CADTH

CADTH RAPID RESPONSE REPORT: SYSTEMATIC REVIEW

Interventions for Temporomandibular Joint Disorder: An Overview of Systematic Reviews

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	September 28, 2018
Report Length:	108 Pages

CADTH

Authors: Kendra Brett, Charlotte Wells, Alison Sinclair, Howard Tenenbaum, Bruce Freeman, Carolyn Spry

Cite As: *Interventions for Temporomandibular Joint Disorder: An Overview of Systematic Reviews*. Ottawa: CADTH; 2018 Sept. (CADTH rapid response report: overview of systematic reviews).

ISSN: 1922-8147 (online)

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Reviewers

External Reviewers

This document was externally reviewed by content experts and the following individuals granted permission to be cited.

Dr. Dawid Pieper, MPH, MSc (Epi)
Head of Department, Evidence-Based Health Services Research
Institute for Research in Operative Medicine
Faculty of Health, School of Medicine
Witten/Herdecke University
Cologne, Germany

Dr. Stacie Saunders, BSc, DDS
Dentist
TMD Therapeutics
Bedford, Nova Scotia

Authorship

Dr. Kendra Brett led the project protocol development; selected studies; extracted, tabulated, and analyzed data; wrote the report; and revised the report based on reviewers' comments.

Charlotte Wells contributed to article selection, study quality assessment, data extraction, tabulation of data, and drafting portions of the review.

Dr. Alison Sinclair contributed to the protocol development; and provided methods guidance, selected studies, extracted data, and provided comments on the report.

Dr. Howard Tenenbaum participated in the conceptualization of clinical approaches to the treatment of temporomandibular disorder and the preparation and review of the protocol and draft reports.

Dr. Bruce Freeman participated in the conceptualization of clinical approaches to the treatment of TMD and the preparation and review of the protocol and draft reports.

Carolyn Spry designed and executed the literature search strategies; wrote the literature search section; and managed report referencing.

All authors approved the final draft report.

Acknowledgements

The authors would like to acknowledge:

- Humaira Nakhuda for her help with screening citations and data extraction.
- Camille Dulong and Chloe Li for their help with data checking.
- Teo Quay for the scoping of the project.
- Kelsey Seal for her contributions to the protocol and initial study selection.
- Michelle Clark for her technical expertise with DistillerSR.
- Paula Murray for her project management efforts.

Conflicts of Interest

Dr. Howard Tenenbaum has received honoraria for travel or article writing from Straumann Group, Izun Pharmaceuticals, and Colgate. Dr. Bruce Freeman has received honoraria for speaking engagements from Speed System Orthodontics, Align Technology, and Propel Orthodontics. No other conflicts of interest were declared.

CADTH

Table of Contents

Tables

Abbreviations

AE	adverse events
Botox	botulinum toxin
CCT	controlled clinical trial
CI	confidence interval
df	degrees of freedom
DSI	double spaces injection
GRADE	grading of recommendation, assessment, development and evaluation
HA	hyaluronic acid
ISI	inferior space injection
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
J	joule
LLLT	low level laser therapy
MA	meta-analysis
MAVO	maximum active vertical opening
MD	mean difference
MIO	maximal interincisal opening
MMO	maximal mouth opening
MO	mouth opening
MPVO	maximum passive vertical opening
NMA	network meta-analysis
NRSI	non-randomized study of intervention
NS	non-statistically significant
NSAID	nonsteroidal anti-inflammatory drug
NTI	nociceptive trigeminal inhibition
PEDro	Physiotherapy Evidence Database
PPT	pressure point threshold
PRP	platelet-rich plasma
RCT	randomized controlled trial
RoB	risk of bias
RS	retrospective study
SMD	standardized mean difference
SR	systematic review
SSI	superior space injection
TENS	transcutaneous nerve stimulation
TMD	temporomandibular disorders
TMJ	temporomandibular joint
TMJD	temporomandibular joint disease
VAS	visual analogue scale
WMD	weighted mean difference

Protocol Amendments

Section	Amendment	Page
Inclusion criteria	Joint ankylosis was also excluded based on clarification from our clinical experts	Table 1
Study selection	SRs in which 75% or more of the studies overlapped, or SRs with only 1 or 2 unique primary studies were evaluated based on their comprehensiveness, the date of the last literature search and key aspects of methodological quality, informed by existing literature on this issue. Modified to include “SRs with only 1 or 2 unique primary studies” as the cut off of 75% was not useful in identifying SRs with a high degree of overlap when there were few primary studies (e.g., ≤ 6 primary studies).	Page 15

SR = systematic review.

Executive Summary

Issue

Temporomandibular disorders (TMD) are disorders involving the temporomandibular joint (TMJ) and associated structures, and affect 5% to 12% of individuals. TMD can lead to chronic pain, tooth grinding, and cervical spine and mobility issues, all of which are precursors to more serious impairment of function. There are a plethora of different strategies to treat TMD, including pharmacological interventions, non-surgical interventions, and surgery.

This overview of reviews aims to summarize evidence regarding the clinical effectiveness and safety of interventions in adults (17 and older) and children (0 to 17) with TMD.

Objectives

The objective of the current report was to answer the following research question:

What are the optimal interventions for the treatment of TMD in children and adults in terms of clinical effectiveness and safety?

Clinical Evidence

Methods

An overview and critical appraisal of systematic reviews (SRs) relevant to the clinical effectiveness of pharmacological and non-pharmacological interventions for TMD was conducted. Published literature was identified by searching the following bibliographic databases: MEDLINE through Ovid; Embase through Ovid; PsycINFO through Ovid; the Cochrane Library through Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The search was limited by study design, with only health technology assessments, SRs, and meta-analyses (MAs) retrieved, and limited to English-language documents published since January 1, 2008. Results were screened independently by two reviewers, and data were extracted by one reviewer and verified by another.

The quality of included SR and MAs were assessed independently by two reviewers using the AMSTAR 2 tool. The results were narratively summarized and categorized based on the interventions and stratified by outcomes.

Results

There were 45 SRs that met the criteria for inclusion into the review. After assessment of overlap in primary studies between the SRs, 22 SRs were included in the final report. Within the 22 SRs, one study was a network meta-analysis, and 13 SRs included an MA within the results.

Interventions covered by the included SRs included psychological interventions, orthodontics, surgical interventions, laser therapy, and occlusal appliances. Outcomes of interest for this report included pain, maximal mouth opening, TMJ clicking, and adverse

events. Overall, the quality of the included studies was low. Based on the AMSTAR 2 assessment, confidence in the SRs was rated high for two included SRs, moderate in one SR, low in three SRs, and critically low in the remaining 16 SRs. Issues contributing to low confidence in some SRs included inappropriate MAs, high heterogeneity of primary studies, potential of publication bias of primary studies, inadequate descriptions of included studies, and no a priori protocols.

Overall, low-quality evidence showed potentially favourable results for long-term cognitive behaviour therapy, low level laser therapy, acupuncture, manual therapy, cyclobenzaprine hydrochloride, Botulinum toxin, Ping-On ointment, inferior or double spaces injections of hyaluronate or prednisolone, open surgery, and arthroscopy. Mixed or neutral results were found regarding stabilization splints and oral pharmacological treatments. Potentially unfavourable results were found for hypnosis and intra-articular injections of corticosteroids. No evidence was found for orthodontic interventions, and very limited evidence was found regarding TMJ clicking and adverse events. However, many studies used differing comparative groups, and many comparisons have critically low confidence associated with them, so these presented results should be interpreted with caution.

Conclusions

Due to the low quality of included literature, the limited evidence regarding TMJ clicking and adverse events, and the heterogeneity of SRs included in this report, firm conclusions regarding the optimal interventions for TMD cannot be made.

Limitations of the current report include exclusion of some primary studies due to overlap in SRs, reliability on interpretations of primary studies by authors of the SRs, low quality of evidence, and large proportions of primary studies rated as high risks for bias. Additionally, as inclusion criteria for the current report were broad, the volume of literature obtained was large and heterogeneous, making solid conclusions based on the current literature challenging.

Context and Policy Issues

Introduction

Temporomandibular disorders (TMDs) are defined by the Royal College of Dental Surgeons of Ontario (RCDSO) as “complex ailments involving the temporomandibular joints themselves and associated structures.”[1] It is estimated that the prevalence of TMD is between 5% and 12%.[2] TMD is associated with chronic orofacial pain, bruxism (tooth grinding), as well as conditions affecting the cervical spine and mobility, all of which can lead to more serious health concerns.[3,4] Symptoms include, but are not limited to, temporomandibular joint (TMJ) pain, noise in the joint, masticatory muscle tenderness, and limited mandibular movement.[5] The TMJ of the mandible connects the jawbone to the skull, and acts as both a rotational and translational joint.[6] The bones that interact in the joint are covered with fibrocartilage and are separated by a shock-absorbing disc to keep movements smooth (for the anatomical features of the TMJ, see Appendix 1, Figure 1).[6] The TMJ allows the jaw to move and perform basic functions such as chewing and talking.[7] Although the underlying cause of many cases of TMJ symptoms are unclear, issues with the joint can arise if the disc erodes or is it not properly aligned, the cartilage is damaged by arthritis, or the joint is damaged by an impact.[6]

This report will focus on the subcategories of TMD based on the RCDSO guidelines which include: masticatory muscle disorders (e.g., myospasm, myofascial pain), internal derangement/disc displacement, arthritides (e.g., osteoarthritis, rheumatoid arthritis), congenital/developmental abnormalities, post-traumatic disorders, and centrally mediated pain syndromes.[1] Other causes of TMJ pain and/or dysfunction, which may present similarly to but are not considered to be TMD, have not been included in the definition of TMD for this report, including direct traumatic injuries (e.g., fractures, dislocation), neoplasms, and idiopathic arthralgias.[1]

Various interventions are available to treat TMD, including pharmacological therapies, surgical and non-surgical procedures, dental appliances, physical therapy, and behavioural and psychosocial interventions. The goals of TMD treatment are to relieve and/or reduce pain and improve mandibular function.[8] The guidelines from the RCDSO recommend considering irreversible procedures (e.g., surgical interventions) only after attempts with more conservative treatments have failed, and only if the symptoms are severe and persistent.[1] Some interventions (e.g., pharmacological interventions and splint interventions) involve a symptom management approach; whereas others, such as surgical and orthodontic approaches, aim to resolve the underlying condition. It is unclear which approaches are the most clinically effective and have the fewest adverse events.

Policy Question

What are the optimal interventions for the treatment of TMD in terms of clinical effectiveness and safety?

Objective

The objective of this report is to inform the policy question through an overview of systematic reviews on the clinical effectiveness and safety of interventions for TMD in adults and children.

Research Question

This overview of SRs addresses the following research question:

What are the clinical benefits and harms of interventions for the treatment of temporomandibular joint disorders?

Methods

This research question covers all interventions in use for TMD and several outcomes. Scoping work conducted on the topic revealed a large number of existing SRs in the field, in which the majority of the interventions used for TMD were evaluated. Therefore an overview of reviews methodology was employed rather than a review of primary studies.

An overview of SRs, with or without meta-analyses or network meta-analyses (NMAs) or in health technology assessments (HTAs), available in the literature on the clinical benefit and harms of interventions for TMD, was conducted. In the expectation that more recent SRs would provide a more comprehensive and current synthesis of the evidence, the primary screen was of SRs published since January 2008. No restriction was placed on the dates of the included primary studies considered from the SRs. A survey of SRs published between

2000 and 2008 confirmed this impression; its results are described in this report's limitations section.

The protocol was written a priori, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P)[9] checklist for guidance on clarity and completeness. There is no version of the PRISMA-P specific to overviews of SRs, however, most of the items in it are also relevant to overviews. Any deviations from the protocol were identified, and reasons for the changes are provided throughout the report and in the Protocol Amendments table.

Literature Search Methods

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the Peer Review of Electronic Search Strategies checklist.[10]

Published literature was identified by searching the following bibliographic databases: MEDLINE through Ovid; Embase through Ovid; PsycINFO through Ovid; the Cochrane Library through Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as MeSH and keywords. The main search concept was temporomandibular joint.

Methodological filters were applied to limit retrieval to HTAs, SRs, and meta-analyses. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published since January 1, 2008. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was run on July 10, 2018. Regular bi-weekly alerts were established to update the search until September 11, 2018. Citations identified in the alerts that met the selection criteria were incorporated into the analysis if they were identified before the completion of the external review period. Any citations identified after the external review period were described in the discussion, with a focus on comparing the results of these new citations with the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters). Google and other Internet search engines were used to search for additional Web-based materials. See Appendix 2 for more information on the grey literature search strategy.

Literature Selection Criteria

Selection criteria for SRs are presented in Table 1.

Table 1: Study Eligibility Criteria for the Clinical Research Question

Populations
Adults (17 and older) and children (0 to 17) with TMD[a] Subgroups based on the following: • Remote/isolated populations • Indigenous Populations • Populations at risk due to: high caries and/or periodontal disease; parafunctional habits (e.g., any abnormal behaviour or functioning of the oral structures and associated muscles.)
Interventions
Pharmacological and non-pharmacological interventions for TMD, including, but not limited to: • Pharmacological interventions (e.g., botulinum toxin, hyaluronate, anxiolytics, antidepressants, muscle relaxants, analgesics) • Surgical interventions (e.g., arthroscopy, arthrocentesis, lavage) • Stabilization splint therapy • Occlusal adjustment • Orthodontics • Physiotherapy (e.g., techniques commonly used by physiotherapists) • Psychological interventions (e.g., cognitive behavioural interventions, relaxation stress reduction) **Exclusions:** • Total joint replacement, including Teflon replacements for TMJ discs
Comparators
• Any alternative intervention for TMD (as listed under Interventions above) • No intervention (e.g., placebo, sham treatment, no intervention)
Outcomes

• Primary outcome: Pain (orofacial/craniofacial, headaches)
• Secondary outcomes:
  ○ Maximal mouth opening or ease of opening (subjective or objectives measures)
  ○ TMJ clicking (painful or non-painful)
  ○ Adverse events

Study Designs
SRs, with or without MAs or NMAs or in HTAs, of randomized controlled studies and/or non-randomized controlled studies **Exclusions:** • Overviews of SRs, or SRs plus primary studies (umbrella reviews) • SRs of case reports or case series • SRs that have been withdrawn for reasons other than being out of date • Earlier versions of SRs that have been updated • Review articles • Editorials, letters, and commentaries • Studies of any design published as conference abstracts, presentations, or thesis documents

Time Frame
• SR published from January 1, 2008 onward

HTA = health technology assessment; MA = meta-analysis; NMA = network meta-analysis; SR = systematic review; TMD = temporomandibular disorders.

[a] TMD is a general term to describe pain and/or dysfunction of the masticatory apparatus including the temporomandibular joint (TMJ), masticatory muscles, and supporting structures. The following subcategories of TMD will be included: (p6).[1]

- Masticatory muscle disorders–myospasm, myofascial pain, pain as a component of systemic disorders such as fibromyalgia, chronic fatigue syndrome.
- Internal derangement/disc displacement — with or without reduction, closed lock.
- Arthritides–osteoarthritis, rheumatoid arthritis, psoriatic arthritis, septic arthritis, gout, pseudo-gout, lupus erythematosus, capsular inflammation.
- Congenital/developmental abnormalities — condylar hyperplasia, condylar hypoplasia/aplasia, coronoid hyperplasia.
- Post-traumatic disorders and centrally mediated pain syndromes (multifactorial and often refractory to treatment).

The following conditions will be excluded: (p.6).[1]

- Direct traumatic injuries, including:
  - fractures of the condyle, condylar neck, coronoid process, or temporal bone
  - joint dislocation, subluxation, or ligamentous/capsular disorders.
- Neoplasms(of the components of the temporomandibular joints or related structures or metastatic).
- Idiopathic arthralgias, dysfunction.
- Joint ankyloses.

Inclusion Criteria

SRs were included if they were published in English and met the selection criteria outlined in Table 1. If an SR included both eligible and ineligible primary study designs (e.g., SRs with comparative and non-comparative data on interventions for TMD), the study was included if it was possible to extract the relevant summary findings only (i.e., only comparative data). For the purposes of this overview of SRs, comparative data included interventions compared against alternative interventions or a placebo/no intervention.

If the total population was mixed (e.g., including patients without TMD), the SR was only included if results for the population of interest were reported separately by the SR authors. There were no limits regarding the age of the patients, the therapy duration, or length of follow-up in the SRs.

Eligible SRs were those that included a detailed description of the search methods (i.e., with at least two electronic sources having been searched, with adequate reporting of years searched, databases used, and keywords or MeSH terms used and, where feasible, the search strategy provided); included a description of comprehensive selection criteria (i.e., defined population, intervention[s], comparator[s], and outcome[s]); assessed the quality, or risk of bias, of the included studies; and synthesized the findings quantitatively or narratively.[11]

Exclusion Criteria

SRs were excluded if they did not meet the inclusion criteria outlined in Table 1, were published in a language other than English, or were duplicate publications (i.e., the same publication identified more than once from different sources [e.g., MEDLINE and grey literature] as opposed to a single SR published multiple times in different journals). Reviews that were not SRs (i.e., narrative reviews or not fully systematic, based on the four criteria for SRs in Inclusion Criteria) were excluded.

SRs in which the intervention or comparator is total joint replacement were excluded, as total joint replacement is only recommended after multiple other treatments have failed to have an effect.[12] SRs were excluded if they did not include any comparative data (e.g.,

results are reported over time or prevalence data). If the SR population was mixed, the SR was excluded if no information was available on the proportion of the total population who met the inclusion criteria or if the results for the patients with TMD were not reported separately.

Literature Screening and Study Selection

Two reviewers independently screened titles and abstracts of all citations retrieved from the literature search in DistillerSR, using the pre-determined selection criteria (see Literature Selection Criteria). Full text of citations deemed to be potentially eligible by either reviewer were retrieved. The reviewers then independently reviewed the full text, applied the pre-determined selection criteria, and compared their lists of included and excluded citations. Any disagreements were resolved through discussion until consensus was reached. SRs deemed to be eligible by both reviewers were included. One reviewer (KB) was involved in screening all of the abstracts and full texts, and the second reviewer was one of three other individuals (KS, HN, CW).

