture, such as dry needling and Traditional Chinese acupuncture; (2) Patient education, such as counseling and home-based education; (3) Physical exercise, such as global posture reeducation, masticatory muscle exercise, and relaxation exercise; (4) Manual therapy, such as upper thoracic manipulation and diacutaneous fibrolysis therapy; (5) Wearable devices, such as temporary implantation devices and splints; (6) Oral drugs; (7) External-use drugs; (8) Therapy equipment, such as phototherapy, laser therapy, vibratory therapy, ultrasound, and anterior repositioning appliance ; (9) Injection; (10) Placebo treatment. If combination therapy is used, a plus sign was used to link the different categories of treatment.

It was important to emphasize that the "Wearable device" was a purely physical intervention, by which the biomechanical mechanism of TMJ could be optimized by a continuous outside force. Nevertheless, "Therapy equipment" induced an internal mechanism from both physical and biochemistry perspectives that could stimulate the TMJ change positively or change the threshold of the TMD patient's proprioception.

#### 2.1.3. Comparators

The eligibility criteria of the comparators were the same as the interventions. Network meta-analysis was particularly flexible for fitting complex models including multi-arm trials and provided credible intervals and rank probabilities for comparing the overall effectiveness of treatments based on the Bayesian approach. All the treatments were ranked by their estimated effect sizes, and then, across all samples, averages for the first rank, second rank, and so on. These estimated probabilities were plotted against the ranks. Therefore, network meta-analysis was feasible to make mixed and indirect intervention comparisons [66].

#### 2.1.4. Outcomes

The score of the Visual Analog Scale (VAS) was chosen as the outcome measure of this systematic review to make the inclusion more comprehensive. All the outcomes were input into two different analyses, one of which was the change in the VAS score more than 48 hours after treatment, and the other was the immediate change in the VAS score within 48 hours after treatment.

#### 2.1.5. Study design

Only studies of randomized controlled clinical trials were included in this systematic review.

### 2.2. Exclusion Criteria

Studies were excluded if: (1) not all the participants in the study meet the eligibility criteria, for example, studies whose participants were TMDs patients who had undergone surgery or younger than 18 years old; (2) the participants in the study were not diagnosed with TMDs according to RDC/TMD; (3) studies evaluated surgical treatments such as minimally invasive surgeries; (4) a published abstract or lack of original data of outcome measures in the eligibility criteria.

### 2.3. Information Sources

Based on the PROSPERO registration information, a comprehensive and reproducible search strategy would be performed on the following databases until May 2021. The studies must be peer-reviewed and published in English. The databases were PubMed, Embase, Medline, Ovid, and CINAHL. Reference lists of included studies were also

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searched. Grey literature was searched to identify potential studies. If data were insufficient, authors would be contacted and requested for missing data.

### 2.4. Search Strategy

The search terms used in each database were as follows: (1) in PubMed, the search string was "((temporomandibular OR TMD OR TMJ) [Title]) AND ((randomized) OR (randomised) [Title/Abstract]) AND ((VAS) OR (visual analog) [Abstract])"; (2) in Medline, CINAHL, and Ovid, the search string was "(TI temporomandibular OR TMD OR TMJ) AND (AB randomized OR randomised) AND (AB VAS or visual analog)"; (3) in Embase, the search string was "temporomandibular OR TMD OR TMJ". The search process was conducted by two independent authors, and a third independent librarian was invited to support the search strategies, checking other synonyms and entry terms to increase their sensitivity and specificity.

### 2.5. Selection process

All potential studies were imported into EndNote X9 (Thomson Reuters, Carlsbad, California, USA) after removing duplicates. Title, abstract, and full-text screening were made by two independent authors. Any disagreement was resolved by a third independent reviewer.

### 2.6. Data Collection Process

Data were extracted by two independent authors. An independent reviewer was invited to check all the collected data.

### 2.7. Data Items

The following information was collected and recorded. (1) Characteristics of participants, such as mean age, gender ratio, type of TMDs, and duration of pain syndrome; (2) Information about intervention programs, such as names of interventions, details of programs, and the categories they could be reclassified; (3) Data would be used in network meta-analyses, such as sample size of every group, endpoints, and the mean value of VAS score with its standard deviation in each record point. All the data was provided in the Supplementary file.

### 2.8. Study risk of bias assessment.

The Cochrane Collaboration Risk of Bias Assessment Tool was used to evaluate the risk of bias in individual studies [67]. All the included studies were assessed by two independent authors. Any disagreement would be discussed, and an independent arbitrator was invited when an agreement could not be met. Agreement between authors was determined by Cohen's Kappa value. Another independent author was asked to check all the items in the evaluation after the whole bias assessment was finished.

### 2.9. Effect Measures

The randomized effect model was used to measure the pooled effects. The effect would be presented in the form of mean differences and their standard deviation (MD ± SD). Since the VAS scores could be presented in two units which are micrometers (mm) or centimeters (cm), all the outcomes would be transferred into the unit of micrometers. It should be emphasized that, if a study reported the VAS scores from more than one perspective, the average score and its standard deviation were calculated by the following formula.

$$\boldsymbol{Mean} = \frac{\sum_{i=1}^{n} \boldsymbol{M_i}}{\boldsymbol{n}}$$

$$\boldsymbol{Standard\ Deviation} = \sqrt{\sum_{i=1}^{n} \boldsymbol{S_i^2}}$$

### 2.10. Synthesis Methods

#### 2.10.1. Study Information Synthesis

All the data items collected were input in a table, as well as the main conclusion about the oxidative stress indicators provided by each included study. The original data of each outcome measure was provided in the Supplementary File.

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#### 2.10.2. Data pre-processing

Data pre-processing were made by two independent investigators. Microsoft Office Excel (Version 16.0, Microsoft Corporation, Redmond, WA, USA) was used to pre-process the original data.

#### 2.10.3. Data synthesis

The network meta-analysis was conducted by the Aggregate Data Drug Information System (ADDIS V1.16.8, http://drugis.org/software/addis/index). A geometry of intervention comparisons was applied to show the evidence structure.

The network geometries provided key information about the strength of evidence and displayed the number and form of interventions by the Bayesian simulation modeling. Every node in the network geometry represented one intervention, the lines referred to a direct comparison between each pair of interventions, while the number of comparison arms was represented by the number on each line [66].

The consistency of the evidence structure was identified at first since the network meta-analysis was based on the homogeneity, similarity, and consistency hypothesis[68]. If there were closed loops in the evidence structure, the evidence structure was more complex, and the network meta-analysis was called a mixed intervention comparison, and inconsistency occurred.