If two or more SRs were found that completely or substantially overlapped in the included primary studies (a primary study was considered to be included if it met the SR's inclusion criteria, and was reported by the SR; primary studies did not have to be included in the meta-analysis), the degree of overlap was judged[13] and reported by building a matrix of included primary studies.[13,14] SRs in which 75% or more of the studies overlapped, or SRs with only one or two unique primary studies, were evaluated based on their comprehensiveness, the date of the last literature search and key aspects of methodological quality, informed by existing literature on this issue.[15] Two reviewers (KB and AS) independently assessed the SRs identified as overlapping on a case-by-case basis to determine which SRs should be included or excluded. Any disagreements were resolved through discussion, involving a third reviewer if necessary. SRs that contained the most evidence (i.e., are the most comprehensive and/or most recent) and were of high methodological quality were preferentially included over less comprehensive SRs or those of lower quality; and those with redundant data (e.g., 100% of primary studies overlapped with another study SR) were identified and excluded. Any overlap of primary studies between the included SRs was identified in matrices (Appendix 9).

Data Extraction

Data from each included study were extracted into DistillerSR (study characteristics; extracted by HN) and Microsoft Word tables (findings; extracted by KB, CW, and AS) by one reviewer and verified by a second reviewer (KB, CW, CL, CD), with disagreements resolved through discussion and consensus. Standardized forms were used to inform the data extraction process. Data were not extracted from figures unless they provided explicit numerical data. Primary studies included in the SRs were not checked for any missing information or to clarify any issues. Authors of the included SRs were not contacted to provide any missing information or clarify any issues.

The following information was extracted from the included SRs:

- first author name, publication year, country (where the SR was conducted or of the corresponding author), and funding sources
- SR design, databases and time frames searched, and quality assessment tool used
- study types, number, and publication years of primary studies included

- number, age, and characteristics of the TMDs of the patients included; and relevant subgroups
- descriptions of the intervention(s) and comparator(s), therapy duration
- descriptions of primary and secondary outcomes reported, length of follow-up
- descriptions of subgroups of interest
- results and conclusions for the outcomes and subgroups of interest, including: number of included studies, treatment effect, confidence intervals, *P* value, measure of heterogeneity
- results of the reviewers' quality assessments of individual studies
- results of the evidence grade, if the body of evidence is graded in the SRs.

For SRs that presented quantitative data in the results, measures of treatment effects (e.g., odds ratio [ORs], or standardized mean difference [SMD]) and whether fixed-effects or random-effects models were used was extracted. Summary results were extracted from SRs that synthesized the study findings qualitatively by reporting the number of primary studies that had positive, neutral, or negative results. Positive results were in favour of the intervention, neutral results reported no difference between the intervention and control, and negative results were in favour of the control.

Data Analysis and Synthesis

Narrative syntheses were undertaken to describe the direction of observed effects across outcomes and interventions for TMD. This employed the use of detailed data tables describing study characteristics and results, supplemented by a summary description of the findings for each type of intervention by outcome. Tables were created to summarize the findings for each class of intervention for each outcome listed in Table 1. We classified outcome data from the SRs as favourable (there is an effect in favour of the intervention), neutral (interventions are equally effective), or unfavourable (there is an effect in favour of the comparator) using the criteria described in Appendix 3. For evidence from SRs with MAs, we reported whether the results were statistically significant or non-statistically significant. For evidence from SRs without MAs, we indicated whether the evidence was inconclusive (i.e., most of the evidence is in one direction, but some of the evidence is in the opposite direction, or demonstrates no difference between interventions).

The outcomes are synthesized narratively, highlighting any trends across SRs, including the direction of the effect and subgroup specific findings. Direct comparisons between interventions are reported as such, and no formal analysis was conducted to indirectly compare interventions that were not directly assessed against each other. Efforts were made to avoid double counting outcome data from primary studies by excluding SRs with a high degree of overlap, and SRs excluded based on their overlap with other SRs are identified in Appendix 6. In cases where more than one SR was included for a given intervention, comparator, and outcome of interest, the overlap of the included primary studies among SRs is presented using a matrix of included primary studies (Appendix 9), and the degree of overlap is considered in our discussion of the findings.

Critical Appraisal of Individual Studies

The quality of the SRs was assessed using the 16 question AMSTAR 2 tool (Appendix 4),[16] designed to critically appraise SRs that include randomized and non-randomized studies of health care interventions. Each question was answered as "yes," or "no," with "yes" indicating very low concern and "no" indicating very high concern about potential bias. Some questions were answered "partial yes," if the minimum criteria for the question was met. Seven of the domains of AMSTAR 2 can critically affect the validity of a review and its conclusions. Our overall level of confidence in the SRs was assessed based on these critical domains, as suggested by the AMSTAR 2 tool (Appendix 4).[16] The quality of each NMA was appraised using the checklist from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) task force guidance document.[17]

The methodological quality of each included SR was assessed by one reviewer (KB or CW) and checked for accuracy and completeness by a second reviewer (KB or CW). Any disagreements were resolved through discussion until consensus was reached, involving a third reviewer if necessary. The reviewers piloted the AMSTAR 2 tool on a sample of included SRs until consistency between the reviewers was reached with no major differences in their ratings (> 80% agreement).

A narrative summary of the quality of the included SRs is provided in the main text of the report to provide the reader with an overview of the quality of the SRs, and a table was used to present the answers to the questions of the AMSTAR 2 tool. Additionally, the SRs were grouped by class of intervention, and we reported the number of AMSTAR 2 criteria that were met by each SR and the number of critical flaws in the SRs, in order to give an estimate of the overall quality of the SRs by intervention category. The quality of the SRs was taken into consideration within the conclusion and discussion sections of the final report.

Summary of Evidence

Quantity of Research Available

A total of 631 citations were identified in the literature search. Following screening of titles and abstracts, 461 citations were excluded and 170 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 125 publications were excluded for various reasons, and 45 met the inclusion criteria. After assessing the SRs for overlap between the primary studies, 23 SRs were excluded due to a high degree of overlap with other more comprehensive SRs. 22 SRs were included in this report. **Error! Reference source not found.** presents the PRISMA[9] flowchart of the study selection and Appendix 6 presents the studies excluded due to overlap.

Summary of Study Characteristics

The characteristics of the included SRs are summarized in Appendix 7.

Study Design

All included studies were SRs. One study[18] was an NMA. Nine SRs included meta-analyses of randomized controlled trials (RCTs),[19-27] three studies had meta-analyses that combined RCTs and non-randomized studies (NRS) in a single analysis,[28-30] and one study[31] included NRS in the SR, but only performed meta-analysis on RCTs.

Country of Origin

Two SRs were conducted in Canada,[19,24] three SRs were conducted in the UK,[20,32,33] four SRs were conducted in Brazil,[23,34-36] and four SRs were conducted in China.[21,27,28,31] The remaining SRs were conducted in South Korea,[22,37] Serbia,[25] US,[26] Sweden,[18] Greece,[38] India,[39] and Yemen.[29,30]

Patient Population

The number of patients in the primary studies included by the SRs ranged from seven patients[22] to 564 patients.[31] Included patients had TMD,[19-28,32,33,35,37] orofacial pain (TMD myalgia and TMJ pain),[18] anchored disc phenomenon,[29,30,39] temporomandibular myofascial pain,[34] or TMJ arthritis.[31,36,38] Included studies were mostly on adult patients only,[18,20,22,24,27-29,31-33,35,36,38] adult and pediatric patients combined,[19,21,23,25,30,34,37] or the age was not reported.[26,39]

Interventions

The SRs included six broad categories of interventions. Six studies examined physiotherapy,[21-24,34,37] nine studies examined pharmacotherapy,[18,24,27,31,33-36,38] and three studies examined splint therapy.[24,25,28] Three studies examined psychological interventions,[19,20,24] two studies examined orthodontics,[26,32] and five studies examined surgical interventions.[29-31,39] Specific details of the interventions are available in the summary of findings and the study characteristics table (Appendix 7).

Comparators

The majority of SRs included either no treatment[19,20,23-26,28,32,37] or placebo/sham as a comparator group.[18,20,22-24,28,32-34,36,37] Other comparators included pharmacological interventions, surgical interventions, physiotherapy interventions, relaxation and hypnosis, splint therapy, and various psychological treatments. More detail on specific comparisons is available in the summary of findings.

Outcome Measures

Four outcomes were of interest in this report: pain, maximal mouth opening (MMO), temporomandibular joint clicking, and adverse events. All of the relevant SRs reported on pain[18-31,33-39] and the majority reported on MMO outcomes.[19-31,34-39] Seven SRs reported on TMJ clicking[26,28,29,31,38] and seven SRs reported on adverse events.[21,31,33,34,37,39] One study[32] found no relevant primary studies, therefore did not report on any outcomes.

Quality Appraisal Tools

Sixteen SRs used the Cochrane Risk of Bias (RoB) tool to assess the quality of the primary studies[19,20,22,24-28,31-34,36-39] and three studies used the Jadad scale.[25,35,38] Three studies used the grading of recommendation, assessment, development and evaluation (GRADE) to assess the quality of outcomes or body of evidence.[18,21,36]

Other quality appraisal tools used included a modified Jadad scale,[21] the Physiotherapy Evidence Database (PEDro) scale,[23] a modified Cochrane RoB,[26] and an RoB tool from the Swedish Agency for Health Technology Assessment and Assessment of Social Services.[18] In addition, some SRs also evaluated the primary studies using reporting guidelines, such as Consolidated Standards of Reporting Trials (CONSORT),[26,27] Meta-analysis of

Observational Studies in Epidemiology (MOOSE),[29,30] and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[29,30]

Summary of Critical Appraisal

The quality assessment of the 22 included SRs,[18-40] conducted with AMSTAR 2[16] (Appendix 4), is presented in Appendix 8.

All but two SRs[19,28] included the population, intervention, comparator group, and outcome(s) as part of the research question and inclusion criteria. In the one SR,[28] the authors reported that they would include placebo controlled splint therapy studies, but then included surgery, physical therapy, and biofeedback as controls, rather than placebo splints. In the other SR,[19] the authors did not specify outcomes of interest in the research question or inclusion criteria, and instead they used clinical experts to select the outcomes that would be important to patients from those found in the primary studies.

Seven of the SRs[18,20,24,32-34,36] included a protocol that was registered with PROSPERO[18,24,34,36] or published online in the Cochrane Database of Systematic Reviews.[20,32,33] Two SRs[23,35] stated that they used a protocol, however, the protocols were registered after the start of the SR, making it possible that the protocol was not written a priori, thus introducing a higher risk of reporting bias. The other 13 SRs do not mention a protocol (critical domain).

Four SRs[22,25,26,38] justified the inclusion of only RCTs. The other SRs did not contain an explanation for including only RCTs, increasing the risk that the SR may have an incomplete summary of the effectiveness and harms of the interventions, or for including RCTs and NRS, increasing the risk that study designs are combined inappropriately in the analysis.

Almost all of the SRs used a comprehensive literature search strategy (critical domain), with only one SR[23] not meeting this criteria, due to the following: failure to report searching the reference lists of the included studies, failure to justify including only English studies, and the failure to consult any dental experts. Overall, the SRs scored well on these criteria, however, the inclusion criteria for this overview stipulated that SRs must have searched at least two databases, provided key word and/or search strategy, and reported the years searched, and therefore SRs not meeting these criteria were already excluded from the overview.

Study selection was not completed in duplicate by six SRs;[22,28-30,35,37] in two SRs[29,30] it was explicitly stated that only one author screened the studies for inclusion, increasing the risk of selection bias, but in the other cases it was unclear whether a second author was involved. Data extraction was not performed in duplicate in six SRs;[29,30,35,37-39] in two of these SRs[29,30] it was explicitly stated that only one author conducted the data extraction (and the data were not reviewed by a second author), whereas it was unclear in the other four SRs if a second author was involved. In four SRs,[29,30,35,37] neither the data extraction nor the study selection was performed in duplicate, and it was not mentioned whether a second author reviewed the data.

Eight SRs[18,20,25,32,33,36,38,39] provided a list of the excluded studies and justified their exclusions (critical domain).

The included studies were described in adequate detail in 13 SRs. In one SR[32] there were no eligible primary studies. Three SRs[21,28,35] did not describe their included studies in adequate detail; missing information included the population and the comparator,[21] the research design and outcomes,[28] and outcomes.[35] Five other SRs[22,25,29,30,38] provided the relevant information, but were lacking sufficient detail for all variables.

Five SRs[21,29-31,35] did not use a satisfactory technique for assessing the risk of bias in the individual studies that were included in SRs (critical domain). Two of the SRs[21,35] used the Jadad score, which did not include all of the necessary components for assessing risk of bias; two SRs[29,30] created their own tool from various reporting guidelines, but it did not have the appropriate criteria; and one SR[31] used the Cochrane RoB tool, however, the figure reporting risk of bias was missing two of the included primary studies and included two studies that were not included in the SR, and therefore, the accuracy of the assessment was compromised. Two other SRs[23,26] used appropriate tools and created their own cut-off values for determining high versus low-quality studies; however, neither SR specified whether this was defined a priori, thus increasing the risk of bias in these assessments. The remaining SRs used the Cochrane RoB tool, or a variation of the tool, to assess the quality of their included RCTs.

Three SRs[20,33,36] reported on the sources of funding for the primary studies included in the SR, of which two were Cochrane reviews.[20,33] It is unclear whether the funding bodies of the primary studies could therefore have introduced bias into the results of the SRs.

Seven of the SRs with available primary studies did not conduct a meta-analysis[33-39] and an eighth SR did not find any relevant primary studies.[32] One SR[18] included a NMA, which was evaluated separately using the checklist from the ISPOR task force guidance document.[17] Of the 13 other SRs that conducted a pairwise meta-analysis, five of them used appropriate methods for statistical combination of the results (critical domain).[20,22,24,27,31] In the other SRs, the authors were not justified in combining their data into a meta-analysis due to variations in interventions (e.g., wear time of the appliances,[26] type of appliance[28]) high heterogeneity,[21,29,30] variations in the control groups (e.g., multiple different controls used[23,25]), and variations in the populations.[19] Additionally, three SRs pooled RCTs and NRS together, which is generally considered inappropriate.[28-30]

One SR[30] assessed the potential impact of the risk of bias of the individual studies on the results of the meta-analysis by conducting a sensitivity analysis that excluded the high risk of bias studies; however, the authors were not justified in conducting a meta-analysis due to high heterogeneity, even after removing the studies with high risk of bias. In four SRs, the authors determined that all of the primary studies had the same risk of bias (low,[31] low or medium risk of bias,[18] unclear,[22] or high[24]) and therefore they could not assess the impact of risk of bias on the results.

Eight SRs[20,22,24,33,34,36,37,39] accounted for risk of bias of the individual studies when interpreting or discussing the results of their review (critical domain). In some of the other SRs, the authors mention the risk of bias of the studies, but they do not discuss how it affects the interpretation of the findings.

Half of the SRs[20,22-24,27,31,33,34,36,37,39] provided an explanation for, and a discussion of the heterogeneity observed in the results of the review. In some of the SRs, they mention the large amount of heterogeneity in their review, however, they do not discuss how it could affect the interpretation of their findings.[18,19,21,25,35,38]

In the SRs that performed a meta-analysis, three SRs[25,26,28] performed an appropriate investigation into publication bias (critical domain). In some SRs, the small number of studies precluded the authors from performing the investigation into small study bias.[19,27] In other SRs,[23,30] the authors conducted a graphical or statistical investigation into publication bias, however, it is not best practice to use these tests when there is a small number of studies (i.e., less than 10).

All but three SRs,[26,27,37] reported on potential sources of conflict of interest, including potential conflicts from funding received for conducting the review.

Based on the critical domains of AMSTAR 2, our overall level of confidence in the SRs was high for two SRs,[33,36] moderate for one SR,[32] low for three SRs[20,34,39] and critically low for the rest of the SRs.

ISPOR Checklist

A simplified checklist from the ISPOR task force was used to evaluate the NMA.[17] The SR was comprehensive with a well-defined scope, and the NMA was conducted using appropriate methods, and the analysis was clearly reported. The interpretation of the network was appropriate. The principle limitation is the data. There were a limited number of studies of sufficient quality and with suitable data for an NMA. The network of studies consisted predominately of studies with a placebo comparator, with few direct comparisons between active treatments, and only one or two studies per arm. Therefore the estimates would be imprecise, and it would not be possible to evaluate the consistency of comparisons made indirectly and comparisons made directly.

Quality of the SRs by Intervention Category

The number of AMSTAR 2 criteria (Appendix 4) that was met by each of the SRs, and our overall confidence of the SRs within each intervention category are summarized in Appendix 8.

Psychological Interventions

The SR by Aggarwal et al.[20] on psychosocial interventions met 13 of the 16 AMSTAR 2 criteria, while the SR by Zhang et al.[19] met five of the 16 criteria. Our level of confidence with the SR by Aggarwal et al.[20] is low, as it had one critical flaw due to not assessing publication bias, however, the small number of studies may have precluded this. Our level of confidence in the SR by Zhang et al.[19] was critically low, as it had five critical flaws, including not having a protocol established a priori, not using appropriate methods for the meta-analysis, and not assessing publication bias.

Physiotherapy – Acupuncture or Laser Therapy

Our overall level of confidence in the SRs on acupuncture and laser therapy was critically low. An SR and meta-analysis on laser therapy by Xu et al.[21] had six critical flaws (and a partial yes on the seventh critical domain) while meeting four of the 16 AMSTAR 2 criteria. Another, SR and meta-analysis on acupuncture by Jung et al.[22] met eight of the 16 criteria, with three critical flaws, including not having a protocol established a priori and not accounting for small study bias. An SR on acupuncture by Cho et al.,[37] which did not include a meta-analysis, met six of the 13 applicable criteria, and had two critical flaws (no protocol established a priori and no list of excluded studies) with other non-critical weaknesses (unclear if study selection and data extraction were performed in duplicate).

Physiotherapy — Manual Therapy

Our overall level of confidence in the SRs on manual physiotherapy was critically low. The SR by Martins et al. on manual manipulative therapy[23] had six critical flaws (and a partial yes on the seventh critical domain) while meeting six of the 16 criteria. Meanwhile the SR by Armijo-Olivo et al. on manual therapy[24] met 11 of the 16 criteria, with two critical flaws (no list of excluded studies and no methods reported for examined publication bias).

Splint Therapy

Our overall level of confidence in the SRs examining splints was critically low. One SR on splint therapy by Pficer et al.[25] met nine of the criteria, with three critical flaws (no protocol established a priori, inappropriate meta-analysis methods, and failing to account for risk of bias when interpreting the results). The other SRs on splint therapies by Zhang et al.[28] and Fricton et al.[26] met four and six of the 16 criteria, respectively, and each had four critical flaws (no protocol established a priori, no list of excluded studies, inappropriate meta-analysis methods, and failing to account for risk of bias when interpreting the results). Both SRs also only partially met the criteria for a comprehensive search strategy, and Fricton et al.[26] only partially met the criteria for a satisfactory assessment of risk of bias.

Orthodontic Interventions

This SR[32] did not include any primary studies, but it met eight of the nine applicable criteria, with no critical weaknesses; therefore we can be moderately confident that there is no research in this area.

Pharmacological — Injections

The two SRs that conducted a meta-analysis by Liu et al.[31] on corticosteroids and Li et al.[27] on superior, double or inferior injection spaces each met eight of the 16 criteria, and our overall level of confidence was critically low for both SRs. The SR by Liu et al.[31] had five critical weaknesses, while the SR by Li et al.[27] had four critical weaknesses. Neither SR had a protocol established a priori, provided a list of excluded studies, accounted for risk of bias when interpreting the results, or adequately investigated small study bias. Liu et al.[31] also did not use a satisfactory technique for assessing risk of bias. The SR that conducted the NMA on the injection or ingestion of various oral pharmacological agents[18] met nine of the 14 applicable criteria. Our overall level of confidence was critically low, with two critical flaws; they did not account for risk of bias when interpreting the results, and they did not adequately account for publication bias.

For the three SRs that did not conduct a MAs, we had critically low confidence in the SRs on platelet-rich plasma[38] and hyaluronic acid,[35] and low confidence in the SR on various injections.[34] The SR by Bousnaki et al.[38] met six of the applicable 13 criteria, and had two critical flaws (no a priori protocol, and no accounting for risk of bias when interpreting the results). The SR by Goiato et al.[35] had four critical flaws, with numerous other non-critical weaknesses, and only fully satisfied one and partially satisfied another of the applicable AMSTAR 2 criteria. There was one critical weakness in the SR by Machado et al.[34] (did not report the list of excluded studies), and otherwise met 10 of the 13 applicable criteria.

Pharmacological — Oral or Topical

The two SRs[33,36] on oral pharmacological drugs did not conduct a meta-analysis, and they both met 12 of the 13 applicable criteria, with no critical flaws, and our overall level of confidence in them is high. The non-critical weakness in both SRs was that they did not

provide an explanation for their selection of study designs; Melo et al.[36] included observational and clinical trials, whereas Mujakperuo et al.[33] only included RCTs.

Surgical

One SR on surgical interventions by Nagori et al.[39] did not conduct a meta-analysis, and met nine of the 13 applicable criteria, with one critical weakness (no protocol established a priori), and we have low confidence in the SR. We have critically low confidence in the other two SRs[29,30] that were both conducted by the same author (Al-Moraissi) without any co-authors, which have six critical flaws and met only three and four of the 16 criteria.

Summary of Findings

Overlap Across Included Systematic Reviews

Any overlap of primary studies across the included SRs is summarized below and presented in Appendix 9 by class of intervention. Overlap is further discussed in the section for each intervention.

Data Analysis and Synthesis

The findings are presented here, for each class of intervention, stratified by outcomes. If two interventions of interest were compared, we classified and reported the intervention the way the SR authors presented it (e.g., for the SR that compared needle acupuncture with occlusal splints, the SR authors considered acupuncture to be the intervention and splints to be the comparator, thus we have reported this in the section considering acupuncture). For each class of intervention, a table is provided and the results are summarized in the text. In the text, the comparisons are organized based on whether the findings were favourable (there is an effect in favour of the intervention), neutral (interventions are equally effective), or unfavourable (there is an effect in favour of the comparator). If an MA was conducted, it was indicated with the abbreviation “MA” and we noted whether the results of the MA were statistically significant or non-statistically significant (NS). If an MA was not conducted, we indicated whether the evidence was inconclusive (i.e., some of the evidence is neutral or in the opposite direction). Appendix 3 contains further details regarding evidence classification.

Psychological Interventions

Two SRs[19,20] examined psychological interventions for TMD. We have low confidence in the results of one SR[20] and critically low confidence in the results from the other SR.[19] They included a total of 18 primary studies, six of which overlapped with studies in other SRs, in particular the SR by Fricton et al.[26]

Generally, the evidence regarding various psychological treatments for TMD was of low quality and at unclear or high risk of bias. Additionally, most of the results from MAs were either inconclusive or insignificant. The interventions that may be associated with improvements in pain are long-term cognitive behavioural therapy alone or in combination with biofeedback and various long-term psychological interventions (that included cognitive behavioural therapy); no favourable results were identified regarding mouth opening. Short-term psychological cognitive behavioural therapy in combination with biofeedback was found to be unfavourable versus usual care in terms of pain. Adverse events and TMJ sounds were not examined in the included SRs examining psychological interventions.

Pain

Two SRs[19,20] examined psychological interventions for pain improvement in TMD. Zhang et al.[19] examined hypnosis or relaxation therapy; whereas Aggarwal et al.[20] examined multiple types of psychological interventions, including habit reversal, hypnosis, cognitive behavioural therapy, biofeedback, and posture self-control. Comparisons included no treatment,[19,20] an alternative psychological intervention,[20] and usual care (which was not well defined).[20] Favourable interventions for which statistically significant differences were found versus controls included long-term cognitive behavioural therapy alone or in combination with biofeedback and various long-term psychological interventions; however, the evidence was associated with unclear or high risk of bias. The detailed findings are reported in Table 2, and have been summarized here.

Psychological interventions for which there were favourable results:

- Long-term (> three months) cognitive behavioural therapy and biofeedback versus usual care (MA; three RCTs, unclear and high risk of bias); statistically significant in MA.[20]
- Long-term (> three months) cognitive behavioural therapy alone versus usual care (MA; four RCTs, unclear and high risk of bias); statistically significant in MA.[20]
- Long-term (> three months) psychosocial interventions (cognitive behavioural therapy, biofeedback, or posture self-control) versus usual care (MA; nine RCTs; unclear or high risk of bias); statistically significant in MA.[20]
- Hypnosis versus no therapy (MA; three RCTs, very low-quality evidence, high heterogeneity); NS.[19]
- Hypnosis versus relaxation (MA; two RCTs, unclear risk of bias); short term (≤ three months); NS.[20]
- Short-term (≤ three months) biofeedback versus usual care (MA; 2 RCTs, unclear and high risk of bias); NS.[20]
- Habit reversal versus wait list control (one RCT, high risk of bias).[20]
- Long-term (> three months) biofeedback versus usual care (one RCT; unclear risk of bias); long term (> three months); inconclusive.[20]
- Posture self-control versus usual care (one RCT, unclear risk of bias); short and long term; inconclusive.[20]

Psychological interventions with neutral results:

- Short-term (≤ three months) cognitive behavioural therapy alone versus usual care (MA; four RCTs, unclear and high risk of bias).[20]

Psychological interventions with unfavourable results:

- Short-term (≤ three months) cognitive behavioural therapy and biofeedback versus usual care (MA; two RCTs, unclear and high risk of bias); statistically significant in MA.[20]

Table 2: Summary of Psychological Interventions for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
No treatment						
Zhang 2015[19]	Hypnosis or relaxation therapy	No therapy	Pain intensity (VAS; 100 mm) MD –9.16 mm; 95% CI, –23.47 mm to 5.14 mm; *P* = 0.21 I^2 = 76%; Tau^2 = 118.68; Chi^2 = 8.17 df = 2 (*P* = 0.02)	Favourable, non-statistically significant	3 RCTs (144)	High Cochrane RoB for all studies GRADE = very low-quality evidence
Aggarwal 2011[20]	Habit reversal	Wait list control	Pain short term (≤ 3 months) SMD –1.31; 95% CI, –1.97 to –0.65; fixed effects	Favourable	1 RCT (20)	High Cochrane RoB
Psychological						
Aggarwal 2011[20]	Hypnosis	Relaxation	Pain short term (≤ 3 months) SMD –1.84; 95% CI, –3.26 to –0.42; *P* = 0.011; fixed effects; I^2 = 0%; Chi^2 = 0.09; df = 1 (*P* = 0.76)	Favourable, statistically significant	2 RCTs (81)	Cochrane RoB: Unclear = 2
Other treatment						
Aggarwal 2011[20]	Cognitive behavioural therapy alone	Usual care[a]	Pain short term (≤ 3 months) SMD 0.03; 95% CI, –0.17 to 0.22; *P* = 0.78; fixed effects; I^2 = 0%; Chi^2 = 2.96; df = 3 (*P* = 0.40)	Neutral	4 RCTs (411)	Cochrane RoB: Unclear = 3 High = 1
Aggarwal 2011[20]	Cognitive behavioural therapy alone	Usual care[a]	Pain long term (> 3 months) SMD –0.25 95% CI, –0.46 to –0.05; *P* = 0.014; fixed effects; I^2 = 0%; Chi^2 = 1.98; df = 3 (*P* = 0.58)	Favourable, statistically significant	4 RCTs (411)	Cochrane RoB: Unclear = 3 High = 1
Aggarwal 2011[20]	Biofeedback alone	Usual care[a]	Pain short term (≤ 3 months) SMD –0.41; 95% CI, –1.06 to 0.25; *P* = 0.23; fixed effects; I^2 = 36%; Chi^2 = 1.56; df = 1 (*P* = 0.21)	Favourable, non-statistically significant	2 RCTs (45)	Cochrane RoB: Unclear = 1 High = 1
Aggarwal 2011[20]	Biofeedback alone	Usual care[a]	Pain long term (> 3 months) SMD –0.09; 95% CI, –0.88 to 0.70; *P* = 0.83; fixed effects	Favourable, inconclusive	1 RCTs (35)	Cochrane RoB: Unclear = 1
Aggarwal 2011[20]	Cognitive behavioural	Usual care[a]	Pain short term (≤ 3 months) SMD 0.46; 95% CI, 0.02 to 0.90; *P* = 0.043;	Unfavourable, statistically	2 RCTs (90)	Cochrane RoB: Unclear = 1

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
	therapy and biofeedback		fixed effects; I^2 = 45%; Chi^2 = 1.81; df = 1 (*P* = 0.18)	significant		High = 1
Aggarwal 2011[20]	Cognitive behavioural therapy and biofeedback	Usual care[a]	Pain long term (> 3 months) SMD –0.52; 95% CI, –0.82 to -0.23; *P* = 0.00053; fixed effects; I^2 = 54%; Chi^2 = 4.31; df = 2 (*P* = 0.12)	Favourable, statistically significant	3 RCTs (196)	Cochrane RoB: Unclear = 1 High = 2
Aggarwal 2011[20]	Posture self-control	Usual care[a]	Pain short term (≤ 3 months) SMD –0.49; 95% CI, –1.09 to 0.11; *P* = 0.11; fixed effects	Favourable, inconclusive	1 RCT (44)	Cochrane RoB: Unclear = 1
Aggarwal 2011[20]	Posture self-control	Usual care[a]	Pain long term (> 3 months) SMD –0.52; 95% CI, –1.13 to 0.18; *P* = 0.088; fixed effects	Favourable, inconclusive	1 RCT (44)	Cochrane RoB: Unclear = 1
Aggarwal 2011[20]	Psychosocial interventions (cognitive behavioural therapy, biofeedback, posture)	Usual care[a]	Pain long term (> 3 months) SMD –0.34; 95% CI, –0.50 to –0.18; *P* = 0.000021; fixed effects; I^2 = 13%; Chi^2 = 9.19; df = 8 (*P* = 0.33)	Favourable, statistically significant	9 RCTs (658)	Cochrane RoB: Unclear = 6 High = 3

GRADE = grading of recommendation, assessment, development and evaluation; MD = mean differences; RCT = randomized controlled trial; RoB = risk of bias; SMD = standardized mean difference; VAS = visual analogue scale.

[a] Usual care not further defined in the SR.

Mouth Opening

One SR[19] examined hypnosis or relaxation therapy compared with no therapy with respect to active MMO. The detailed findings are reported in Table 3. Hypnosis or relaxation therapy was found to have unfavourable results when compared with no therapy in one RCT (result statistically significant) and the SR authors considered the evidence quality low.

Table 3: Summary of Psychological Interventions for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
		No treatment				
Zhang 2015[19]	Hypnosis or relaxation therapy	No therapy	Change in Active (voluntary) MMO: MD –2.63 mm; 95% CI, –3.30 to –1.96 mm; *P* < 0.001	Unfavourable	1 RCT	Cochrane RoB: high GRADE = low-quality evidence

CI = confidence interval; GRADE = grading of recommendation, assessment, development and evaluation; MD = mean differences; MMO = maximal mouth opening; RCT = randomized controlled trial; RoB = risk of bias; TMD = temporomandibular disorder.

Physiotherapy — Acupuncture or Laser Therapy

Three SRs[21,22,37] examined acupuncture or laser therapy for TMD, and we have critically low confidence in the results from all three SRs. One SR[34] examined dry needling for TMD symptoms, as well as different substance injections. The SRs included a total of 73 primary studies, of which 21 primary studies overlapped with studies in the other SRs, including either overlapping with each other[22,34,37] or with SRs on splint therapy.[26,28]

Overall, much of the evidence regarding acupuncture and laser therapies for the treatment of TMD had unclear or high risk for bias and there was substantial heterogeneity. Interventions that may be associated with improvements in pain are low level laser therapy (LLLT) (versus placebo) and acupuncture (versus sham acupuncture). LLLT may also be associated with improvements in mouth opening (versus placebo). While there were favourable results reported with respect to TMJ clicking noises (acupuncture versus sham or wait list), the significance was inconclusive. Limited information regarding adverse events was reported; one RCT in one SR reported minimal adverse events for patients undergoing needle acupuncture versus occlusal splints. None of the comparisons yielded statistically significantly unfavourable results.

Pain

One SR[21] examined LLLT for pain improvement in TMD. Two SRs[22,37] examined needle acupuncture for pain improvement in TMD. One SR[34] examined dry needling for pain improvement. Comparisons included placebo/sham treatment,[21,22,37] no treatment,[37] occlusal splints, [37] false needling,[34] and injection of other substances.[34] Interventions associated with statistically significantly favourable results regarding pain were various dosages of LLLT and needle acupuncture. The detailed findings are reported in Table 4, and have been summarized here.

Acupuncture and laser therapy interventions with favourable results were:

- LLLT versus placebo (MA; 19 RCTs, low to high quality, very high heterogeneity); statistically significant.[21]
  - Subgroup analyses showed that low dosage, unknown dosage, high dosage, short-term follow-up, and long-term follow-up subgroups all had favourable results.
- Needle acupuncture versus sham acupuncture.
  - Sham: penetrating needle, non-penetrating needle, laser (MA; five RCTs, low to moderate risk of bias); statistically significant in MA.[22]
  - Sham: non-penetrating needle or laser (three RCTs, low and unclear risk of bias); inconclusive.[37]
- Needle acupuncture versus wait list control (three RCTs, unclear and high risk of bias).[37]
- Dry needling versus false needling (two RCTs, low risk of bias), inconclusive.[34]
- Dry needling versus oral methocarbamol/paracetamol (one RCT, high risk of bias), inconclusive.[34]

Acupuncture and laser therapy interventions with neutral results with respect to pain were:

- Needle versus sham acupuncture (nonacupoints) (one RCT, unclear risk of bias).[37]
- Needle acupuncture versus occlusal splints (two RCTs, unclear and high risk of bias).[37]
- Dry needling versus substance injection (local anesthetic, lidocaine) (four RCTs, low and unclear risk of bias).[34]

Table 4: Summary of Acupuncture or Laser Therapy Physiotherapy Interventions for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (number of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Placebo or Sham										
Xu 2018[21]	LLLT	Placebo	Mean difference pain (VAS, unspecified) score from baseline: WMD = 15.43 mm; 95% CI, 3.61 mm to 27.26 mm; *P* = 0.01 I^2 = 98%; Tau^2 = 791.31 Chi^2 = 1,240.82 Df = 22 (*P* < 0.00001) 12 RCTs not included in MA: positive: 8 neutral: 4	Favourable, statistically significant	19 RCTs (679) in MA 12 RCTs not discussed	Jadad quality scored ranged from 3 to 8. (8 = high quality) GRADE not provided.	Low dosage (≤ 50 J/cm2) WMD = 15.09 mm; 95% CI, 5.37 mm to 24.80 mm; *P* = 0.002 I^2 = 93%, Tau^2 = 227.60, Chi^2 = 138.30, df = 10 (*P* < 0.00001)	Favourable, statistically significant	10 RCTs (278)	Jadad quality scored ranged from 4 to 8. GRADE = Very low⊕OOO
							Unknown dosage WMD = 36.31 mm; 95% CI, 10.63 mm to 61.98 mm; *P* = 0.006 I^2 = 99%, Tau^2 = 677.31, Chi^2 = 306.15, df = 3 (*P* < 0.00001)	Favourable, statistically significant	4 RCTs (183)	Jadad quality scored ranged from 3 to 8. GRADE = Low⊕⊕OO
							High dosage (> 50 J/cm2) WMD = 5.52mm; 95% CI, –5.52 mm to 16.56 mm; *P* = 0.33 I^2 = 80%, Tau^2 = 193.98,	Favourable, non-statistically significant	7 RCTs (218)	Jadad quality scored ranged from 4 to 8. GRADE = Low⊕⊕OO

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (number of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
							Chi^2= 35.10, df = 7 (*P* < 0.0001)			
							Short-term follow up (≤ 2 weeks) WMD = 17.66 mm; 95% CI, 9.94 mm to 25.38 mm; *P* < 0.00001 I^2 = 90%, Tau^2 = 146.77, Chi^2= 113.11, df = 11 (*P* < 0.00001)	Favourable, statistically significant	10 RCTs (340)	Jadad quality scored ranged from 3 to 8. GRADE = Low⊕⊕OO
							Long-term follow up (> 2 weeks) WMD = 13.85 mm; 95% CI, –7.73 mm to 35.38 mm; *P* = 0.21 I^2 = 99%, Tau^2 = 1290.12, Chi^2 = 694.10, df = 10 (*P* < 0.00001)	Favourable, non-statistically significant	9 RCTs (339)	Jadad quality scored ranged from 4 to 8. GRADE = Very low⊕OOO
Jung 2011[22]	Needle acupuncture	Sham acupuncture (penetrating needle, non-penetrating needle, laser)	Pain intensity (VAS, 100mm and 10 cm): WMD = –13.63; 95% CI, –21.16 to –6.10; *P* = 0.0004 I^2 = 0%;	Favourable, statistically significant	5 RCTs (107)	Low Cochrane RoB = 4 RCTs Moderate Cochrane RoB= 1 RCT				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (number of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
			Tau^2= 0 Chi^2 = 1.46 df = 4 (*P* = 0.83)							
Cho 2010[37]	Needle acupuncture	Sham acupuncture (non-penetrating needle or laser)	Pain: positive: 2 neutral: 1	Favourable, inconclusive	3 RCTs (65)	Cochrane RoB: Low = 1 Unclear = 2				
Cho 2010[37]	Needle acupuncture	Sham acupuncture (nonacupoints)	Pain: neutral: 1	Neutral	1 RCT (18)	Cochrane RoB: Unclear = 1				
Machado 2018[34]	Dry needling	False needling (short needles)	Pressure pain threshold (PPT): Positive: 2 Pain intensity (VAS): Neutral: 1 (only reported in one RCT)	Favourable, inconclusive	2 RCTs (62 patients)	Cochrane RoB: Low RoB in randomization and blinding, unclear for allocation concealment.				
No Treatment										
Cho 2010[37]	Needle acupuncture	Wait list control	Pain: positive: 3	Favourable	3 RCTs (138)	Cochrane RoB: Unclear = 1 High = 2				
Splint / Occlusal Appliances										
Cho 2010[37]	Needle acupuncture	Occlusal splints	Pain: neutral: 2	Neutral	2 RCTs (160)	Cochrane RoB: Unclear = 1 High = 1				
Pharmacological Oral										
Machado 2018[34]	Dry needling	Methocarbamol/paracetamol (oral)	Pain (VAS): positive	Favourable, inconclusive	1 RCT (21)	Cochrane RoB: blinding high risk of bias, randomization low, allocation unclear.				
Pharmacological — Injections										
Machado 2018[34]	Dry needling	Substance injection (local anesthetic, lidocaine)	Pain improvement: neutral 4	Neutral	4 RCTs (120 patients in 3 trials; unknown in fourth)	Cochrane RoB: Unclear risk of bias in randomization and allocation				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (number of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
						concealment. Low RoB in blinding for 2/4, unclear for 2/4.				