There were two approaches to identifying the inconsistency. On one hand, the random-effects standard deviations were calculated under both consistency and inconsistency models to identify if there was inconsistency within interventions. If the random-effects standard deviations under the two models were identical, it meant that there w a good consistency with the interventions. On the other hand, the P-values calculated in the analysis of the node splitting were checked to determine which model could be used. The node-splitting analysis is an alternative method to assess inconsistency in network meta-analysis. It assessed whether direct and indirect evidence on a split node was in agreement. The node-splitting analysis was performed within a Bayesian framework and was computationally more intensive than other approaches. Whether the identified discrepancy was statistically significant was determined by examining the calculating of respective Bayesian P-values. If the P-value of all the direct and indirect evidence comparisons were larger than 0.05, the consistency model could be used to conduct the network meta-analysis[69].

If there was no relevant inconsistency, a consistency model was used to conclude the relative effect of the included interventions[70], and the network meta-analysis was called an adjusted indirect intervention comparison. Under the consistency model, the results were shown in the rank probability plot [71].

The ranking of measures and probability was made to facilitate simultaneous inference regarding interventions. The ranking of treatments was made according to the probability of each intervention being the most effective or the least effective with the overall sum of the percentage in each row or column being 1.00 (100%).

### 2.11. Reporting bias assessment

According to The Cochrane Collaboration Risk of Bias Assessment Tool, if the included study had a pre-registered protocol number and all the outcomes in the proto-col were fully matched with those reported in the article, this study was regarded to have a low risk of selective reporting. Meanwhile, if the included study had a pre-registered protocol number but the outcomes reported in the article were not fully matched with those registered in the protocol, this study was regarded to have a high risk of selective reporting. At last, if the included study didn't have a pre-registered protocol number, this study was regarded to have an unclear risk of selective reporting. The results of the bias assessment were provided in the risk of bias assessment results

### 2.12. Certainty Assessment

A mixed comparison of treatments was applied to assess the certainty of the evidence for each subgroup of participants. According to the principle of mixed comparison of treatments, the network meta-analysis only included the evidence structure with one or more closed loops. Evidence structures without any closed loop were excluded.

The Confidence in Network Meta-Analysis (CINeMA https://cinema.ispm.unibe.ch) was used to evaluate the confidence and assess the reporting bias in the findings from the network meta-analysis [72, 73]. According to the method research of CINeMA[73], if the item "within-study bias" was "Major concern", the confidence should be downgraded by one level, whereas if other items were "Some concern", the confidence would be downgraded by one level and if they were "Major concern", the confidence would be downgraded by two levels.

## 3. Results

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### 3.1. Study selection

The search yielded 2563 titles and abstracts for screening. After removing 544 duplicated studies, 2019 studies were included in the records screening. Since only randomized controlled trials (RCTs) would be included in this systematic review, 1842 studies that were not RCTs were excluded, and 177 studies were included for full-text article assessment for eligibility. Among the 177 studies, there were 32 studies excluded because of lack of data, 28 studies were excluded due to their ineligible design, 20 study was excluded because of their ineligible interventions, and 51 study was excluded because of their ineligible participants. Eventually, 46 studies were included in the final analysis. The flow diagram was presented in Figure 1.

### 3.2. Study characteristics

According to the results of study selection, all included studies recruited patients with chronic pain caused by TMDs. 8 studies reported the pre-48-hour effect of non-surgical interventions on pain caused by TMDs, and 2 of the 8 studies recruited patients with chronic pain caused by articular TMDs, while 2 studies recruited patients with pain caused by mix-type TMDs, other 6 studies recruited patients with pain caused by myogenic TMDs. At the same time, 31 studies reported the post-48-hour effect of non-surgical interventions on pain caused by TMDs and 8 studies reported both the post- and pre-48 hours effect of non-surgical interventions on pain caused by TMDs. All included studies reported the long effects. 9 of the 8 studies recruited patients with chronic pain caused by articular TMDs, while 10 studies recruited patients with pain caused by mix-type TMDs, and the other 20 studies recruited patients with pain caused by myogenic TMDs. Detailed information on all included studies was provided in Supplementary S1.

### 3.3. Results of individual studies

The result of the risk of bias assessment is shown in Figure 2. After discussion, a consensus was obtained for all items. Overall results were shown in Figure 2a, and the overall bias could be seen in Figure 2b.

### 3.3. Results of syntheses

The network plots of the interventions in the network meta-analysis were presented in Figure 3. The network plots corresponding to the uploaded dataset were automatically drawn with equally sized nodes and edges. The node size was weighted according to the sample size of each intervention, while the edge width was weighted according to the study number of each direct comparison. Nodes were colored according to the proportion of studies with low (green), moderate (yellow), and high (red) risk of bias (RoB), and the edges were colored according to the average RoB of the included studies in each comparison.

The results of the consistency and inconsistency analysis with their numbers of iterations were provided in Table 1, while Table 2 and Figure 4 showed the ranking of treatments based on the probability of each intervention being the most effective or the least effective.

#### 3.3.1. Pre-48-hour Effect

The evidence structure of the pre-48-hour effect on patients with chronic pain caused by myogenic TMDs was presented in Figure 3(a). According to the network plot, there were 7 interventions in this mixed comparison. Unless the direct comparison between “TE” and “Placebo” had 2 arms, other direct comparisons had 1 arm.

According to Table 1, the random effects standard deviations of the consistency model and its 95% confidence intervals were 10.82(1.98, 16.69), while those of the inconsistency model was 10.67(1.72, 16.70). Since the random effect standard deviations of the consistency model and that of the inconsistency model were almost equal. It meant that the analysis under the consistency model had good validity.

The results in Table 2 showed that “WD” had the most probability to become the best choice in reducing the chronic pain caused by myogenic TMDs within 48 hours after treatment (0.45 in Rank 7), whereas “E” had the least probability (0.45 in Rank 1).

#### 3.3.2. Post-48-hour Effect

The evidence structures of the post-48-hour effect on chronic pain caused by mix-type TMDs, articular TMDs, and myogenic TMDs were presented in Figure 3(b), Figure 3(c), and Figure 3(d). According to these network plots, there were 11, 10, and 12 interventions in the mixed comparisons. There were 4 arms in the direct comparison between “OD” and “Placebo” in the evidence structure of chronic pain caused by articular TMDs, and there were 3, 3, and 4 arms in the direct comparisons between “OD”, “TE”, “TE” and “Placebo” in the evidence structure of chronic pain caused by myogenic TMDs. Other direct comparisons in these evidence structures had only 1 arm.