CI = confidence interval; GRADE = grading of recommendation, assessment, development and evaluation; J = Joule; LLLT = low level laser therapy; MD = mean differences: RCT = randomized controlled trial; RoB = risk of bias; SMD = standardized mean difference; VAS = visual analogue scale; WMD = weighted mean difference.

Mouth Opening

One SR[21] examined LLLT versus placebo for maximum active and passive vertical opening. One SR[22] examined needle acupuncture versus sham acupuncture for MMO. One SR[37] examined needle acupuncture compared with sham acupuncture, a wait list control, and occlusal splints. One SR[34] examined dry needling versus false needling or methocarbamol/paracetamol for MMO. The findings are reported in Table 5, and have been summarized here.

Acupuncture and laser interventions that had favourable results:

- LLLT versus placebo, maximum active vertical opening (MA; eight RCTs, medium to high quality, very high heterogeneity); statistically significant in MA.[21]
    - Low dosage, unknown dosage, high dosage, short-term follow up, and long-term follow up subgroups all favourable.
- LLLT versus placebo, maximum passive vertical opening (MA; three RCTs, medium to high quality, very high heterogeneity); statistically significant in MA.[21]
- Needle acupuncture versus sham acupuncture (sham = penetrating needle, non-penetrating needle, laser) (two RCTs, low risk of bias); inconclusive.[22]
- Needle acupuncture versus sham acupuncture (sham = non-penetrating needle or laser) (1 RCT, low risk of bias); inconclusive.[37]
- Needle acupuncture versus wait list control (one RCT, high risk of bias), inconclusive.[37]

Acupuncture or laser interventions with neutral results:

- Needle acupuncture versus occlusal splints (two RCTs, unclear and high risk of bias).[37]
- Dry needling versus false needling (two RCTs, low or unclear risk of bias).[34]
- Dry needling versus oral methocarbamol/paracetamol (one RCT, high risk of bias).[34]

Table 5: Summary of Acupuncture or Laser Therapy Physiotherapy Interventions for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Placebo or Sham										
Xu 2018[21]	LLLT	Placebo	MAVO WMD = 6.37 mm; 95% CI, 2.82 mm to 9.93mm; *P* = 0.0004 I^2 = 95%; Tau^2 = 26.47 Chi^2 = 155.78 df = 8 (*P* < 0.0001)	Favourable, statistically significant	8 RCTs (301) in MA	Jadad quality scored ranged from 4 to 8. GRADE not provided.	Low dosage (≤ 50 J/cm^2) WMD = 6.41 mm; 95% CI, –0.84 mm to 13.66 mm; *P* = 0.08 I^2 = 95%, Tau^2 = 63.49, Chi^2 = 82.27, df = 4 (*P* < 0.00001)	Favourable, non-statistically significant	5 RCTs (145)	Jadad quality scored ranged from 4 to 8. GRADE = Very low⊕OOO
							Unknown dosage WMD = 8.09 mm; 95% CI, 3.73 mm to 12.45 mm; *P* = 0.0003 I^2 = 91%, Tau^2 = 9.00, Chi^2 = 10.97, df = 1 (*P* = 0009)	Favourable, statistically significant	2 RCTs (111)	Jadad quality scored ranged from 4 to 8. GRADE = Very low⊕OOO
							High dosage (> 50 J/cm^2) WMD = 4.18 mm; 95% CI, 2.4 mm to 5.94 mm; *P* < 0.00001 I^2 = 0%, Tau^2= 0, Chi^2= 0.52 df = 1 (*P* = 0.47)	Favourable, statistically significant	1 RCT (45)	Jadad quality scored ranged from 4 to 8. GRADE = Low⊕ ⊕ OO

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
							Short-term follow up (≤ 2 weeks) WMD = 8.32 mm; 95% CI, –6.16 mm to 22.80mm; *P* = 0.26 I^2 = 98%, Tau ^{2}= 106.81, Chi^2 = 45.33, df = 1 (*P* < 0.00001)	Favourable, non-statistically significant	2 RCTs (60)	Jadad quality scored ranged from 4 to 8. GRADE = Low⊕OOO
							Long-term follow up (> 2 weeks) WMD = 5.79 mm; 95% CI, 3.18 mm to 8.39 mm; *P* < 0.0001 I^2 = 84%, Tau^2 = 9.37, Chi^2 = 37.65, df = 6 (*P* < 0.00001)	Favourable, statistically significant	6 RCTs (241)	Jadad quality scored ranged from 4 to 8. GRADE = Low⊕⊕OO
Xu 2018[21]	LLLT	Placebo	MPVO WMD = 6.96 mm; 95% CI, 1.99 mm to 11.93mm; *P* = 0.006 I^2 = 92%; Tau^2 = 16.26, Chi^2 = 23.90, df = 2 (*P* < 0.00001)	Favourable, statistically significant	3 RCTs (144)	Jadad quality scored ranged from 5 to 8. GRADE not provided.				
Jung 2011[22]	Needle acupuncture	Sham acupuncture (penetrating needle, non-penetrating needle, laser)	Maximum mouth opening: positive: 1 neutral: 1	Favourable, inconclusive	2 RCTs	Low Cochrane RoB = 2 RCTs				
Cho 2010[37]	Needle acupuncture	Sham acupuncture (non-penetrating needle)	MO: positive:1	Favourable, inconclusive	1 RCT (27)	Cochrane RoB: Low = 1				
Machado 2018[34]	Dry needling	False needling (short needles)	MMO: positive 1, neutral 1.	Neutral	2 RCTs (62 patients)	Cochrane RoB: Low risk of bias				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
						in randomization and blinding, unclear for allocation concealment.				
No treatment										
Cho 2010[37]	Needle acupuncture	Wait list control	MO: positive: 1	Favourable, inconclusive	1 RCT (38)	Cochrane RoB: High = 1				
Splint/ Occlusal appliances										
Cho 2010[37]	Needle acupuncture	Occlusal splints	MO: neutral: 2	Neutral	2 RCTs (160)	Cochrane RoB: Unclear = 1 High = 1				
Pharmacological Oral										
Machado 2018[34]	Dry needling	Methocarbamol/paracetamol	MMO: neutral	Neutral	1 RCT (21)	Cochrane RoB: blinding high risk of bias, randomization low, allocation unclear.				

CI = confidence interval; GRADE = grading of recommendation, assessment, development and evaluation; J = Joule; LLLT = low level laser therapy; MD = mean differences: MAVO = maximum active vertical opening; MMO = maximal mouth opening; MO = mouth opening; MPVO = maximum passive vertical opening; RCT = randomized controlled trial; RoB = risk of bias; SMD = standardized mean difference; WMD = weighted mean difference.

TMJ Clicking

One SR[21] examined LLLT versus placebo for TMJ noises. One SR[37] examined needle acupuncture compared with sham acupuncture, a wait list control, and occlusal splints for TMJ noises. Of the comparisons reported, results were either favourable or neutral; none of the SRs reported unfavourable results with respect to TMJ clicking. The detailed findings are reported in Table 6, and have been summarized here.

Acupuncture or laser interventions with favourable results:

- Needle acupuncture versus sham acupuncture (non-penetrating needle) (one RCT, low risk of bias), inconclusive.[37]
- Needle acupuncture versus wait list control (one RCT, high risk of bias), inconclusive.[37]

Acupuncture or laser interventions with neutral results:

- LLLT versus placebo (three RCTs, low to medium quality).[21]
- Needle acupuncture versus occlusal splints (two RCTs, unclear and high risk of bias).[37]

Table 6: Summary of Acupuncture or Laser Therapy Physiotherapy Interventions for TMJ Clicking

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Xu 2018[21]	LLLT	Placebo	positive: 1 neutral: 2	Neutral	3 RCTs	Jadad score positive study = 3 neutral studies = 5, 6
Cho 2010[37]	Needle acupuncture	Sham acupuncture (non-penetrating needle)	Joint sound: positive:1	Favourable, inconclusive	1 RCTs (27)	Cochrane RoB: Low = 1
No Treatment						
Cho 2010[37]	Needle acupuncture	Wait list control	Joint sound: positive: 1	Favourable, inconclusive	1 RCT (38)	Cochrane RoB: High= 1
Splint/ Occlusal Appliances						
Cho 2010[37]	Needle acupuncture	Occlusal splints	Joint sound: neutral: 2	Neutral	2 RCTs (150)	Cochrane RoB: Unclear = 1 High = 1

LLLT = low level laser therapy; RCT = randomized controlled trial; RoB = risk of bias.

Adverse Events

Adverse events were not well reported in the primary studies captured in the SRs for acupuncture or LLLT in TMD. The findings are reported in Table 7. In one SR,[21] nine RCTs (medium to high quality) reported no adverse events, but the other 22 primary studies did not report on adverse events. Two SRs[22,37] reported that only one primary study reported on adverse events when comparing needle acupuncture with sham laser therapy; this primary study overlapped between the SRs and reported no adverse events. One RCT (high risk of bias) reported that there were minimal adverse events in the SR comparing needle acupuncture with occlusal splints.[37] The other studies in these SRs did not report on adverse events.

Table 7: Summary of Acupuncture or Laser Therapy Physiotherapy Interventions for Adverse Events in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Xu 2018[21]	LLLT	Placebo	No adverse events reported	Favourable	9 RCTs	Jadad scores from 4 to 8
Jung 2011[22]	Needle acupuncture	Sham laser acupuncture	No adverse events reported	Favourable, inconclusive	1 RCT	Low Cochrane RoB
Cho 2010[37]	Needle acupuncture	Sham laser acupuncture	No adverse events reported	Favourable, inconclusive	1 RCT	Unclear Cochrane RoB
Splint/ Occlusal Appliances						
Cho 2010[37]	Needle acupuncture	Occlusal splints	Minimal adverse events	Unfavourable, inconclusive	1 RCT	High Cochrane RoB

LLLT = low level laser therapy; RCT = randomized controlled trial; RoB = risk of bias.

Physiotherapy — Manual Therapy

Two SRs[23,24] examined the effects of manual therapy for TMD, and we have critically low confidence in the results from both SRs. These SRs reported on 57 primary studies and examined a variety of manual therapies such as jaw or neck exercises. The SR by Armijo-Olivo et al.[24] included 49 primary studies, of which 13 overlapped with primary studies across multiple SRs. The SR by Martins et al.[23] examined eight primary studies, half of which studies overlapped with the other manual therapy SR.[24] The SR by Armijo-Olivo et al.[24] examined their results based on type of TMD: arthrogenous, myogenous, or mixed; whereas the SR conducted by Martins et al.[23] grouped all TMD types together.

Overall, much of the evidence regarding manual and physical therapies for the treatment of TMD was of moderate quality. Interventions that may be associated with improvements in pain are manual therapy targeted to the orofacial region (versus other controls; in patient with myogenous TMD) and manual therapy plus jaw exercises (versus other control; in patients with arthrogenous TMD). Musculoskeletal manual approaches (versus active control) may be associated with unfavourable pain results. Posture correcting exercises (versus no treatment; in patients with myogenous TMD), musculoskeletal manual approaches (versus active control), manual therapy plus jaw exercises (versus other control; in patients with arthrogenous TMD), and manual therapy plus exercises (versus other control; patients with mixed types of TMD) may be associated with improvements in mouth opening. None of the comparisons yielded statistically significantly unfavourable results. Adverse events and TMJ clicking noises were not reported.

Pain

Two SRs[23,24] reported on a variety of manual therapies or exercises for improving pain in TMD. Both SRs used control groups that combined two or more alternatives (either treatment [e.g., botulinum toxin, splint, and education] or no treatment) into one control group. No direct comparisons were made between manual physiotherapy and other classes of interventions. The findings are reported in Table 8, and have been summarized below.

Physiotherapy interventions with favourable results with respect to pain:

- Jaw exercises alone or combined with exercise program versus other control (in patients with myogenous TMD) (MA; five RCTs, moderate quality), NS.[24]
- Jaw or neck exercises alone or as part of a conservative regimen versus other control (in patients with arthrogenous TMD) (MA; four RCTs, low quality), NS.[24]
- Manual therapy targeted to the orofacial region versus other control (in patients with myogenous TMD) (MA; three RCTs, moderate quality), statistically significant in MA.[24]
- Manual therapy plus jaw exercises versus other control (in patients with arthrogenous TMD) (MA; five RCTs, moderate quality), statistically significant in MA.[24]

Physiotherapy interventions with unfavourable results:

- Musculoskeletal manual approaches versus active control (MA; three RCTs, high quality), statistically significant in MA.[23]
- General jaw exercise program versus other control (mixed TMD) (MA; five RCTs, moderate quality), NS.[24]

Table 8: Summary of Manual Physiotherapy Interventions for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary studies and/or Body of Evidence (reported by SR authors)
Other treatments						
Martins 2016[23]	Musculoskeletal manual approaches	Active control (conventional conservative treatment, usual care, home exercises)	Pain (VAS, unspecified) during active mouth opening: MD 1.70; 95% CI, 0.98 to 2.43; $P < 0.00001$; random effects $I^2 = 22\%$; $Tau^2 = 0.10$; $Chi^2 = 2.58$; df = 2 ($P = 0.28$)	Unfavourable, statistically significant	3 RCTs (128)	PEDro scale (out of 10): 6 (high quality): 3 RCTs
Armijo-Olivo 2016[24]	Jaw exercises alone or combined with exercise program in myogenous TMD	Other therapy (education or splint)	Reduced pain intensity: SMD = 0.43; 95% CI, –0.02 to 0.87; $I^2 = 49\%$ ($P = 0.10$)	Favourable, non-statistically significant	5 RCTs (175)	High Cochrane RoB for most of the studies. Concealment of allocation unclear for 4 studies, and 1 study was not concealed. Adherence and co-interventions were unclear for most of the studies. No intention to treat for 4 studies. GRADE = Moderate quality because of RoB
Armijo-Olivo 2016[24]	Manual therapy targeted to the orofacial region in myogenous TMD	Other therapy (wait list, self-care and exercises, botulinum toxin)	Reduced pain intensity: MD = 1.35 cm; 95% CI, 0.91 to 1.78; $I^2 = 0\%$ ($P = 0.78$)	Favourable, statistically significant	3 RCTs (88)	Cochrane RoB: Concealment of allocation unclear for 2 of the studies, and 1 study was not concealed. Adherence and co-interventions unclear for all studies. No intention to treat for 2 studies. GRADE = Moderate quality because of RoB
Armijo-Olivo 2016[24]	Jaw/neck exercises alone or as part of a conservative	Other therapy (education, splint, no	Reduced pain intensity: SMD = 0.68; 95% CI, –0.04 to	Favourable, non-statistically significant	4 RCTs (146)	Cochrane RoB: Concealment of allocation unclear for all studies. Blinding was unclear for 3 of the studies, and 1 study did not have

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary studies and/or Body of Evidence (reported by SR authors)
	regimen in arthrogenous TMD	treatment)	1.40; random effects; I^2 = 73% (*P* =0.01)			appropriate blinding. Adherence and co-interventions unclear for all studies. No intention to-treat analysis for 2 studies. GRADE = Low quality because of RoB and inconsistency.
Armijo-Olivo 2016[24]	Manual therapy plus jaw exercises in arthrogenous TMD	Other therapy (splint, self-care, medication)	Reduced pain intensity: SMD = 0.40; 95% CI, 0.13 to 0.68; *P* = 0.004; I^2 = 0%; Tau^2 = 0.00; Chi^2 = 2.90; df = 4 (*P* = 0.58)	Favourable, statistically significant	5 RCTs (213)	Cochrane RoB: Concealment of allocation unclear for most of the studies. Blinding was appropriate for most of the studies. Adherence unclear for most of the studies. No or unclear intention to treat for 2 studies. GRADE = Moderate quality because of RoB.
Armijo-Olivo 2016[24]	General jaw exercise program in mixed TMD	Other therapy (splint, education, standard conservative care)	Reduced pain intensity: SMD = –0.06; 95% CI, –0.50 to 0.38; I^2 = 41% (*P* = 0.14)	Unfavourable, non-statistically significant	5 RCTs (162)	Cochrane RoB: Concealment of allocation unclear for 4 of the studies. One study did not have appropriate allocation concealment. Appropriate blinding was unclear for most of the studies. Adherence and co-interventions unclear for all studies. GRADE = Moderate quality because of RoB.

CI = confidence interval; GRADE = grading of recommendation, assessment, development and evaluation; MD = mean differences: PEDro = Physiotherapy Evidence Database; RCT = randomized controlled trial; RoB = risk of bias; SMD = standardized mean difference; TMD = temporomandibular disease; VAS = visual analogue scale.

Mouth Opening

Two SRs[23,24] reported on a variety of manual therapies or exercises for improving MMO in TMD. Comparisons included no treatment, surgery, and control groups that combined two or more alternatives (treatments or no treatment) into one control group. The findings are reported in Table 9, and have been summarized.

Physiotherapy interventions with favourable results:

- Posture correcting exercises (in patients with myogenous TMD) versus no treatment (MA; two RCTs, moderate quality), statistically significant in MA.[24]
- Manual therapy versus no treatment (mixed TMD) (MA; two RCTs, low quality), NS.[24]
- Musculoskeletal manual approaches versus active control (MA; five RCTs, low and high quality), statistically significant in MA.[23]
- Jaw exercises alone or combined with exercise program versus other control (in patients with myogenous TMD) (MA; four RCTs, low quality), NS.[24]
- Jaw or neck exercises alone or as part of a conservative regimen versus other control (in patients with arthrogenous TMD) (MA; three RCTs, low quality), NS[24]
- Manual therapy plus jaw exercises versus other control (in patients with arthrogenous TMD) (MA; four RCTs, moderate quality), statistically significant in MA.[24]
- Manual therapy plus exercises versus other control (patients with mixed types of TMD) (MA; two RCTs, moderate quality), statistically significant in MA[24]

Physiotherapy interventions with unfavourable results with respect to mouth opening:

- Jaw or neck exercises alone or as part of a conservative regimen versus exercises plus arthrocentesis or arthroscopy (in patients with arthrogenous TMD) (MA; two RCTs, low quality), NS.[24]
- General jaw exercise program versus other control (mixed TMD) (MA; seven RCTs, moderate quality), NS.[24]

Table 9: Summary of Manual Physiotherapy Interventions for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
No Treatment						
Armijo-Olivo 2016[24]	Posture correcting exercises in myogenous TMD	No treatment control	Maximum pain free opening: MD = 5.54 mm; 95% CI, 2.93 to 8.15; $P < 0.0001$; $I^2 = 6\%$; $Tau^2 = 0.21$; $Chi^2 = 1.06$; df = 1 ($P = 0.30$)	Favourable, statistically significant	2 RCTs (100)	Unclear Cochrane RoB for both studies. Concealment of allocation unclear for both studies, no intention-to-treat analysis. GRADE = Moderate quality because of RoB.
Armijo-Olivo 2016[24]	Manual therapy and mixed TMD	No treatment control	Mouth opening: MD = 17.33 mm; 95% CI, –10.39 to 45.08; random effects; $I^2 = 100\%$ ($P = 0.000001$)	Favourable, non-statistically significant	2 RCTs (96)	Cochrane RoB: The concealment of the allocation is unclear for both studies. Appropriate blinding was unclear for one study. The intention to treat was unclear for one study. GRADE = Low quality because of RoB, inconsistency, and imprecision.
Surgical						
Armijo-Olivo 2016[24]	Jaw/neck exercises alone or as part of a conservative regimen in arthrogenous TMD	Exercises plus arthrocentesis or arthroscopy	Active mouth opening: MD = –1.01mm; 95% CI, –5.43 to 3.42; random effects; $I^2 = 76\%$ ($P = 0.04$)	Unfavourable, non-statistically significant	2 RCTs (131)	Cochrane RoB: Concealment of allocation not appropriate for both studies. Blinding was not appropriate for both studies. Adherence and co-interventions unclear for both studies. GRADE = Low quality because of RoB and inconsistency.
Other Treatment						
Martins 2016[23]	Musculoskeletal manual approaches	Active control (superficial massage; splint; conventional conservative treatment such as usual care, home exercises)	Active MMO: SMD 0.83; 95% CI, 0.42 to 1.25; $P < 0.0001$; random effects $I^2 = 44\%$; $Tau^2 = 0.10$ $Chi^2 = 7.19$ Df = 4 ($P = 0.13$)	Favourable, statistically significant	5 RCTs (311)	PEDro scale (out of 10): 5 (low quality): 2 RCTs 6 (high quality): 3 RCTs
Armijo-Olivo 2016[24]	Jaw exercises alone or combined with exercise program in myogenous TMD	Other therapy (education or splint therapy)	Maximum pain free opening: MD = 5.94 mm; 95% CI, –1.0 to 12.87; random effects; $I^2 = 88\%$ ($P < 0.00001$)	Favourable, non-statistically significant	4 RCTs (131)	Unclear Cochrane RoB for most of the studies. Concealment of allocation not clear for 3 studies, and 1 study was not concealed. All studies did not perform intention-to-treat analysis. GRADE= Low quality because of RoB and inconsistency.
Armijo-Olivo 2016[24]	Jaw/neck Exercises Alone or as Part of a	Other therapy (education, splint therapy, or no	Active mouth opening: MD = 3.13 mm; 95% CI, –1.96 to	Favourable, non-statistically significant	3 RCTs (126)	Cochrane RoB: Concealment of allocation not clear for all studies. Blinding was unclear for 2 of the studies, and 1 study did not have appropriate

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
	Conservative Regimen in Arthrogenous TMD	treatment)	8.23; random effects; I^2 = 79% (*P* = 0.009)			blinding. Adherence and co-interventions unclear for all of the studies. GRADE = Low quality because of RoB and inconsistency.
Armijo-Olivo 2016[24]	Manual Therapy Plus Jaw Exercises in Arthrogenous TMD	Other therapy (splint, self-care, medication)	Active mouth opening: MD = 3.58 mm; 95% CI, 1.46 to 5.70; I^2 = 0% (*P* = 0.93)	Favourable, statistically significant	4 RCTs (152)	Cochrane RoB: Concealment of allocation unclear for all studies. Blinding was appropriate for most of the studies. Adherence unclear for all studies. GRADE = Moderate quality because of RoB.
Armijo-Olivo 2016[24]	General Jaw Exercise Program in Mixed TMD	Other therapy (splint, education, standard conservative care)	Mouth opening: MD = –0.25 mm; 95% CI, –2.08 to 1.57; *P* = 0.79 I^2 = 0%; Tau^2 = 0.00 Chi^2 = 2.63 df = 6 (*P* = 0.85)	Unfavourable, non-statistically significant	7 RCTs (270)	Cochrane RoB: Concealment of allocation unclear for 4 of the studies. Three studies did not have appropriate allocation concealment. Appropriate blinding was unclear for most of the studies. Adherence and co-interventions unclear for all studies. Most of the studies did not perform an intention-to-treat analysis. GRADE= Moderate quality because of RoB.
Armijo-Olivo 2016[24]	Manual Therapy Plus Exercises for Mixed TMD	Other therapy (home exercises and education)	Mouth opening: MD = 6.10 mm; 95% CI, 1.11 to 11.09; random effects; I^2 = 82% (*P* =0.02)	Favourable, statistically significant	2 RCTs (83)	Cochrane RoB: Concealment of allocation unclear for both studies. Appropriate blinding was unclear for one study and not appropriate for the other study. The intention to treat was unclear for one study and not performed for the other study. GRADE = Moderate quality because of inconsistency.

CI = confidence interval; GRADE = grading of recommendation, assessment, development and evaluation; MD = mean differences: MO = mouth opening; MMO = maximal mouth opening; PEDro = Physiotherapy Evidence Database; RCT = randomized controlled trial; RoB = risk of bias; SMD = standardized mean difference; TMD = temporomandibular disease.

Splint Therapy

Three SRs[25,26,28] examined splint therapy for TMD treatment, and we had critically low confidence in the results from all three SRs. These SRs reported on 89 primary studies, with more than half of the studies within each SR overlapping with the primary studies from the other splint therapy SRs or SRs on other topics.

Stabilization splints (versus non-occluding appliances), splints (hard, soft, or unspecified; versus other control) and hard stabilization appliances (versus non-occluding appliances) may be associated with improvements in pain scores. None of the comparisons yielded statistically significantly unfavourable results with respect to pain scores. Splints (hard, soft, or unspecified) (versus other control) may be associated with improvements in mouth opening; however, one SR found that stabilization splints (versus other control) had unfavourable results. None of the comparisons examining TMJ clicking yielded statistically significantly favourable or unfavourable results. Adverse events were not well reported and the study reporting adverse events had statistically inconclusive results.

Pain

Three SRs[25,26,28] examined various splint therapies compared with other splints, appliances, placebo, or other controls for pain improvement in TMD. The findings are reported in Table 10, and have been summarized here.

Splint therapy interventions with favourable results were:

- Stabilization splint versus non-occluding appliances (MA; six RCTs, low to high quality), statistically significant in MA.[25]
- Stabilization splint versus other control (MA, seven RCTs, mostly low to high quality, high heterogeneity), NS.[25]
- Splint (hard, soft, or unspecified) versus other control (MA; six RCTs, very high or high risk of bias), statistically significant in MA.[28]
- Soft resilient appliance versus placebo (one RCT, low quality), inconclusive.[26]
- Hard stabilization appliance versus no treatment (MA; three RCTs, low quality), NS.[26]
- Soft resilient appliance versus no treatment or palliative treatment (one RCT, low quality), inconclusive.[26]
- Hard stabilization appliance versus transcutaneous nerve stimulation (TENS) (three RCTs, low quality), inconclusive.[26]
- Hard stabilization appliances versus occlusal adjustments (one RCT, low quality), inconclusive.[26]
- Hard stabilization appliances versus non-occluding appliances (MA; seven RCTs, moderate quality), statistically significant in MA.[26]
- Stabilization appliance versus pharmacological agent (analgesic or antidepressant) (two RCTs, very low to low quality), inconclusive.[26]
- Stabilization appliance versus anterior positioning appliance (two RCTs, low to moderate quality), inconclusive.[26]
- Stabilization appliance versus anterior bite plate (one RCT, low quality), inconclusive.[26]
- Stabilization appliance versus nociceptive trigeminal inhibition (NTI) appliance (two RCTs, moderate quality), inconclusive.[26]

Splint interventions with neutral results:

- Stabilization splint versus other control (MA; six RCTs, moderate to high quality).[25]
- Hard stabilization appliances versus behavioural therapy (five RCTs, moderate quality).[26]
- Flat appliance versus behavioural feedback (one RCT, low quality).[26]
- Hard stabilization appliance versus self-care (one RCT, high quality).[26]
- Stabilization appliance at night versus jaw exercises (one RCT, low quality).[26]
- Soft resilient appliances versus Acuhealth (electronic acupuncture point simulator) (one RCT, low quality).[26]
- Anterior positioning appliance 24 hours a day versus anterior positioning appliance daytime or nighttime only (two RCTs, low quality).[26]
- Stabilization appliance versus localized occlusal interference device (one RCT, low quality).[26]

Splint interventions with unfavourable results:

- Stabilization splint versus occlusal appliances (MA; six RCTs, low quality), NS.[25]
- Soft resilient (anterior positioning) appliance versus manual mobilization and exercises (one RCT, low quality), inconclusive.
- Hard stabilization appliance versus acupuncture (MA; three RCTs, low quality), NS.[26]
- Hard stabilization appliances versus disc-repositioning onlays (one RCT, very low quality), inconclusive.[26]
- Stabilization appliance 1 mm thick versus stabilization appliance 4.42 mm thick or 8.15 mm thick (one RCT, low quality), inconclusive.[26]

Table 10: Summary of Splint Therapy for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Fricton 2010[26]	Soft resilient appliance	Placebo	Pain improvement: positive	Favourable, inconclusive	1 RCT (40)	Quality score 53%. Did not meet minimum level I criteria
No Treatment						
Fricton 2010[26]	Hard stabilization appliances	No treatment	Pain improvement: OR = 2.14; 95% CI, 0.80 to 5.75; Random effects; Z value = 1.51; *P* = 0.12 Heterogeneity *P* = 0.13	Favourable, non-statistically significant	3 RCTs (216)	Quality score 58% Only 1 RCT met minimum level I criteria
Fricton 2010[26]	Soft resilient appliance	No treatment or palliative treatment	Pain improvement: positive	Favourable, inconclusive	1 RCT (30)	Quality score 47%. Did not meet minimum level I criteria
Psychological						
Fricton 2010[26]	Hard stabilization appliances	Behavioural therapy (biofeedback, stress management)	Pain improvement (≤ 8 weeks): positive or neutral (5 RCTs) Pain improvement (6 to 12 months): (high-quality studies) positive or negative. (additional studies): neutral	Neutral	5 RCTs (≤ 8 weeks; 185) 4 RCTs (6 to 12 months; 215)	Quality score 59%. 2 RCTs met minimum level I criteria
Fricton 2010[26]	Flat appliance	Behavioural therapy (biofeedback)	Pain improvement: neutral	Neutral	1 RCT (30)	Quality score: 47%. Did not meet minimum level I criteria
Fricton 2010[26]	Hard stabilization appliances (flat plane hard acrylic)	Self-care	Pain improvement (3 and 12 months): neutral	Neutral	1 RCT (132)	Quality score: 87%. Met minimum level I criteria
Physiotherapy — Manual Therapy/Exercise Therapy						
Fricton 2010[26]	Hard stabilization appliances	Transcutaneous nerve stimulation (TENS)	Pain improvement: Positive: 2 neutral: 1	Favourable, inconclusive	3 RCTs (69)	Quality score 49%, No RCTs met minimum level I criteria
Fricton 2010[26]	Stabilization appliance at night	Jaw exercises	Pain improvement: neutral	Neutral	1 RCT (23)	Quality score 40%. Did not meet minimum level I criteria

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Fricton 2010[26]	Soft resilient appliance (soft anterior positioning appliance)	Manual mobilization and exercises	Pain improvement: negative	Unfavourable, inconclusive	1 RCT (36)	Quality score 53%. Did not meet minimum level I criteria
Physiotherapy — Acupuncture						
Fricton 2010[26]	Hard stabilization appliances	Acupuncture	Pain improvement: OR = 0.58; 95% CI, 0.12 to 2.90; Random effects; Heterogeneity *P* = 0.008	Unfavourable, non-statistically significant	3 RCTs (167)	Quality score 56%. No RCTs met minimum level I criteria
Fricton 2010[26]	Soft resilient appliances	Acuhealth (electronic acupuncture point simulator)	Pain improvement: neutral	Neutral	1 RCT (40)	Quality score 53%. Did not meet minimum level I criteria
Splint/ Occlusal Appliances						
Pficer 2017[25]	Stabilization splint	Occlusal appliances	Pain reduction short term (≤ 3 months): OR = 0.74; 95% CI, 0.45 to 1.22; *P* = 0.24 I^2 = 0%; Tau^2 = 0.0, Chi^2= 2.02, df = 5 (*P* =0.85)	Unfavourable, non-statistically significant	6 RCTs (289)	Jadad quality score: 2: 3 RCTs 3: 3 RCTs
Fricton 2010[26]	Hard stabilization appliances	Occlusal adjustment	Pain improvement: positive	Favourable, inconclusive	1 RCT (30)	Quality score 47%. Did not meet minimum level I criteria
Pficer 2017[25]	Stabilization splint	Non-occluding appliances	Pain reduction short term (≤ 3 months): OR = 4.18; 95% CI, 2.17 to 8.03; *P* < 0.0001 I^2 = 16%; Tau^2 = 0.11, Chi^2= 5.93, df = 5 (*P* =0.31)	Favourable, statistically significant	6 RCTs (251)	Jadad quality score: 2: 1 RCT 3: 1 RCT 4: 1 RCT 5 (high quality): 3 RCTs
Fricton 2010[26]	Hard stabilization appliances	Non-occluding appliances	Pain improvement: OR = 2.45; 95% CI, 1.56 to 3.86; Random effects; Z value = 3.89; *P* = 0.00 Heterogeneity *P* = 0.86	Favourable, statistically significant	7 RCTs (385)	Quality score: 66%. 3 met minimum level I criteria
Fricton 2010[26]	Hard stabilization appliances	Disc-repositioning onlays	Pain improvement: negative	Unfavourable, inconclusive	1 RCT (41)	Quality score 33%. Did not meet minimum level I criteria
Fricton 2010[26]	Anterior positioning appliance (24 hours)	Anterior positioning appliance daytime or nighttime only	Pain improvement (1 month and 3 months): neutral	Neutral	2 RCTs (140)	Quality scores 47% and 53%. Did not meet minimal level I criteria
Fricton 2010[26]	Stabilization appliance	Anterior positioning appliance	Pain improvement: positive Success (50% functional pain reduction, 20% increase mouth opening): positive	Favourable, inconclusive	2 RCTs (96)	Quality scores 40% and 67%. Did not meet minimal level I criteria
Fricton 2010[26]	Stabilization appliance (1 mm thick)	Stabilization appliance (4.42 mm thick or 8.15 mm thick)	Pain improvement (1 mm versus others; 1 month): negative	Unfavourable, inconclusive	1 RCT (60)	Quality score 60%. Did not meet minimal level I criteria
Fricton 2010[26]	Stabilization appliance	Anterior bite plate	Pain improvement: positive	Favourable, inconclusive	1 RCT (19)	Quality score 47%. Did not met minimal level I criteria

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Fricton 2010[26]	Stabilization appliance	Localized occlusal interference device	Pain improvement neutral	Neutral	1 RCT (55)	Quality score 40%. Did not met minimal level I criteria
Fricton 2010[26]	Stabilization appliance	Nociceptive trigeminal inhibition appliance	Pain improvement: positive: 1 neutral 1 (higher quality)	Favourable, inconclusive	2 RCTs (66)	Quality scores 60% and 73%. One of two met level I criteria
Pharmacological Oral						
Fricton 2010[26]	Stabilization appliance	Pharmacological (analgesics and antidepressants)	Pain improvement: positive or neutral.	Favourable, inconclusive	2 RCTs (66)	Quality score 27% and 47%. Did not meet minimum level I criteria
Other Treatments						
Pficer 2017[25]	Stabilization splint	Control (acupuncture, laser therapy, no treatment, counselling, behavioural therapy)	Pain reduction short term (≤ 3 months): OR = 2.77; 95% CI, 0.85 to 9.05; *P* = 0.09 I^2 = 76%; Tau^2 = 1.85, Chi^2= 24.81, df = 6 (*P* =0.0004)	Favourable, non-statistically significant	7 RCTs (308)	Jadad quality score: 2: 5 RCTs 3: 1 RCT 5 (high quality): 1 RCT
Pficer 2017[25]	Stabilization splint	Control (non-occluding appliances, occlusal appliances, no treatment)	Pain reduction long term (> 3 months): OR = 1.01; 95% CI, 0.26 to 3.96; *P* = 0.99 I^2 = 79%; Tau^2 = 2.26, Chi^2= 23.97, df = 5 (*P* = 0.0002)	Neutral	6 RCTs (251)	Jadad quality score: 3: 5 RCTs 5 (high quality): 1 RCT
Zhang 2016[28]	Splint (hard, soft, or unspecified)	Control (control appliance, biofeedback/ stress management, arthrocentesis, physical therapy)	Perceived pain on VAS (unspecified): WMD = 2.02, 95% CI, 1.55 to 2.49; I^2 = 0% (*P* = 0.558)	Favourable, statistically significant	6 RCTs (unclear)	Cochrane RoB high or very high for all studies

CI = confidence interval; OA = osteoarthritis; OR = odds ratio; RCT = randomized controlled trial; RoB = risk of bias; TMD = temporomandibular disease; TMJ = temporomandibular joint; VAS = visual analogue scale.