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According to Table 1, in the mixed treatments comparisons of the post-48-hour effect on chronic pain with mixed and articular TMDs, the random effects standard deviations of the consistency model and its 95% confidence intervals were 20.87 (2.27, 39.97) and 11.41 (0.81, 46.41), while those of the inconsistency model was 19.48 (2.18, 39.95) and 10.41 (0.42, 47.39). Since the random-effect standard deviations of the consistency model and that of the inconsistency model in each evidence structure were almost equal. It means that the analysis under the consistency model in each mixed comparison had good validity.

The results in Table 2 showed that, for patients with chronic pain caused by mix-type TMDs, "Platelet-rich plasma I + WD" had the most probability to become the best choice in reducing the chronic pain caused by mix-type TMDs after 48 hours after treatment (0.43 in Rank 11), whereas "EDU" had the least probability to become the best option (0.36 in Rank 1). At the same time, "TE" had the most probability to become the best choice in reducing the chronic pain caused by articular TMDs after 48 hours after treatment (0.58 in Rank 1), whereas "A" had the least probability to become the best option (0.35 in Rank 1).

When it came to chronic pain caused by myogenic TMDs, in the mixed treatments comparisons of the post-48-hour effect, the random effects standard deviations of the consistency model and its 95% confidence intervals were 7.56(0.40, 19.27), while those of the inconsistency model was 6.98 (1.60, 18.77). Since there were closed loops in the evidence structure, the P-values in Node-splitting analysis were taken into consideration. According to the results of node-splitting, the P-values of all comparisons were larger than 0.05, which means that the analysis under the consistency model in each mixed comparison had good validity.

The results in Table 2 showed that, for patients with chronic pain caused by myogenic TMDs, "WD" had the most probability to become the best choice in reducing the chronic pain caused by mix-type TMDs after 48 hours after treatment (0.63 in Rank 12), whereas "MT" had the least probability to become the best option (0.68 in Rank 1).

### 3.4. Confidence Assessment

Table 3 provided partial results of the confidence assessment made by CINeMA, in which only the evidence structures whose confidence ratings were moderate or high were provided. According to Table 3, the mixed comparison between manual therapy and placebo, the indirect comparison between manual therapy and therapy equipment application in pre-48 hours effect for patients with chronic pain caused by myogenic TMDs, and the mixed comparisons of external-used drugs and placebo as well as therapy equipment application and placebo in the post-48-hour effect for patients with chronic pain caused by myogenic TMDs had high confidence ratings.

The whole results of confidence assessments of each evidence structure were provided in Supplementary S2.

## 4. Discussion

The purpose of this systematic review is to identify the most potential treatment protocol in dealing with pain caused by TMDs through a mixed comparison of interventions based on a network meta-analysis. According to the results of the network meta-analysis, the main findings of the review are as follows.

First, for patients with chronic pain caused by myogenic TMDs, the application of wearable devices has the most probability to become the best choice in reducing the chronic pain caused by mix-type TMDs after treatment (45% in 48 hours post-treatment and 0.63% after 48 hours post-treatment). The wearable devices applied in this review include splints and implantation devices. Previous studies have demonstrated that treating patients with occlusal splints could increase cervical spine range of motion and decrease cervical spine pain in patients with TMDs [74]. Moreover, other previous studies reported superior outcomes for patients with cervicogenic headache, who also exhibited TMJ impairments, if they received manual therapy directed to both the cervical spine and TMJ compared to the cervical spine alone [46, 75]. The studies with similar outcomes, diagnoses, and comparing a physical exercise program with other treatments such as education [76, 77] or splints therapy were pooled and the result showed that there was a trend to favor exercise therapy on pain-free maximum opening and pain intensity when compared with a control group, considered clinically relevant favoring the exercise group [78-80]. For pain intensity, the effect size was moderate and there is no significant difference was found in the pain-free maximum opening when performing sensitivity analysis in exercise therapy versus education [81, 82]; however, when comparing exercises versus splint therapy, a statistically and clinically meaningful difference was found between the groups favoring exercises [79, 83]. One study investigated the effectiveness of manual therapy alone versus splint, or manual therapy when combined with splint versus splint alone or manual therapy alone in subjects with TMDs on masticatory EMG signal. The results showed that the manual therapy and splint alone did not change the EMG signal of the masseter or anterior temporal muscles significantly. However, the combination of manual therapy and splint therapy led to a reduction in the intensity of signs and symptoms in patients with severe TMDs and sleep bruxism [81]. When comes to implantation devices, which are characterized by

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the temporary implantation of epidermal devices in trigger points in the neck or back, with no anesthesia [82, 84-86]. Persistent physical stimulation of dermal nerve endings related to the dermatomes involved in each patient elicits the sustained release of enkephalins, leading to the deactivation of neurons involved in pain, muscle dysfunction, and neurogenic inflammation [87]. Structures in the thalamus and brainstem activated by stimuli applied far from the painful zone are also capable of triggering similar effects [88-90]. According to the evidence mentioned above, it could be assumed that implantation would work through a neural mechanism [82, 84-87].

Second, a combination of platelet-rich plasma injection and wearable therapy devices is more likely to be the best choice for reducing pain in a long term after treatment for patients with mix-type TMDs. The potential action mechanism of platelet-rich plasma injection is that tissue injury would also lead to the release of substances, which include prostaglandins, neurotransmitters, and cytokines that activate the endings of nociceptors resulting in action potential discharge, any of these same fibers also exhibit robust responses to injection of one or more algogenic substances into the muscle or joint tissue, which suggests that they function as polymodal nociceptors [91]. However, according to the results of the confidence assessment conducted by CINeMA, the confidence rating of the evidence related to the platelet-rich plasma injection is from “Low” to “Very Low”. The reason might be that there is still a lack of studies with high quality identifying the effect of platelet-rich plasma injection.

Another discrete injection protocol uses nerve growth factor (NGF), which would be released upon tissue injury, into the masseter muscle. This protocol could produce a punctate region of muscle mechanical sensitization that is confined to the injection site in the absence of gross tissue inflammation. Injection of NGF produces rapid sensitization of muscle nociceptors to mechanical stimulation that is mediated through activation of the tropomyosin receptor kinase A (TrkA) receptor, which is a neurotrophin receptor that selectively binds NGF. NGF could induce a phenotypic change in non-nociceptive afferent fibers that innervate the muscles to make them begin to exhibit properties of nociceptors [92]. Afterward, human subjects injected with NGF report a discrete area of muscle tenderness at the site of injection that does not spread, and is only painful upon palpation or occasionally when opening the jaw. This sensitization lasts several weeks after a single injection and is greater in women than in men [93]. Therefore, this protocol might be valuable for studying localized tender areas in the masticatory muscles, which are a consistent feature of myofascial TMDs.