Note: Quality score as defined by Fricton et al.: The percentage was based on 15 items selected from the CONSORT reporting standard as assessing quality rather than only reporting. The number of items considered adequately met was divided. The minimal level I criteria for low risk of bias were randomization process, blinding of outcome methods, comparable groups, and handling of withdrawals or dropouts in the data analysis, identified as part of a quality appraisal based on CONSORT.[26]

Mouth Opening

Three SRs[25,26,28] examined splint therapies versus other interventions for MMO improvement in TMD. The findings are reported in Table 11, and have been summarized here.

Splint interventions with favourable results:

- Splint (hard, soft, or unspecified) versus other control (MA; five RCTs, very high risk of bias), statistically significant in MA.[28]

Splint interventions with neutral results:

- Hard stabilization appliances versus behavioural therapy (two RCTs, low and high quality).[26]
- Flat appliance versus behavioural therapy (one RCT, low quality).[26]

- Hard stabilization appliance versus self-care (one RCT, high quality).[26]
- Hard stabilization appliance versus non-occluding appliances (four RCTs, low to moderate quality).[26]
- Anterior positioning appliance for 24 hours versus anterior positioning appliance daytime or nighttime (two RCTs, low quality).[26]
- Stabilization appliance versus nociceptive trigeminal inhibition (NTI) appliance (one RCT, moderate quality).[26]
- Stabilization appliance versus pivot appliance (one RCT, moderate quality).[26]

Splint interventions with unfavourable results:

- Stabilization splint versus other control (MA; seven RCTs, low to high quality), statistically significant in MA.[25]
- Soft resilient appliances versus manual mobilization and exercises (one RCT, low quality), inconclusive,[26]

Table 11: Summary of Splint Therapy for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or body of Evidence (reported by SR authors)
Psychological						
Fricton 2010[26]	Hard stabilization appliances	Behavioural therapy (biofeedback, stress management)	Mouth opening (≤ 8 weeks: positive 1, neutral 1. Mouth opening (6 months): Negative 1.	Neutral	2 RCTs (68)	Quality score: 40% and 87%. One met minimum level I criteria for reducing bias
Fricton 2010[26]	Flat appliance	Behavioural therapy (biofeedback)	Mouth opening (range of motion): neutral	Neutral	1 RCT (30)	Quality score: 47%. Did not meet minimum level I criteria for reducing bias
Fricton 2010[26]	Hard stabilization appliances (flat plane hard acrylic)	Self-care	Range of motion, joint sounds, etc. (3 and 12 months): neutral	Neutral	1 RCT (132)	Quality score: 87% Met minimum level I criteria
Physiotherapy Manual Therapy						
Fricton 2010[26]	Soft resilient appliance (soft anterior positioning appliance)	Manual mobilization and exercises	Mouth opening improved: negative	Unfavourable, inconclusive	1 RCT (36)	Quality score 53%. Did not meet minimum level I criteria
Splint/ Occlusal Appliances						
Fricton 2010[26]	Hard stabilization appliances	Non-occluding appliances	Mouth opening: positive 2, neutral 2.	Neutral	4 RCTs (250)	Quality scores: 53% to 67%. One RCT met minimum level I criteria
Other Appliances						
Pficer 2017[25]	Stabilization splint	Control (non-occluding appliances, occlusal appliances, physical therapy, laser therapy,	MMO: SMD = –0.30; 95% CI, –0.59 to –0.01;	Unfavourable, statistically significant	7 RCTs (298)	Jadad quality score: 3: 5 RCTs 4:1 RCT 5 (high quality): 1

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or body of Evidence (reported by SR authors)
		exercise and counselling)	*P* = 0.04 I^2 = 33%; Tau^2= 0.05 Chi^2= 9.01, df = 6 (*P* =0.17)			RCT
Zhang 2016[28]	Splint (hard, soft, or unspecified)	Control (control appliance, arthrocentesis, no treatment, self-care)	Change in MMO: MD = 5.39 mm, 95% CI, 3.96 mm to 6.81 mm; I^2 = 48.9% (*P* = 0.098)	Favourable, statistically significant	5 RCTs (122)	All very high Cochrane RoB
Fricton 2010[26]	Anterior positioning appliance 24 hours	Anterior positioning appliance daytime or nighttime only	Range of motion (3 months): positive. Limited opening (3 months): neutral	Neutral	2 RCTs (140)	Quality scores 47% and 53%. Did not meet minimal level I criteria
Fricton 2010[26]	Stabilization appliance	Nociceptive trigeminal inhibition appliance	Range of motion: neutral	Neutral	1 RCTs (38)	Quality score: 73%. Met level I criteria
Fricton 2010[26]	Stabilization appliance	Pivot appliance	Jaw mobility: neutral	Neutral	1 RCT (74)	Quality score 67%. Did not meet minimal level I criteria

MMO = maximal mouth opening; RCT = randomized controlled trial; RoB = risk of bias.

TMJ Clicking

Two SRs[26,28] examined splint therapies for improvements in TMJ clicking. The findings are reported in Table 12, and have been summarized here.

Splint interventions with favourable results:

- Splint (flat, anterior positioning, unspecified) versus other control (MA; 4 RCTs, high risk of bias), NS.[28]

Splint interventions with neutral results regarding TMJ clicking:

- Hard stabilization appliances versus TENS (one RCT, low quality).[26]
- Hard stabilization appliances versus non-occluding appliances (one RCT, moderate quality).[26]
- Anterior positioning appliance for 24 hours versus anterior positioning appliance daytime or nighttime only (two RCTs, low quality).[26]

Table 12: Summary of Splint Therapy for TMJ Clicking in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Physiotherapy — Manual Therapy						
Fricton 2010[26]	Hard stabilization appliances	Transcutaneous nerve stimulation (TENS)	Joint sounds: neutral	Neutral	1 RCT (24)	Quality score 40%. Did not meet minimum level I criteria.
Splint						
Fricton 2010[26]	Hard stabilization appliances	Non-occluding appliances	Joint sounds: neutral	Neutral	1 RCT (90)	Quality score 67%. Met minimum level I criteria.
Other Treatments						
Zhang 2016[28]	Splint (flat, anterior positioning, unspecified)	Control (control appliance, physical therapy, no treatment)	Rate of healing from TMJ clicking: RR = 1.17; 95% CI, 0.69 to 1.98; fixed effects; I^2 = 0% (P = 0.701)	Favourable, non-statistically significant	4 RCTs (170)	All very high Cochrane RoB
Fricton 2010[26]	Anterior positioning appliance 24 hours	Anterior positioning appliance daytime or nighttime only	Joint sounds (1 month): positive. Limited opening (3 months): neutral	Neutral	2 RCTs (140)	Quality scores 47% and 53%. Did not meet minimal level I criteria

RCT = randomized controlled trial; RoB = risk of bias; TENS = transcutaneous nerve stimulation; TMJ = temporomandibular joint.

Adverse Events

On SR[26] reported on adverse events from one RCT; the findings are reported in Table 13. Evidence from one low quality RCT comparing stabilization appliances with nociceptive trigeminal inhibition (NTI) appliances only reported adverse effects for the patients randomize to the NTI intervention.

Table 13: Summary of Splint therapy Interventions and adverse events in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies	Quality of Primary studies and/or Body of Evidence (reported by SR authors)
		Other treatments				
Fricton 2010[26]	Stabilization appliance	Nociceptive trigeminal inhibition appliance	Adverse effects (minor): described only for NTI. 12% patients had 1 mm mobility of incisors, and 1 patient developed anterior open bite.	Favourable, inconclusive	1 RCT (28)	Quality score 60%. Did not met minimal level I criteria

NTI = nociceptive trigeminal inhibition; RCT = randomized controlled trial.

Orthodontic Interventions

One SR[32] was identified on the use of orthodontics for treating TMD; however, no primary studies were identified in the SR and therefore no results could be reported. We have moderate confidence in the results of this SR, as there were no critical flaws.

Pharmacological — Injections

Six SRs[18,27,31,34,35,38] investigated the effects of injecting various pharmacological agents for TMD symptoms. We have low confidence in the results from one SR,[34] and critically low confidence in the results from the other five SRs. One of these SRs[18] also investigated the effects of oral pharmacological agents, while another of these SRs[34] also examined the use of dry needling as an intervention for TMD. These six SRs included 74 primary studies, with 25 of these primary studies overlapping mainly with primary studies included in four of these SRs.[18,31,34,35] Two of the SRs did not contain any overlapping primary studies.[27,38] One of the SRs[18] included a network meta-analysis (NMA).

The risk of bias relating to the evidence regarding pharmacological injections was mixed, though most of the statistically significantly favourable results had low, medium, and moderate risk of bias. Injectable pharmacological interventions that may be associated with improvements in pain were cyclobenzaprine hydrochloride (versus placebo), botulinum toxin (versus placebo), inferior space injection or double spaces injection of hyaluronate or prednisolone (versus the same drug administered as a superior space injection), and ping-on (versus placebo). None of the comparisons yielded statistically significantly unfavourable results with respect to pain. Inferior space injection or double spaces injection of hyaluronate or prednisolone (versus the same drug administered as a superior space injection) may also be associated with improvements in mouth opening and corticosteroid intra-articular injection after arthrocentesis (versus saline or Ringer's lactate intra-articular injection with arthrocentesis) may be associated with unfavourable mouth opening results. None of the injectable pharmacological intervention comparisons yielded statistically significantly favourable or unfavourable results with respect to TMJ clicking or adverse events.

Pain

Six SRs[18,27,31,34,35,38] investigated the effects of injecting various pharmacological agents for pain in TMD. The findings are reported in Table 14, and have been summarized below.

Injectable pharmacological interventions with favourable results with respect to pain:

- Cyclobenzaprine hydrochloride versus placebo (NMA; eight RCTs, low to medium risk of bias), statistically significant in NMA.[18]
- Botulinum toxin versus placebo (site unspecified) (NMA; eight RCTs, low to medium risk of bias), statistically significant in NMA.[18]
- Inferior joint space injection or double joint spaces injection of hyaluronate or prednisolone versus superior joint space injection (same drug as intervention) (MA; three RCTs, moderate risk of bias), statistically significant in MA.[27]
- Platelet-rich plasma (PRP) injection (intra-articular) with arthrocentesis versus Ringer's lactate injection (intra-articular) with arthrocentesis (two RCTs, high risk of bias), inconclusive.[38]
- PRP injection (intra-articular) with arthrocentesis versus saline injection (intra-articular) with arthrocentesis (one RCT, high risk of bias), inconclusive.[38]
- Corticosteroid injection (intra-articular) after arthrocentesis versus Ringer's lactate or saline injection (intra-articular) with arthrocentesis (MA; five RCTs, low risk of bias), NS.[31]

- Hyaluronate injections versus placebo injections (site unspecified) (three RCTs, medium risk of bias).[18]
- Clonazepam versus placebo (NMA; eight RCTs, low to medium risk of bias), NS.[18]
- Propranolol versus placebo (NMA; eight RCTs, low to medium risk of bias), NS.[18]
- Tizanidine hydrochloride versus placebo (NMA; eight RCTs, low to medium risk of bias), NS.[18]
- Ping-on ointment versus placebo (NMA; eight RCTs, low to medium risk of bias), statistically significant in NMA.[18]
- Nonsteroidal anti-inflammatory disease (NSAID) injection versus placebo (site unspecified) (one RCT, medium risk of bias).[18]
- PRP injection (intra-articular) with arthrocentesis versus hyaluronate injection (intra-articular) with arthrocentesis (three RCTs, high risk of bias), inconclusive.[38]

Injectable pharmacologic interventions with neutral results regarding pain:

- Botulinum toxin injection versus saline injection (muscle injection) (five RCTs, unclear risk of bias).[34]
- Granisetron injection versus saline injection (site unspecified) (two RCTs, unclear risk of bias).[34]
- Ketamine injection versus placebo injection (muscle injection) (one RCT, unclear risk of bias). [34]
- Hyaluronic acid intra-articular injections versus intra-articular injections of other drugs (seven RCTs, one retrospective study, low- and high-quality studies).[35]
- Hyaluronate two-needle injection versus hyaluronate one-needle injection (site unspecified) (one RCT, medium risk of bias).[18]
- Hyaluronate injections versus plasma rich growth factor injections (site unspecified) (one RCT, medium risk of bias).[18]
- Botulinum toxin injection versus fascial manipulation (site unspecified) (1 RCT, high risk of bias).[34]
- Botulinum toxin injection versus laser therapy (site unspecified) (1 RCT, high risk of bias).[34]

Injectable pharmacologic interventions with unfavourable results regarding pain:

- Granisetron versus placebo (NMA; eight RCTs, low to medium risk of bias), NS.[18]
- Corticosteroid intra-articular injection versus hyaluronate intra-articular injection (MA; three RCTs, low risk of bias), NS[31] (Therefore, favourable, NS for hyaluronate injection.)

Table 14: Summary of Pharmacological Injections for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Placebo or Sham										
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Ringer's lactate injection with arthrocentesis (intra-articular)	positive: 1 neutral: 1	Favourable, inconclusive	2 RCTs	Cochrane RoB Performance bias = high Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Saline injection with arthrocentesis (intra-articular)	6 to 12 months Positive: 1 18 to 24 months Neutral = 1	Favourable, inconclusive	1 RCT	Cochrane RoB Performance bias = unclear Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Liu 2018[31]	Corticosteroid injection (intra-articular) after arthrocentesis	Ringer's lactate or saline injection (intra-articular) with arthrocentesis	Pain VAS (0 to 10): MD = –0.36; 95% CI, –0.73 to 0.01; *P* = 0.06; fixed effects; I^2 = 0%; Chi^2 = 3.86 df = 4 (*P* = 0.43)	Favourable, non-statistically significant	5 RCTs (200)	Low Cochrane RoB = 5 RCTs	Pain VAS (0 to 10): Short term (3 to 4 weeks) MD = –0.13; 95% CI, –0.60 to 0.33; *P* = 0.57; fixed effects; I^2 = 0%; Chi^2 = 0.96; df = 1 (*P* = 0.33)	Favourable, non-statistically significant	2 RCTs (88)	Low RoB = 2 RCTs
							Pain VAS (0 to 10): Long term (> 6 months) MD = –0.74; 95% CI, –1.34 to –0.13; *P* = 0.02; fixed effects; I^2 = 0%; Chi^2 = 0.49; df = 2 (*P* = 0.78)	Favourable, statistically significant	3 RCTs (112)	Low RoB = 2 RCTs

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Häggman-Henrikson 2017[18]	Hyaluronate injections (site unspecified) (TMD mainly associated with TMJ pain)	Placebo injection (site unspecified)	Pain: Positive: 3	Favourable	3 RCTs	All medium SBU RoB				
Häggman-Henrikson 2017[18]	Cyclobenzaprine hydrochloride	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –1.24 (–1.68 to –0.80); I^2 (network) = 64% NMA; fixed-effects model	Favourable, statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Häggman-Henrikson 2017[18]	Clonazepam	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –0.33 (–1.23 to 0.57); I^2 (network) = 64% NMA; fixed-effects model	Favourable, non-statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB.				
Häggman-Henrikson 2017[18]	Propranolol	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –0.40 (–2.49 to 1.69); I^2 (network) = 64% NMA; fixed-effects model	Favourable, non-statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Häggman-Henrikson 2017[18]	Tizanidine hydrochloride	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –0.36 (–0.86 to 0.15); I^2 (network) = 64% NMA; fixed-effects model	Favourable, non-statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Häggman-Henrikson 2017[18]	Botox (site unspecified)	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –1.32 (–2.31 to –0.33); I^2 (network) = 64% NMA; fixed-effects model	Favourable, statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Machado 2018[34]	Botox injected (muscle)	Placebo injected (saline) (muscle)	Pain intensity (VAS): positive 2, neutral 3. PPT: neutral 1.	Neutral	5 RCTs (170)	Cochrane RoB: Low RoB in randomization and blinding 3. Low risk allocation concealment 2.				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
						Otherwise unclear.				
Machado 2018[34]	Granisetron injected (site unspecified)	Placebo injected (saline) (site unspecified)	Pain intensity (VAS): positive 1, neutral 1 (PPT): neutral 2.	Neutral	2 RCTs (58)	Cochrane RoB: Low RoB randomization and blinding, unclear for allocation concealment.				
Häggman-Henrikson 2017[18]	Granisetron	Placebo	Pain reduction: Absolute change 0 to 10 VAS: 0.50 (–1.41 to 2.41); I^2 (network) = 64% NMA; fixed-effects model	Unfavourable, non-statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Häggman-Henrikson 2017[18]	Ping-on	Placebo	Pain reduction: Absolute change 0 to 10 VAS: –2.15 (–3.11 to –1.19); I^2 (network) = 64% NMA; fixed-effects model	Favourable, statistically significant	8 RCT (334 patients; NMA)	Low to medium SBU RoB				
Machado 2018[34]	Ketamine injected (muscle)	Placebo injected (saline) (muscle)	Pain (VAS, PPT): neutral 1.	Neutral	1 RCT (14)	Low SBU RoB for blinding, unclear for randomization, allocation concealment.				
Häggman-Henrikson 2017[18]	NSAID injection (Tenoxicam)	Placebo	Pain reduction: Positive:1	Favourable	1 RCT	Medium SBU RoB				
Pharmacological Injections										
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	HA injection with arthrocentesis (intra-articular)	Positive: 2 Neutral: 1	Favourable, inconclusive	3 RCTs	Cochrane RoB Performance bias = unclear or high Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Liu 2018[31]	Corticosteroid injection (intra-articular)	Hyaluronate injection (intra-articular)	Pain intensity VAS (0 to 10): MD = 0.61; 95% CI, –0.32 to 1.54; *P* = 0.20; fixed effects;	Unfavourable, non-statistically significant	3 RCTs (143)	Low Cochrane RoB = 3 RCTs	Pain VAS: Short term (3 to 4 weeks) MD = 0.36; 95% CI, –0.72 to 1.43	Unfavourable, non-statistically significant	2 RCTs (103)	Low RoB = 2 RCTs

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
			I^2 = 0%; Chi^2= 1.06 df = 2 (*P* = 0.59)				*P* = 0.52; fixed effects I^2 = 0%; Chi^2 = 0.17 df = 1 (*P* = 0.68)			
Li 2012[27]	Inferior joint space injection (ISI) or double joint spaces injection (DSI) of hyaluronate or prednisolone	Superior space injection (SSI) (same drug as intervention)	Pain intensity (VAS, 100mm): MD = –9.01 mm; 95% CI, –14.42 to –3.60; *P* = 0.001; random effects I^2 = 55%; Tau^2 = 12.58 Chi^2 = 4.45 df = 2 (*P* = 0.11)	Favourable, statistically significant	3 RCTs (280)	All RCTs = Moderate Cochrane RoB	DSI vs. SSI MMO: MD = –7.19; 95% CI, –13.61 to -0.78; *P* = 0.03; random effects I^2 = 56%; Tau^2 =12.10 Chi^2 = 2.29 df = 1 (*P* = 0.13)	Favourable, statistically significant	2 RCTs (166)	All RCTs = Moderate risk of Bias
							ISI vs. SSI MMO: MD = –13.16; 95% CI, –20.07 to –6.25; *P* = 0.0002; random effects	Favourable, statistically significant	1 RCT (104)	All RCTs = Moderate risk of Bias
Goiato 2016[35]	Hyaluronic acid (Intra-articular injections)	Intra-articular injections of other drugs (corticosteroids, NSAID)	Pain positive: 2 neutral: 6	Neutral	7 RCTs 1 retrospective study	Jadad quality score Low quality (0 to 2): 0 High quality (3 to 5): 8 studies				
Häggman-Henrikson 2017[18]	Hyaluronate injections 2 needle injection (site unspecified) (TMD mainly associated with TMJ pain)	Hyaluronate injections 1 needle injection (site unspecified) TMD-joint (TMD mainly associated with TMJ pain)	Pain Neutral: 1	Neutral	1 RCT	Medium SBU RoB				
Physiotherapy manual therapy										
Machado 2018[34]	Botox injection (muscle)	Fascial manipulation	Pain (VAS): neutral	Neutral	1 RCT (30)	Cochrane RoB High risk of bias for blinding, unclear for				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
						randomization, allocation concealment.				
Physiotherapy Laser Therapy										
Machado 2018[34]	Botox injection (unspecified)	Laser therapy	Pain (VAS): neutral	Neutral	1 RCT (15)	Low Cochrane RoB for randomization blinding of assessor, high risk for blinding of patient, allocation concealment unclear.				
Other treatments										
Häggman-Henrikson 2017[18]	Hyaluronate injections (site unspecified) (TMD mainly associated with TMJ pain)	Plasma rich growth factor injections (site unspecified)	Pain Neutral: 1	Neutral	1 RCT	Medium SBU RoB				

Botox = botulinum toxin; DSI = double space injection; HA = hyaluronic acid; ISI = inferior space injection; MD = mean difference; NSAID = nonsteroidal anti-inflammatory drug; PRP = platelet-rich plasma; RCT = randomized controlled trial; RoB = risk of bias; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; SSI = superior apace injection; TMD = temporomandibular disease; VAS = visual analogue scale.

Risk of bias in Bousnaki 2018 = Selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; reporting bias: selective reporting; other bias.

Mouth Opening

Five SRs[27,31,34,35,38] examined the injection of various pharmacological agents for MMO in TMD. The findings are reported in Table 15, and have been summarized here.

Injectable pharmacological interventions with favourable mouth opening results:

- PRP injection (intra-articular) with arthrocentesis versus Ringer's lactate injection (intra-articular) with arthrocentesis (two RCTs, high risk of bias), inconclusive.[38]
- Ketamine versus saline injection (muscle injection) (one RCT, unclear risk of bias), inconclusive.[34]
- Inferior joint space injection or double spaces injection of hyaluronate or prednisolone versus superior joint space injection (same drug as intervention) (MA; four RCTs, moderate risk of bias), statistically significant in MA.[27]

Injectable pharmacological interventions with neutral mouth opening results:

- PRP injection (intra-articular) with arthrocentesis versus saline injection (intra-articular) with arthrocentesis (one RCT, high risk of bias).[38]
- Botulinum toxin injection versus saline injection (muscle injection) (five RCTs, unclear risk of bias).[34]
- Granisetron injection versus saline injection (site unspecified) (one RCT, low risk of bias).[34]
- Botulinum toxin injection versus fascial manipulation (muscle injection) (one RCT, high risk of bias).[34]
- PRP injection (intra-articular) with arthrocentesis versus hyaluronate injection (intra-articular) with arthrocentesis (three RCTs, unclear risk of bias).[38]
- Hyaluronic acid intra-articular injections versus intra-articular injections of other drugs (two RCTs, one RS, high quality).[35]

Injectable pharmacological interventions with unfavourable mouth opening results:

- Corticosteroid intra-articular injection after arthrocentesis versus saline or Ringer's lactate intra-articular injection with arthrocentesis (MA; four RCTs, low risk of bias), statistically significant in MA.[31]
- Corticosteroid intra-articular injection versus hyaluronate intra-articular injection (MA; three RCTs, low risk of bias), NS.[31]

Table 15: Summary of Pharmacological Injections for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Placebo or Sham										
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Ringer's lactate injection with arthrocentesis (intra-articular)	positive: 1 neutral: 1	Favourable, inconclusive	2 RCTs	Cochrane RoB Performance bias = high Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Saline injection with arthrocentesis (intra-articular)	Neutral: 1	Neutral	1 RCT	Cochrane RoB Performance bias = unclear Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Liu 2018[31]	Corticosteroid injection (intra-articular) after arthrocentesis	Ringer's lactate or saline injection (intra-articular) with arthrocentesis	MIO: MD = –1.26 mm; 95% CI, –1.82 mm to –0.71 mm; $P < 0.00001$ $I^2 = 80\%$; random effects; $Chi^2 = 15.14$; df = 3 ($P = 0.002$)	Unfavourable, statistically significant	4 RCTs	Low Cochrane RoB = 4 RCTs	MIO: Short term (3 to 4 weeks) MD = 0.11 mm; 95% CI, –0.81 mm to 1.02 mm; $P = 0.82$; fixed effects; $I^2 = 0\%$; $Chi^2 = 0.22$ df = 1 ($P = 0.64$)	Favourable, non-statistically significant	2 RCTs	Low Cochrane RoB = 2 RCTs

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
							MIO: Long term (> 6 months) MD = –2.06mm; 95% CI, –2.76mm to –1.36mm; *P* < 0.00001; fixed effects; I^2 = 28%; Chi^2= 1.38 df= 1 (*P* = 0.24)	Unfavourable, statistically significant	2 RCTs	Low Cochrane RoB = 2 RCTs
Machado 2018[34]	Botox injected (muscle)	Placebo injected (saline) (muscle)	MMO: neutral 5	Neutral	5 RCTs (170)	Cochrane RoB: Low risk of bias in randomization and blinding 3. Low risk allocation concealment 2. Otherwise unclear.				
Machado 2018[34]	Granisetron injected (site unspecified)	Placebo injected (saline) (site unspecified)	MMO: neutral	Neutral	1 RCTs (40)	Cochrane RoB: Low risk bias randomization, blinding, and allocation concealment.				
Machado 2018[34]	Ketamine injected (muscle)	Placebo injected (saline) (muscle)	MMO: positive 1.	Favourable, inconclusive	1 RCT (14)	Cochrane RoB: Low risk of bias for blinding, unclear for randomization, allocation concealment.				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Physiotherapy Manual Therapy										
Machado 2018[34]	Botox injection (muscle)	Fascial manipulation	MMO: neutral	Neutral	1 RCT (30)	Cochrane RoB: high risk of bias for blinding, unclear for randomization, allocation concealment.				
Pharmacological Injections										
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	HA injection with arthrocentesis (intra-articular)	Positive: 1 Neutral: 2	Neutral	3 RCTs	Cochrane RoB Performance bias = unclear or high Detection bias = high Low RoB for selection, attrition, reporting, and other biases				
Liu 2018[31]	Corticosteroid injection (intra-articular)	Hyaluronate injection (intra-articular)	MIO: MD = –1.96 mm; 95% CI, –6.06 mm to 2.14 mm; *P* = 0.35; fixed effects I^2 = 0%; Chi^2 = 0.50 df = 2 (*P* = 0.78)	Unfavourable, non-statistically significant	3 RCTs (143)	Low Cochrane RoB = 3 RCTs	MIO: Short term (3 to 4 weeks) MD = –1.40 mm; 95% CI, –6.28 mm to 3.48 mm; *P* = 0.57; fixed effects I^2 = 0%; Chi^2 = 0.33 df = 1 (*P* = 0.57)	Unfavourable, non-statistically significant	2 RCTs	Low Cochrane RoB = 2 RCTs

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Li 2012[27]	Inferior joint space injection (ISI) or double joint spaces injection (DSI) of hyaluronate or prednisolone	Superior joint space injection (SSI) (same drug as intervention)	MMO: MD = 2.88 mm; 95% CI, 1.40 mm to 4.36 mm; *P* = 0.0001; random effects I^2 = 68%; Tau^2 =1.46 Chi^2 = 9.27 df = 3 (*P* = 0.03)	Favourable, statistically significant	4 RCTs (326)	All RCTs = Moderate Cochrane RoB	DSI vs. SSI MMO: MD = 2.54 mm; 95% CI, 1.10 mm to 3.98 mm; *P* = 0.0005; random effects I^2 = 0%; Tau^2 =0.00 Chi^2 = 0.08 df= 1 (*P* = 0.78)	Favourable, statistically significant	2 RCTs (166)	All RCTs = Moderate Cochrane RoB
							ISI vs. SSI MMO: MD = 3.07 mm; 95% CI, 0.32 mm to 5.81 mm; *P* = 0.03; random effects I^2 = 86%; Tau^2 = 3.41 Chi^2 = 7.29 df = 1 (*P* = 0.007)	Favourable, statistically significant	2 RCTs (160)	All RCTs = Moderate Cochrane RoB
Goiato 2016[35]	Intra-articular injections of hyaluronic acid	Intra-articular injections of other drugs (corticosteroids, NSAID)	Joint function: positive: 1 neutral: 2	Neutral	2 RCTs 1 retrospective study	Jadad quality score Low quality (0 – 2): 0 High quality (3 -5): 3 studies				

Botox = botulinum toxin; CI = confidence interval; HA = hyaluronic acid; MD = mean difference; MIO = maximal interincisal opening; MMO = maximal mouth opening; NSAID = nonsteroidal anti-inflammatory drugs; PRP = platelet-rich plasma; RCT = randomized controlled trial; RoB = risk of bias.

Risk of bias in Bousnaki 2018 = Selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; reporting bias: selective reporting; other bias.

TMJ Clicking

One SR[38] reported on the effects of injections of PRP for joint noises in TMD. The findings are reported in Table 16, and have been summarized below.

Pharmacological comparisons with favourable results:

- PRP injection with arthrocentesis versus Ringer's lactate injection with arthrocentesis (intra-articular) (two RCTs, high risk of bias), inconclusive.[38]

Pharmacological comparisons with neutral results:

- PRP injection with arthrocentesis versus saline injection with arthrocentesis (intra-articular) (one RCT, high risk of bias).[38]
- PRP injection with arthrocentesis versus hyaluronic acid injection with arthrocentesis (intra-articular) (one RCT, high risk of bias).[38]

Table 16: Summary of Pharmacological Injections for TMJ Clicking in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Ringer's lactate injection with arthrocentesis (intra-articular)	Positive: 1 Neutral: 1	Favourable, inconclusive	2 RCTs	Cochrane RoB Performance bias = high Detection bias = high Low RoB for selection, attrition, reporting, and other biases
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	Saline injection with arthrocentesis (intra-articular)	Neutral: 1	Neutral	1 RCT	Cochrane RoB Performance bias = unclear Detection bias = high Low RoB for selection, attrition, reporting, and other biases
Pharmacological Injections						
Bousnaki 2018[38]	PRP injection with arthrocentesis (intra-articular)	HA injection with arthrocentesis (intra-articular)	Neutral: 1	Neutral	1 RCTs	Cochrane RoB Performance bias = high Detection bias = high Low RoB for selection, attrition, reporting, and other biases

HA = hyaluronic acid; PRP = platelet-rich plasma; RCT = randomized controlled trial; RoB = risk of bias.

Risk of bias in Bousnaki 2018 = selection bias: random sequence generation and allocation concealment; performance bias: blinding of participants and personnel; detection bias: blinding of outcome assessment; attrition bias: incomplete outcome data; reporting bias: selective reporting; other bias.

Adverse Events

Two SRs[31,34] reported on adverse events following injections for TMD treatments. None of the interventions were found to be favourable or unfavourable, but were rather all neutral. The findings are reported in Table 17, and have been summarized here.

Injectable pharmacological interventions with neutral results:

- Granisetron injection versus saline injection (site unspecified) (two RCTs, unclear risk of bias).[34]

- Botulinum toxin injection versus fascial manipulation (muscle injection) (one RCT, high risk of bias).[34]
- Corticosteroids versus hyaluronate (intra-articular) (three RCTs, low and unclear risk of bias).[31]

Table 17: Summary of Adverse Events With Pharmacological Injection interventions for TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo Or Sham						
Machado 2018[34]	Granisetron injected	Placebo injected (saline)	Adverse events: neutral: 1, not reported: 1	Neutral	2 RCTs (58)	Low Cochrane RoB randomization and blinding, unclear for allocation concealment.
Physiotherapy Manual Therapy						
Machado 2018[34]	Botox injection (muscle)	Fascial manipulation (muscle)	Adverse events: neutral No relevant adverse events, only mild discomfort with chewing	Neutral	1 RCT (30)	High Cochrane RoB for blinding, unclear for randomization, allocation concealment.
Pharmacological Injections						
Liu 2018[31]	Corticosteroids (intra-articular)	Hyaluronate (intra-articular)	Neutral = 3	Neutral	3 RCTs	Low Cochrane RoB = 2 RCTs Unclear RoB = 1 RCT

Botox = botulinum toxin RCT = randomized controlled trial; RoB = risk of bias.

Pharmacological — Oral or Topical

Two SRs[33,36] examined the effects of oral pharmacological agents in the treatment of TMD, and we have high confidence in the results of these SRs. These SRs contained 14 primary studies, of which four overlapped with the SR by Häggman-Henrikson et al.,[18] which investigated pharmacological agents that were administered orally or through an injection, however, we have critically low confidence in that latter SR.

Overall, much of the evidence regarding oral and topical pharmacological had low or unclear risk for bias. With respect to pain — none of the comparisons yielded statistically significantly favourable or unfavourable results; the majority were neutral. For mouth opening, the majority of the information had high risk for bias or was deemed low quality by study authors; no statistically significantly favourable or unfavourable results were reported. Adverse events were reported in one SR (reported in three RCTs) comparing various dosages of glucosamine and ibuprofen and glucosamine with placebo. No statistical tests were performed and the risk of bias was rated as low and high.

Pain

Three SRs[18,33,36] reported on oral or topical pharmacological agents for improving pain in TMD. Comparisons included placebos in 10 instances,[18,33,36] other oral drugs in two instances,[36] and a control that grouped multiple treatment types.[18] The findings are reported in Table 18, and have been summarized below.

Oral or topical pharmacological interventions with favourable results:

- Melatonin tablets versus placebo (one RCT, low risk of bias), inconclusive.[18]
- Anticonvulsant versus placebo (one RCT, low risk of bias), inconclusive.[33]
- Topical NSAIDs versus placebo (one RCT, low and unclear risk of bias), inconclusive.[33]

Oral or topical pharmacological interventions with neutral results:

- Glucosamine sulphate (400 mg three times per day) versus placebo (one RCT, low risk of bias).[36]
- Benzodiazepine versus placebo (four RCTs, low and unclear risk of bias).[33]
- Topical capsaicin versus placebo (one RCT, unclear and low risk of bias).[33]
- Oral NSAIDS versus placebo (three RCTS, low and unclear risk of bias).[33]
- Muscle relaxant versus placebo (one RCT, low risk of bias).[33]
- Oral chondroitin-glucosamine versus placebo (one RCT, low risk of bias).[33]
- Oral propranolol versus placebo (one RCT, low risk of bias).[33]
- Glucosamine sulphate (1,500 mg/day) versus Ibuprofen (400 mg two times/day) (one RCT, high risk of bias).[36]
- Glucosamine sulphate (500 mg three times/day) versus Ibuprofen (400 mg three times/day) (one RCT, very low quality evidence).[36]
- NSAIDS versus other control (four RCTs, medium risk of bias).[18]

Table 18: Summary of Oral or Topical Pharmacological Interventions for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Häggman-Henrikson 2017[18]	Melatonin tablets TMD-muscle (TMD mainly associated with myalgia)	Placebo	Reduction in pain intensity: Positive = 1	Favourable, inconclusive	1RCT	Low SBU RoB
Melo 2018[36]	Glucosamine sulphate (400 mg three times/day)	Placebo	Pain (6 weeks): Neutral: 1	Neutral	1 RCT (59)	Low Cochrane RoB GRADE = Very low quality
Mujakperuo 2010[33]	Oral benzodiazepines (clonazepam, prazepam, diazepam)	Placebo	Pain neutral: 4	Neutral	4 RCTs (158)	Cochrane RoB:[a] Sequence: 3 unclear, 1 low Allocation: 4 unclear Blinding: 4 low Incomplete outcomes: 2 unclear, 2 low Reporting: 4 low Other: 1 high, 3 unclear
Mujakperuo 2010[33]	Oral Anticonvulsant (Gabapentin)	Placebo	Pain positive: 1	Favourable, inconclusive	1 RCT (44)	Cochrane RoB:[a] Sequence: low Allocation: low Blinding: low Incomplete outcomes: low Reporting: low Other: high

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Mujakperuo 2010[33]	Topical capsaicin	Placebo	Pain neutral: 1	Neutral	1 RCT (30)	Cochrane RoB:[a] Sequence: unclear Allocation: unclear Blinding: low Incomplete outcomes: unclear Reporting: low Other: low
Mujakperuo 2010[33]	Oral NSAIDS (diclofenac, naproxen, COX-2 inhibitor [celecoxib], piroxicam)	Placebo	Pain positive: 1 neutral: 3	Neutral	3 RCTs (127) (4 different NSAIDS evaluated)	Cochrane RoB:[a] Sequence: 2 unclear, 1 low Allocation: 2 unclear, 1 low Blinding: 3 low Incomplete outcomes: 2 unclear, 1 low Reporting: 3 low Other: 1 unclear, 2 low
Mujakperuo 2010[33]	Topical NSAID (methyl salicylate)	Placebo	Pain positive: 1	Favourable, inconclusive	1 RCT (28)	Cochrane RoB:[a] Sequence: low Allocation: low Blinding: low Incomplete outcomes: unclear Reporting: low Other: unclear
Mujakperuo 2010[33]	Muscle relaxant (cyclobenzaprine)	Placebo	Pain neutral: 1	Neutral	1 RCT 28	Cochrane RoB:[a] Sequence: low Allocation: unclear Blinding: low Incomplete outcomes: low Reporting: low Other: Unclear
Mujakperuo 2010[33]	Oral chondroitin-glucosamine	Placebo	Pain neutral: 1	Neutral	1 RCT (34)	Cochrane RoB:[a] Sequence: low Allocation: low Blinding: low Incomplete outcomes: low Reporting: low Other: low
Mujakperuo 2010[33]	Oral propranolol	Placebo	Pain neutral: 1	Neutral	1 RCT (80)	Cochrane RoB:[a] Sequence: low Allocation: low Blinding: low Incomplete outcomes: low Reporting: low Other: low
Pharmacological Oral						
Melo 2018[36]	Glucosamine sulphate (1500 mg/day)	Ibuprofen (400 mg two times/day)	Pain (12 weeks): Neutral: 1	Neutral	1 RCT (60)	High Cochrane RoB
Melo 2018[36]	Glucosamine sulphate (500 mg three times/day)	Ibuprofen (400 mg three times/day)	Pain (12 weeks): Neutral: 1	Neutral	1 RCT (39)	Low Cochrane RoB Very low quality (GRADE –pain outcome)

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Other Treatments						
Häggman-Henrikson 2017[18]	NSAIDS TMD-joint (TMD mainly associated with TMJ pain)	Control (placebo, splint, arthroscopy, glucosamine)	Reduction in pain intensity: Positive: 2 Neutral: 2	Neutral	4 RCTs	All medium SBU RoB

GRADE = grading of recommendation, assessment, development and evaluation; NSAIDS = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial; RoB = risk of bias; SBU = Swedish Agency for Health Technology Assessment and Assessment of Social Services; TMD = temporomandibular disease; TMJ = temporomandibular joint.