The last main finding of this systematic review is that application of therapy equipment has the most potential in reducing pain in a long term after treatment for patients with articular TMDs. The value and therapeutic potential of comprehensive interventions have been demonstrated in other clinical research. For example, a previous study found that a combination of TE and neuroscience education programs is more effective than the neuroscience education program alone for improving pain, related disability, and kinesiophobia in patients with mechanical low back pain [55]. Another systematic review and meta-analysis concluded that multi-model therapies including TE might be more effective in reducing kinesiophobia than uni-modal therapy from the only physical or psychological perspective [19]. These results were also supported by another systematic review and meta-analysis, whose result claimed that moderate evidence supports the effectiveness of TE for low back pain. [94]. The effectiveness of a multi-disciplinary manual therapy program including TE for TMDs has been also proposed [95, 96] in other systematic reviews.

Although it might be encouraging that the results of this network meta-analysis have been supported by a lot of evidence, one limitation of this review is that it is impossible to eliminate publication bias and heterogeneity between studies, because, first, it could not be guaranteed that all intervention protocols in the included studies have similar quantity and quality. For example, there are so few interventions that from a psychological perspective included in this review that the weight allocation of each intervention in the network meta-analysis would be affected. Second, this review only included studies published in English, which will induce extra publication bias. Last but not the least, the included studies in this review reported results with different intervals of pain evaluation. Those studies induced the heterogeneity of interval of time to evaluate the pain scale, making the confidence rating lower than estimated.

Another limitation of this systematic review is that although systematic reviews are considered to be the highest form of evidence for the development of clinical decisions, individual randomized clinical trials (RCTs) provide evidence that has a lower level of confidence for its general applicability [97]. Designing effective RCTs and implementing them is challenging, and consequently, the clinician is often working without adequate evidence for making clinical decisions about which treatment(s) to provide to a given patient. A systematic review of 30 systematic reviews regarding treatments for pain syndrome caused by TMDs indicates that most patients with TMDs pain without behavioral or psychological involvement, benefit from simple treatments, whereas those patients with TMDs pain and major behavioral or psychological disturbances require a combined therapeutic approach. The combined approach is, of course, where the clinical decision-making is difficult, in that RCTs generally focus on only one treatment, not combinations of treatments, and for a given patient population that may or may not represent all the patients.

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Consequently, RCTs often provide little assistance to the clinician, and systematic reviews provide insight into general patterns of treatments.

Last but not the least, based on the PROSPERO registration timing of this systematic review, the literature search was updated only until May 2021, therefore, it cannot be ignored that other high-quality RCTs of non-surgical interventions for TMDs were published during the writing and review period of this review, thereby increasing the publication bias and underlying heterogeneities of this review.

Even within these limitations, currently available information could show that assigning a given patient to a basic framework – for example, with versus without behavioral or psychological involvement, and acute versus chronic pain – could help clinicians better understand how to begin to tailor treatments. Moreover, to understand that treatments with consistently negative outcomes are to be avoided in favor of more useful and evidence-based models regarding what kind of treatment will be more likely to be helpful.

## 5. Other Information

### 5.1. Registration and protocol

This review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA 2020) [98]. Literature screening criteria and study search strategy were proposed and agreed upon by two independent authors. The PROSPERO Registration Number of this systematic review and network meta-analysis was CRD42021253442.

### 5.2. Support

This review was supported by

### 5.3. Competing interests

The authors declare no competing interests.

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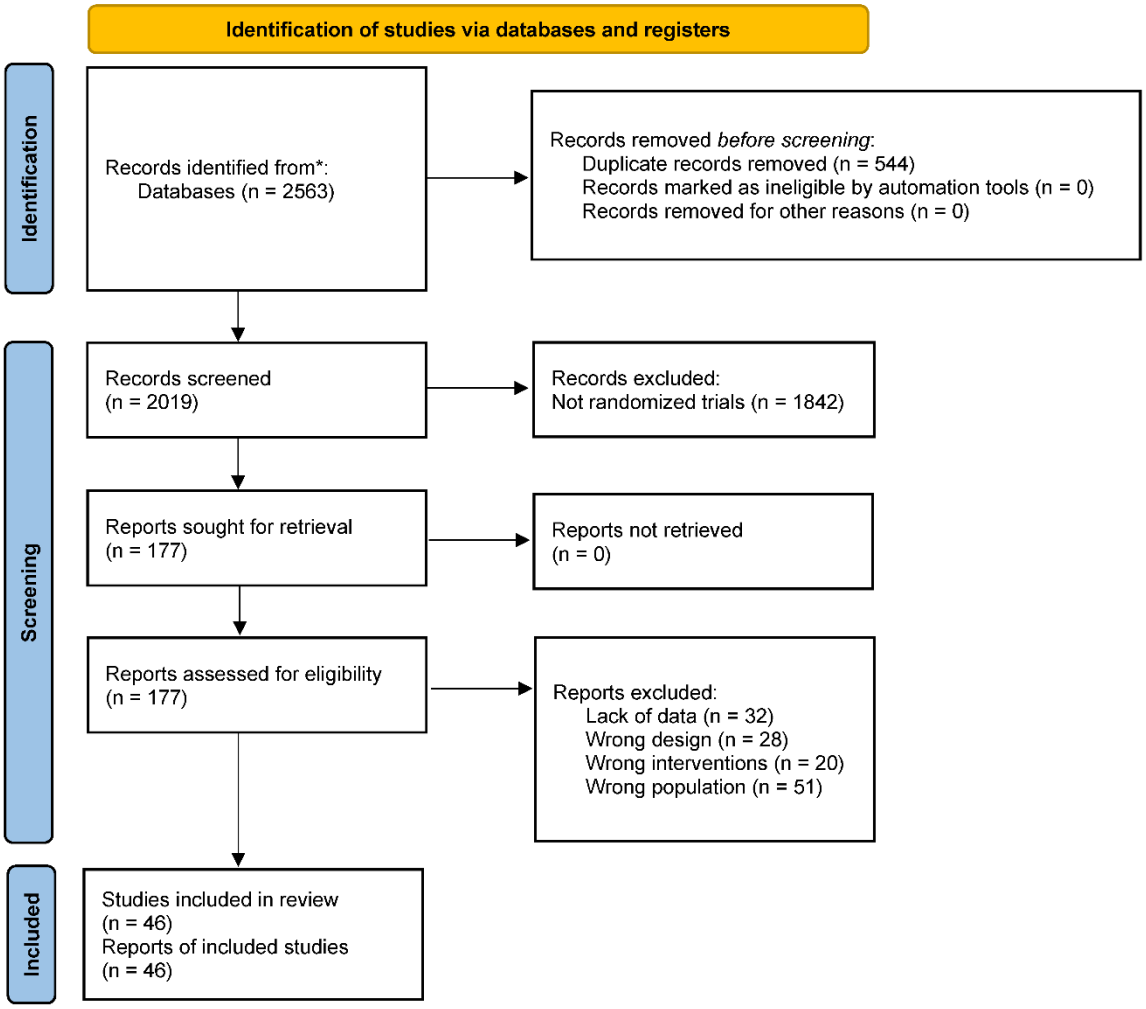


**Figure 1.** The PRISMA 2020 flow diagram of search and study selection.

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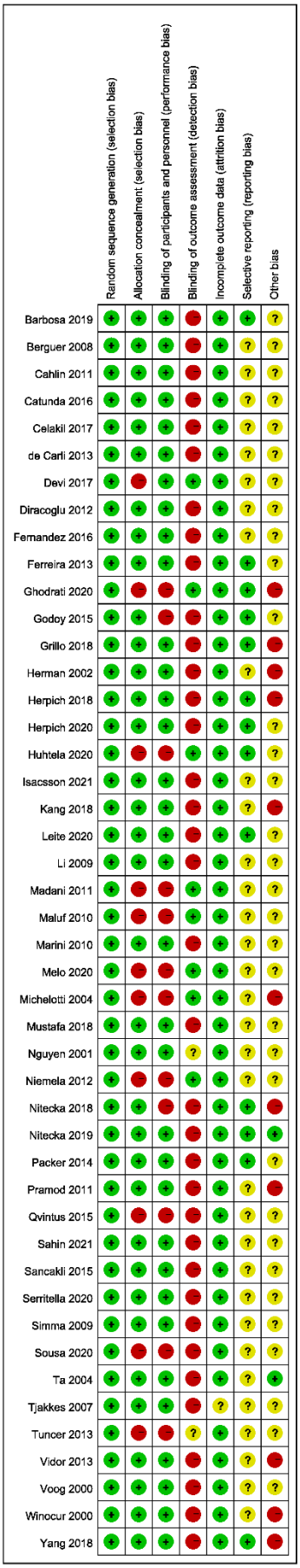


**(a)**

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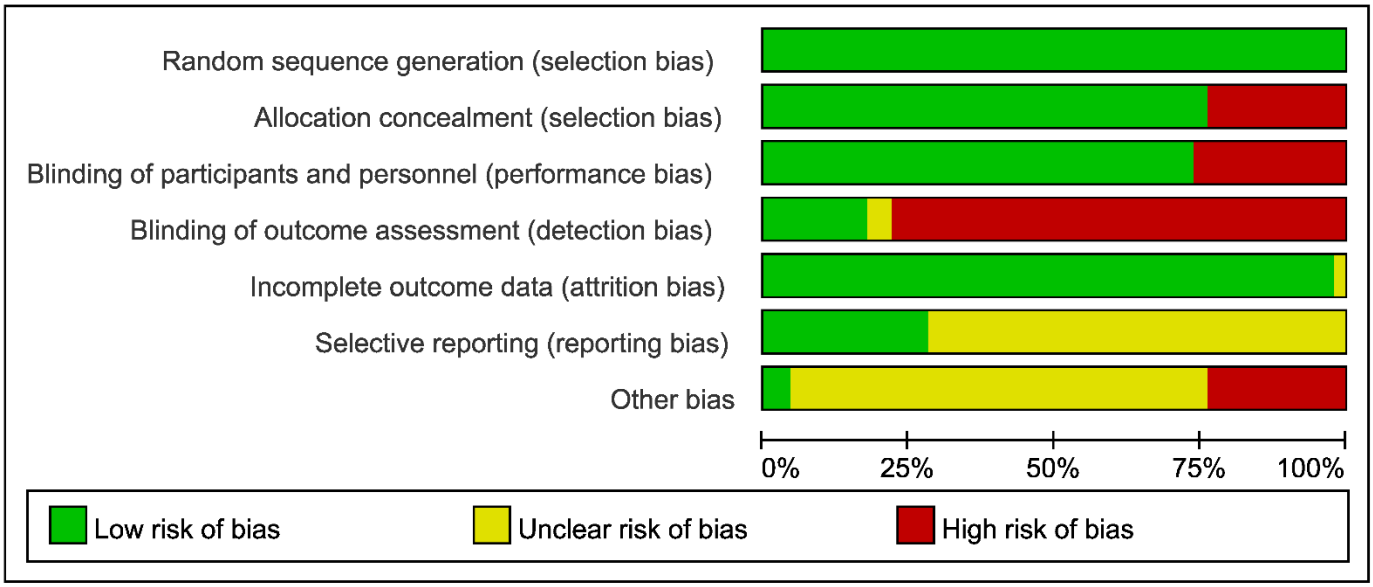


**(b)**

**Figure 2.** The result of the risk of bias assessment. (**a**) Risk of bias summary; (**b**) Risk of bias graph.

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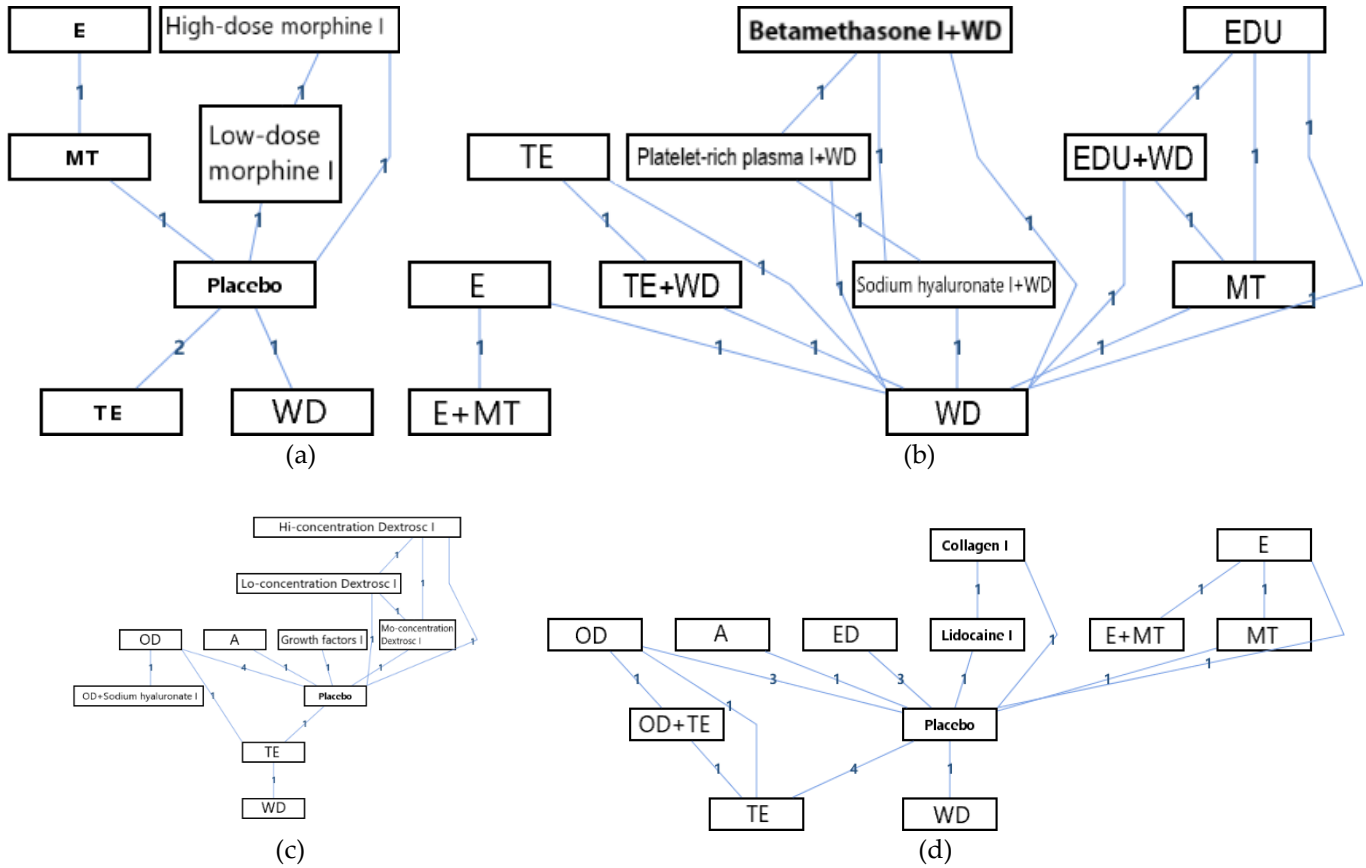


**Figure 3.** The network plots of the interventions in network meta-analysis. (a) Effect in 48 hours for chronic pain caused by myogenic TMDs; (b) Effect after 48 hours for chronic pain caused by mix-type TMDs; (c) Effect after 48 hours for chronic pain caused by articular TMDs; (d) Effect after 48 hours for chronic pain caused by myogenic TMDs. (MT: manual therapy; TE: therapy equipment; I: injection; ED: external-used drugs; OD: oral drugs; E: exercise; WD: wearable devices; N: no concern; S: some concern; M: major concern; A: acupuncture; EDU: patient education; Hi: high; Mo: moderate; Lo: low.)

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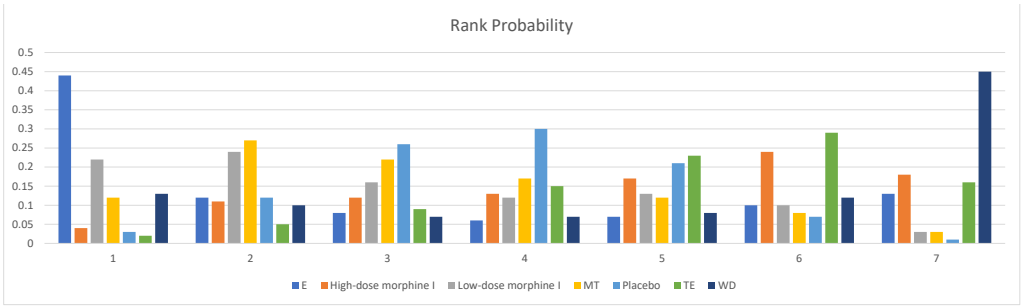
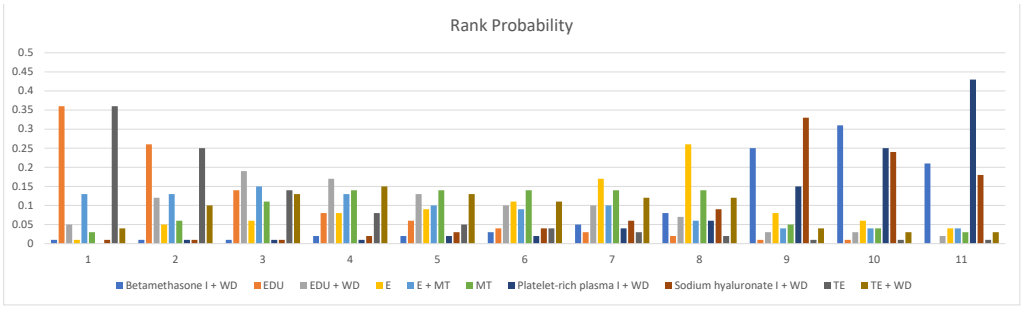



(a)

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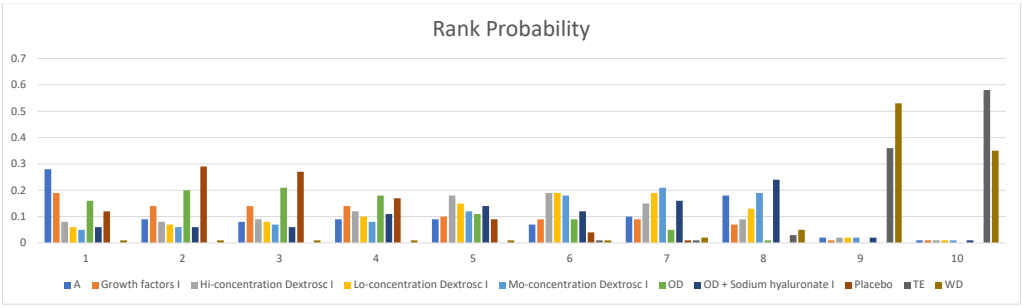
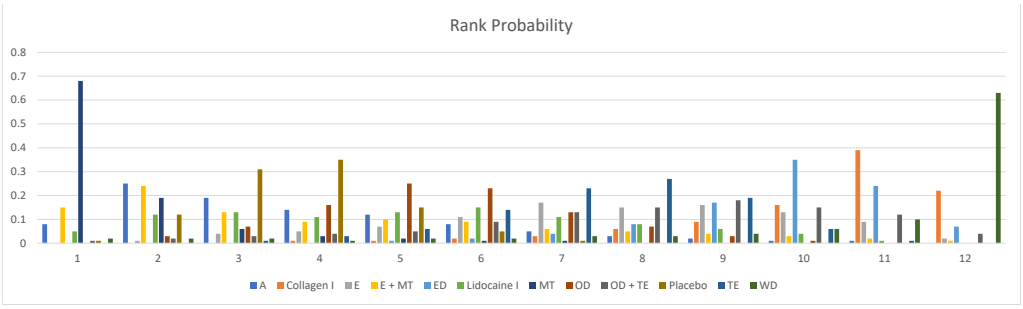



(c)




(d)

**Figure 4.** The rank probabilities of the interventions in network meta-analysis. (a) Effect in 48 hours for chronic pain caused by myogenic TMDs; (b) Effect after 48 hours for chronic pain caused by mix-type TMDs; (c) Effect after 48 hours for chronic pain caused by articular TMDs; (d) Effect after 48 hours for chronic pain caused by myogenic TMDs. (MT: manual therapy; TE: therapy equipment; I: injection; ED: external-used drugs; OD: oral drugs; E: exercise; WD: wearable devices; N: no concern; S: some concern; M: major concern; A: acupuncture; EDU: patient education; Hi: high; Mo: moderate; Lo: low.)

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**Table 1.** The results of the consistency and inconsistency analysis.

| Outcome | Populations | Interventions | Consistency Model | | Inconsistency Model | | Node-splitting | |
|---|---|---|---|---|---|---|---|---|
| | | | RESD | Iterations | RESD | Iterations | Comparisons | P-value |
| Effect in 48 hours | Chronic pain caused by myogenic TMDs | E, High-dose morphine I, Low-dose morphine I, MT, Placebo, TE, WD | 10.82(1.98, 16.69) | 50,000 | 10.67(1.72, 16.70) | 50,000 | | |
| Effect after 48 hours | Chronic pain caused by mix-type TMDs | Betamethasone I + WD; EDU; EDU + WD; E; E + MT; MT; Platelet-rich plasma I + WD; Sodium hyaluronate I + WD; TE; TE + WD; WD | 20.87 (2.27, 39.97) | 50,000 | 19.48 (2.18, 39.95) | 50,000 | | |
| | Chronic pain caused by articular TMDs | A; Growth factors I; Hi-concentration Dextrosc I; Lo-concentration Dextrosc I; Mo-concentration Dextrosc I; OD; OD + Sodium hyaluronate I; Placebo; TE; WD | 11.41 (0.81, 46.41) | 100,000 | 10.41 (0.42, 47.39) | 100,000 | | |
| | Chronic pain caused by myogenic TMDs | A; Collagen I; E; E + MT; ED; Lidocaine I; MT; OD; OD + TE; Placebo; TE; WD | 7.56(0.40, 19.27) | 100,000 | 6.98 (1.60, 18.77) | 100,000 | E, MT<br>E, Placebo<br>MT, Placebo<br>OD, Placebo<br>OD, TE<br>Placebo, TE | 0.21<br>0.18<br>0.19<br>0.18<br>0.18<br>0.16 |

RESD: Random-effects standard deviations, Mean (95% CI); MT: manual therapy; TE: therapy equipment; I: injection; ED: external-used drugs; OD: oral drugs; E: exercise; WD: wearable devices; N: no concern; S: some concern; M: major concern; A: acupuncture; EDU: patient education; Hi: high; Mo: moderate; Lo: low.

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Table 2. The rank probability rank of each mixed interventions comparison.

| Outcome | Population | Intervention | R1 | R2 | R3 | R4 | R5 | R6 | R7 | R8 | R9 | R10 | R11 | R12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Effect in 48 hours | Chronic pain caused by myogenic TMDs | E | 0.44 | 0.12 | 0.08 | 0.06 | 0.07 | 0.10 | 0.13 | | | | | |
| | | High-dose morphine I | 0.04 | 0.11 | 0.12 | 0.13 | 0.17 | 0.24 | 0.18 | | | | | |
| | | Low-dose morphine I | 0.22 | 0.24 | 0.16 | 0.12 | 0.13 | 0.10 | 0.03 | | | | | |
| | | MT | 0.12 | 0.27 | 0.22 | 0.17 | 0.12 | 0.08 | 0.03 | | | | | |
| | | Placebo | 0.03 | 0.12 | 0.26 | 0.30 | 0.21 | 0.07 | 0.01 | | | | | |
| | | TE | 0.02 | 0.05 | 0.09 | 0.15 | 0.23 | 0.29 | 0.16 | | | | | |
| | | WD | 0.13 | 0.10 | 0.07 | 0.07 | 0.08 | 0.12 | 0.45 | | | | | |
| Effect after 48 hours | Chronic pain caused by mix-type TMDs | Betamethasone I + WD | 0.01 | 0.01 | 0.01 | 0.02 | 0.02 | 0.03 | 0.05 | 0.08 | 0.25 | 0.31 | 0.21 | |
| | | EDU | 0.36 | 0.26 | 0.14 | 0.08 | 0.06 | 0.04 | 0.03 | 0.02 | 0.01 | 0.01 | 0.00 | |
| | | EDU + WD | 0.05 | 0.12 | 0.19 | 0.17 | 0.13 | 0.10 | 0.10 | 0.07 | 0.03 | 0.03 | 0.02 | |
| | | E | 0.01 | 0.05 | 0.06 | 0.08 | 0.09 | 0.11 | 0.17 | 0.26 | 0.08 | 0.06 | 0.04 | |
| | | E + MT | 0.13 | 0.13 | 0.15 | 0.13 | 0.10 | 0.09 | 0.10 | 0.06 | 0.04 | 0.04 | 0.04 | |
| | | MT | 0.03 | 0.06 | 0.11 | 0.14 | 0.14 | 0.14 | 0.14 | 0.14 | 0.05 | 0.04 | 0.03 | |
| | | Platelet-rich plasma I + WD | 0.00 | 0.01 | 0.01 | 0.01 | 0.02 | 0.02 | 0.04 | 0.06 | 0.15 | 0.25 | 0.43 | |
| | | Sodium hyaluronate I + WD | 0.01 | 0.01 | 0.01 | 0.02 | 0.03 | 0.04 | 0.06 | 0.09 | 0.33 | 0.24 | 0.18 | |
| | | TE | 0.36 | 0.25 | 0.14 | 0.08 | 0.05 | 0.04 | 0.03 | 0.02 | 0.01 | 0.01 | 0.01 | |
| | | TE + WD | 0.04 | 0.10 | 0.13 | 0.15 | 0.13 | 0.11 | 0.12 | 0.12 | 0.04 | 0.03 | 0.03 | |
| | | WD | 0.00 | 0.01 | 0.06 | 0.14 | 0.24 | 0.27 | 0.18 | 0.08 | 0.01 | 0.00 | 0.00 | |
| | Chronic pain caused by articular TMDs | A | 0.28 | 0.09 | 0.08 | 0.09 | 0.09 | 0.07 | 0.10 | 0.18 | 0.02 | 0.01 | | |
| | | Growth factors I | 0.19 | 0.14 | 0.14 | 0.14 | 0.10 | 0.09 | 0.09 | 0.07 | 0.01 | 0.01 | | |
| | | Hi-concentration Dextrosc I | 0.08 | 0.08 | 0.09 | 0.12 | 0.18 | 0.19 | 0.15 | 0.09 | 0.02 | 0.01 | | |
| | | Lo-concentration Dextrosc I | 0.06 | 0.07 | 0.08 | 0.10 | 0.15 | 0.19 | 0.19 | 0.13 | 0.02 | 0.01 | | |
| | | Mo-concentration Dextrosc I | 0.05 | 0.06 | 0.07 | 0.08 | 0.12 | 0.18 | 0.21 | 0.19 | 0.02 | 0.01 | | |
| | | OD | 0.16 | 0.20 | 0.21 | 0.18 | 0.11 | 0.09 | 0.05 | 0.01 | 0.00 | 0.00 | | |
| | | OD + Sodium hyaluronate I | 0.06 | 0.06 | 0.06 | 0.11 | 0.14 | 0.12 | 0.16 | 0.24 | 0.02 | 0.01 | | |

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| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Placebo** | 0.12 | 0.29 | 0.27 | 0.17 | 0.09 | 0.04 | 0.01 | 0.00 | 0.00 | 0.00 | | |
| | **TE** | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.03 | 0.36 | 0.58 | | |
| | **WD** | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.01 | 0.02 | 0.05 | 0.53 | 0.35 | | |
| **Chronic pain caused by myogenic TMDs** | **A** | 0.08 | 0.25 | 0.19 | 0.14 | 0.12 | 0.08 | 0.05 | 0.03 | 0.02 | 0.01 | 0.01 | 0.00 |
| | **Collagen I** | 0.00 | 0.00 | 0.00 | 0.01 | 0.01 | 0.02 | 0.03 | 0.06 | 0.09 | 0.16 | 0.39 | 0.22 |
| | **E** | 0.00 | 0.01 | 0.04 | 0.05 | 0.07 | 0.11 | 0.17 | 0.15 | 0.16 | 0.13 | 0.09 | 0.02 |
| | **E + MT** | 0.15 | 0.24 | 0.13 | 0.09 | 0.10 | 0.09 | 0.06 | 0.05 | 0.04 | 0.03 | 0.02 | 0.01 |
| | **ED** | 0.00 | 0.00 | 0.00 | 0.00 | 0.01 | 0.02 | 0.04 | 0.08 | 0.17 | 0.35 | 0.24 | 0.07 |
| | **Lidocaine I** | 0.05 | 0.12 | 0.13 | 0.11 | 0.13 | 0.15 | 0.11 | 0.08 | 0.06 | 0.04 | 0.01 | 0.00 |
| | **MT** | 0.68 | 0.19 | 0.06 | 0.03 | 0.02 | 0.01 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | **OD** | 0.00 | 0.03 | 0.07 | 0.16 | 0.25 | 0.23 | 0.13 | 0.07 | 0.03 | 0.01 | 0.00 | 0.00 |
| | **OD + TE** | 0.01 | 0.02 | 0.03 | 0.04 | 0.05 | 0.09 | 0.13 | 0.15 | 0.18 | 0.15 | 0.12 | 0.04 |
| | **Placebo** | 0.01 | 0.12 | 0.31 | 0.35 | 0.15 | 0.05 | 0.01 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| | **TE** | 0.00 | 0.00 | 0.01 | 0.03 | 0.06 | 0.14 | 0.23 | 0.27 | 0.19 | 0.06 | 0.01 | 0.00 |
| | **WD** | 0.02 | 0.02 | 0.02 | 0.01 | 0.02 | 0.02 | 0.03 | 0.03 | 0.04 | 0.06 | 0.10 | 0.63 |

R: rank; MT: manual therapy; TE: therapy equipment; I: injection; ED: external-used drugs; OD: oral drugs; E: exercise; WD: wearable devices; N: no concern; S: some concern; M: major concern; A: acupuncture; EDU: patient education; Hi: high; Mo: moderate; Lo: low.

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Table 3. The results of confidence assessment (only High and Moderate). 9

| Outcome | Population | Evidence Structure | Comparison | Number of studies | Within-study bias | Reporting bias | Indirectness | Imprecision | Heterogeneity | Incoherence | Confidence rating |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Effect in 48 hours | Chronic pain caused by myogenic TMDs | Mixed | MT: Placebo | 2 | S | N | N | N | N | N | High |
| | | | Placebo: TE | 12 | M | N | N | N | N | N | Moderate |
| | | Indirect | MT: TE | 0 | S | N | N | N | N | N | High |
| Effect after 48 hours | Chronic pain caused by myogenic TMDs | Mixed | Collagen I: Lidocaine I | 2 | M | N | N | N | N | N | Moderate |
| | | | Collagen I: Placebo | 2 | M | N | N | N | N | N | Moderate |
| | | | ED: Placebo | 6 | S | N | N | N | N | N | High |
| | | | Lidocaine I: Placebo | 2 | M | N | N | N | N | N | Moderate |
| | | | MT: Placebo | 1 | S | N | N | S | N | N | Moderate |
| | | | OD: Placebo | 17 | S | N | N | N | S | N | Moderate |
| | | | Placebo: TE | 6 | S | N | N | N | N | N | High |
| | | Indirect | ED: MT | 0 | S | S | N | N | N | N | Moderate |
| | | | ED: TE | 0 | S | S | N | N | N | N | Moderate |
| | | | Lidocaine I: TE +OD | 0 | S | S | N | N | N | N | Moderate |
| | | | MT: OD | 0 | S | S | N | N | N | N | Moderate |
| | | | MT:TE | 0 | S | S | N | N | N | N | Moderate |
| | | | MT: TE +OD | 0 | S | S | N | N | N | N | Moderate |
| | | | OD: Placebo | 0 | S | S | N | N | N | N | Moderate |
| | | | Placebo : TE + OD | 0 | S | S | N | N | N | N | Moderate |
| | Chronic pain caused by mix-type TMDs | Mixed | E: TE + E | 2 | M | N | N | N | N | N | Moderate |
| | | | E: WD | 1 | M | N | N | N | N | N | Moderate |
| | | | MT: WD | 1 | M | N | N | N | N | N | Moderate |

MT: manual therapy; TE: therapy equipment; I: injection; ED: external-used drugs; OD: oral drugs; E: exercise; WD: wearable devices; N: no concern; S: some concern; M: major concern. 10 11

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