[a] Cochrane RoB: Judgment of whether sequence generation was adequate, if there was evidence of allocation concealment, blinding and incomplete outcome data had been addressed. We also examined study publications for any evidence of selective reporting of outcomes or any other issues that may bias the results

Mouth Opening

One SR[36] reported on oral pharmacological agents for improving mouth opening in TMD, with all comparisons having neutral results. No topical agents were examined. The findings are reported in Table 19, and have been summarized here.

Oral pharmacological interventions with neutral results:

- Glucosamine sulphate (400 mg three times/day) versus placebo (one RCT, very low-quality evidence)[36]
- Glucosamine sulphate (1,500 mg/day) versus Ibuprofen (400 mg two times/day) (one RCT, high risk of bias)[36]
- Glucosamine sulphate (500 mg three times/day) versus Ibuprofen (400 mg three times/day) (one RCT, very low-quality evidence)[36]

Table 19: Summary of Oral Pharmacological Interventions for MMO in TMD

First author, Year	Intervention	Comparison	Findings	Summary of evidence	Number and type of studies (# of participants)	Quality of primary studies and/or body of evidence (reported by SR authors)
Placebo or Sham						
Melo 2018[36]	Glucosamine sulphate (400 mg three times/day)	Placebo	MMO (6 weeks): Neutral: 1	Neutral	1 RCT (59)	Low Cochrane RoB GRADE: Very low quality
Pharmacological Oral						
Melo 2018[36]	Glucosamine sulphate (1,500 mg/day)	Ibuprofen (400 mg two times/day)	MMO (12 weeks): Neutral: 1	Neutral	1 RCT (60)	High Cochrane RoB
Melo 2018[36]	Glucosamine sulphate (500 mg three times/day)	Ibuprofen (400 mg three times/day)	MMO (12 weeks): Neutral: 1	Neutral	1 RCT (39)	Low Cochrane RoB GRADE: Very low quality

GRADE = grading of recommendation, assessment, development and evaluation; mg = milligrams; MMO = maximal mouth opening; RCT = randomized controlled trial; RoB = risk of bias.

Adverse Events

One SR[36] reported on adverse events related to glucosamine sulphate versus ibuprofen or placebo in treating TMD. No adverse event information regarding topical agents was identified. The findings are reported in Table 20, and have been summarized here.

Oral pharmacological interventions with favourable results:

- Glucosamine sulphate (1,500 mg/day) versus Ibuprofen (400 mg two times/day) (one RCT, high risk of bias).[36]
- Glucosamine sulphate (500 mg three times/day) versus Ibuprofen (400 mg three times/day) (one RCT, low risk of bias).[36]

Oral pharmacological interventions with unfavourable results:

- Glucosamine sulphate (400 mg three times/day) versus placebo (one RCT, low risk of bias).[36]

Table 20: Summary of Adverse Events From Oral Pharmacological Interventions in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Placebo or Sham						
Melo 2018[36]	Glucosamine sulphate (400 mg three times/day)	Placebo	AEs (6 weeks) (includes gastrointestinal side effects): Negative: 1 (no statistical test)	Unfavourable, inconclusive	1 RCT (59)	Low Cochrane RoB
Melo 2018[36]	Glucosamine sulphate (1,500 mg/day)	Ibuprofen (400 mg two times/day)	AEs (12 weeks) Positive: 1 (no statistical test)	Favourable	1 RCT (60)	High Cochrane RoB
Melo 2018[36]	Glucosamine sulphate (500 mg three times/day)	Ibuprofen (400 mg three times/day)	AEs (12 weeks) Positive: 1 (no statistical test)	Favourable	1 RCT (39)	Low Cochrane RoB

AE = adverse event; RCT = randomized controlled trial; RoB = risk of bias.

Surgical Interventions

Three SRs[29,30,39] examined surgical interventions for improving TMD symptoms. These SRs included a total of 18 primary studies, of which five overlapped; one primary study overlapped between two of the surgical studies,[29,30] and the other four overlapped with SRs on manual therapy[24] and pharmacotherapy.[35]

One SR[30] compared arthrocentesis with arthroscopy, and we have critically low confidence in the results of this SR. One SR[39] compared single puncture with double needle arthrocentesis, and we have low confidence in the results of this review. One SR[29] compared open surgery and arthroscopic lysis and lavage with arthroscopy, and we have critically low confidence in the results from this SR.

The evidence regarding surgical interventions was mixed with respect to risk of bias and quality. Overall, open surgery may be associated with more favourable results than arthroscopic surgery with respect to pain and mouth opening, but not TMJ clicking (none of the comparisons yielded statistically significantly favourable or unfavourable results with respect to that outcome). Arthroscopy may be associated with more favourable results with

respect to pain and mouth opening, with fewer adverse events. However, most differences were not statistically significant. There was significant heterogeneity associated with the MA that compared arthrocentesis with arthroscopy.

Pain

The three SRs examining surgical interventions reported pain outcomes.[29,30,39] The findings are reported in Table 21 and have been summarized here.

Surgical interventions with favourable results:

- Open surgery versus arthroscopic surgery (MA, three RCTs, one controlled clinical trial [CCT], low to moderate risk of bias), statistically significant in MA.[29]

Surgical interventions with neutral results:

- Single puncture arthrocentesis versus double puncture arthrocentesis (five RCTs, low to high quality).[39]

Surgical interventions with unfavourable results:

- Arthrocentesis versus arthroscopy (MA, two RCTs, two CCTs, two RS, low to moderate risk of bias, high heterogeneity), statistically significant in MA[30] (Therefore, favourable for arthroscopy).
- Arthroscopic lysis and lavage versus arthroscopy (MA, one CCT, one RS, moderate risk of bias), NS.[29] (Therefore, favourable, NS for arthroscopy).

Mouth Opening

Two of the included SRs reported mouth opening outcomes.[29,39] The findings are reported in Table 22, and have been summarized here.

Surgical interventions with favourable results:

- Open surgery versus arthroscopic surgery (MA, one RCT, one CCT, low to moderate risk of bias), NS.[29]

Surgical interventions with neutral results:

- Single puncture arthrocentesis versus double puncture arthrocentesis (five RCTs, low to high quality).[39]

Surgical interventions with unfavourable results:

- Arthrocentesis versus arthroscopy (MA, two RCTs, two CCTs, two RS, low to moderate risk of bias, high heterogeneity), statistically significant in MA[30] (Therefore, favourable for arthroscopy).
- Arthroscopic lysis and lavage versus arthroscopy (MA, one CCT, one RS, moderate risk of bias), statistically significant in MA[29] (Therefore, favourable for arthroscopy).

Table 21: Summary of Surgical Interventions for Pain in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Surgical										
Al-Moraissi, 2014[30]	Arthrocentesis	Arthroscopy	*Pain (VAS, unspecified)* WMD = –0.44 95% CI, –0.57 to –0.31, Z = 6.44, *P* = 0.00001, fixed effects, χ^2 = 41.73, df = 5, (*P* < 0.0001) I^2 = 88%	Unfavourable, statistically significant	2 RCT 2 CCT 2 RS (AC n = 134; AS n = 147)	4 studies moderate RoB 2 studies low RoB[a]	High-quality studies only Pain (VAS) MD = –0.57 95% CI, –0.72 to –0.43, Z = 7.88, *P* < 0.00001), fixed effects; χ^2 = 7.71, df = 1, *P* = 0.005, I^2 = 87%	Unfavourable, non-statistically significant	2 RCTs (81)	Low RoB
Nagori, 2018[39]	Single puncture arthrocentesis	Double needle arthrocentesis	*Pain:* Neutral = 5	Neutral	5 RCTs (186 participants, 1 study not reported)	Cochrane RoB: Low to high quality				
Al-Moraissi, 2015[29]	Open surgery	Arthroscopic surgery	*Pain, SMD*: –0.40; 95% CI, –0.79 to –0.01; *P* = 0.05, fixed effects; χ^2 = 1.64, df = 3, *P* = 0.65, I^2 = 0%	Favourable, statistically significant	3 RCTs 1 CCT (AS n = 53; OS n = 51)	Low to moderate RoB[a]				
Al-Moraissi, 2015[29]	Arthroscopic lysis and lavage	Arthroscopic surgery	*Pain (VAS, unspecified):* WMD = –0.18; 95% CI –0.74 to –0.38;	Unfavourable, non-statistically significant	1 CCT 1 RS (ALL, n = 150; AS n = 100)	Moderate RoB[a]				

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
			P = 0.53, fixed effects; χ^2 = 0.61, df = 3, *P* = 0.89, I^2 = 0%							

AC = arthrocentesis; ALL = arthroscopic lysis and lavage; AS= arthroscopy; CCT = controlled clinical trial; MD = mean difference; OS = open surgery; RCT = randomized controlled trial; RoB = Risk of Bias; RS = retrospective study; SMD = standardized mean difference; WMD = weighted mean difference.

[a] The classification of the RoB potential for each study was based on the following five criteria: (1) random selection in the population, (2) definition of inclusion and exclusion criteria, (3) report of losses to follow-up, (4) validated measurements, and (5) statistical analysis.

Table 22: Summary of Surgical Interventions for MMO in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Surgical										
Al-Moraissi, 2014[30]	Arthrocentesis	Arthroscopy	Maximal interincisal opening WMD = –1.86 mm; 95% CI, –2.93 mm to –0.79 mm, Z = 3.41, *P* = 0.0006 χ^2 = 27.16, df = 5 (*P* < 0.0001), I^2 = 82%	Unfavourable, statistically significant	2 RCT 2 CCT 2 RS (AC = n = 134; AS n = 147)	4 studies moderate RoB 2 studies low RoB[a]	High-quality studies only Maximal interinscial opening MD = –5.28 mm (95% CI –7.10 mm to –3.46 mm), Z = 5.69, (*P* < 0.00001) χ^2 = 0.68, df = 1, *P* = 0.41, I^2 = 0%	Unfavourable, statistically significant	2 RCTs (81 participants)	Low RoB

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)	Details of Subgroup and Meta-Analysis	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies
Nagori, 2018[39]	Single puncture arthrocentesis	Double needle arthrocentesis	MMO: Neutral = 5	Neutral	5 RCTs (186 participants, 1 study number of participants not reported)	Cochrane RoB: Low to high quality				
Al-Moraissi, 2015[29]	Open surgery	Arthroscopic surgery	Maximal interincisal opening, > 35 mm, cumulative: OR = 1.33; 95% CI, 0.56 to 3.18; *P* = 0.52, fixed effects χ^2 = 0.12, df = 2, *P* = 0.94, I^2 = 0%	Favourable, non-statistically significant	2 RCTs 1 RS (OS, n = 48; AS n = 54)	Low to moderate RoB[a]				
Al-Moraissi, 2015[29]	Arthroscopic lysis and lavage	Arthroscopic surgery	Maximal interincisal opening (1 to 2 years): WMD = –11.09 mm; 95% CI –16.57 mm to –5.60 mm; *P* = 0.0001, fixed effects; χ^2 = 7.01, df = 1, *P* = 0.008, I^2 = 86%	Unfavourable, statistically significant	1 CCT 1 RS (ALL, n = 67; AS n = 46)	Moderate RoB[a]				

AC = arthrocentesis; AS = arthroscopy; CCT = controlled clinical trial; CI = confidence interval; MD = mean difference; MMO = maximal mouth opening; OR = odds ratio; RCT = randomized controlled trial; RoB = Risk of Bias; RS = retrospective study; WMD = weighted mean difference.

[a] The classification of the RoB potential for each study was based on the following five criteria: (1) random selection in the population, (2) definition of inclusion and exclusion criteria, (3) report of losses to follow-up, (4) validated measurements, and (5) statistical analysis.

TMJ Clicking

One SR[29] reported on joint noise or TMJ clicking for surgical interventions. The findings are reported in Table 23, and have been summarized here.

Surgical interventions with unfavourable results:

- Open surgery versus arthroscopic surgery (MA, two RCTs, one CCT, low to moderate risk of bias), NS.[29]

Table 23: Summary of Surgical Interventions for TMJ Clicking in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of Studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Surgical						
Al-Moraissi, 2015[29]	Open surgery	Arthroscopic surgery	*Clicking, joint tenderness/ pain, and crepitation:* OR = 1.74; 95% CI, 0.76 to 3.98; *P* = 0.19, fixed effects, χ^2 = 0.98, df = 2, *P* = 0.61, I^2 = 0%	Unfavourable, non-statistically significant	2 RCTs 1 RS (AS n = 54; OS n = 48)	Low to moderate RoB[a]

AS = arthroscopy or arthroscopic surgery; CI = confidence interval; OR = odds ratio; OS = open surgery; RCT = randomized controlled trial; RoB = Risk of Bias; RS = retrospective study; WMD = weighted mean difference.

[a] The classification of the RoB potential for each study was based on the following five criteria: (1) random selection in the population, (2) definition of inclusion and exclusion criteria, (3) report of losses to follow-up, (4) validated measurements, and (5) statistical analysis.

Adverse Events

One SR[29] reported on adverse events for surgical interventions. The findings are reported in Table 24, and have been summarized below.

Surgical interventions with unfavourable results:

- Arthrocentesis versus arthroscopy (MA, two RCTs, one CCT, one RS, low to moderate risk of bias), NS[30] (Therefore, favourable, NS for arthroscopy).

Table 24: Summary of Surgical Interventions for Adverse Events in TMD

First Author, Year	Intervention	Comparison	Findings	Summary of Evidence	Number and Type of studies (# of participants)	Quality of Primary Studies and/or Body of Evidence (reported by SR authors)
Surgical						
Al-Moraissi, 2015[29]	Arthrocentesis	Arthroscopy	*Incidence of post-operative complications, OR:* 1.15; 95% CI, 0.30 to –4.43, Z = 0.20, *P* = 0.84 χ^2 =0.49, df = 2, *P* < 0.78, I^2 = 0%	Unfavourable, non-statistically significant	2 RCT 1 CCT 1 RS (AC n = 78; AS n = 92)	4 studies moderate RoB 2 studies low RoB[a]

AC= arthrocentesis; AS= arthroscopy or arthroscopic surgery; CCT = controlled clinical trial; CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial; RoB = Risk of Bias; RS = retrospective study.

[a] The classification of the RoB potential for each study was based on the following five criteria: (1) random selection in the population, (2) definition of inclusion and exclusion criteria, (3) report of losses to follow-up, (4) validated measurements, and (5) statistical analysis.

Limitations

Selection of evidence

Quality assessment of the included SRs found that there was a low level of concern regarding their identification and the selection of primary studies (i.e., the SRs included the components of PICO (i.e., population, intervention, comparator group, and outcome), they used a comprehensive literature search, and they performed the study selection in duplicate). However, the overview would not have captured primary studies that were not included in the SRs (e.g., very recently published studies). In addition, due to the high degree of overlap between SRs, it was necessary to exclude some SRs that contained only a small number of unique primary studies (i.e., one to four studies) in an effort to avoid double counting primary studies and overrepresenting certain findings. Due to the high volume of literature identified, it is unlikely that these studies would have contributed substantially to our findings as there was very little usable data or the studies examined unusual or uncommon interventions. Numerous SRs investigated multiple types of interventions compared with multiple different comparator interventions (rather than restricting their SR to one intervention compared with one comparator), therefore, substantial overlaps between some SRs remained. The splint therapy SRs had a particularly high degree of overlap with each other, which suggests an overrepresentation of this evidence. The decision to include or exclude SRs based on their primary studies was done on a case-by-case basis in order to find a balance between avoiding double counting evidence and avoiding missing important findings. Two reviewers were involved, and followed general criteria for exclusion, but subjectivity could not be avoided.

Available granularity of evidence

The overviews methodology allowed us to bring together, appraise and synthesize the results related SRs, and thus we were able to capture a large number of interventions, comparators, and outcomes that would not have been feasible in a SR of primary studies. There are limitations to the methodology — when the unit of analysis is a SR, instead of a primary study, did not allow for direct comparisons of primary studies included in the SRs.

Instead, this report relied on the quality/risk of bias assessments and interpretations made by the authors of the SRs. In addition, an overview of SRs does not capture the heterogeneity in methods and assumptions across the included primary studies. For example, the wear time for stabilization splints can vary across primary studies, or the type of manual therapy can differ across studies included in a meta-analysis, but this information is not typically provided. In addition, many of the findings were presented without statistical testing or numerical data, and we cannot be certain that the evidence was interpreted appropriately by the SR authors. Furthermore, a large portion of the evidence was only presented in narrative summaries which caused challenges with data extraction as well as applying our classification system to summarize the evidence, which involved some subjectivity. We mitigated some of the subjectivity by using paired reviewers.

Quality of evidence

A key limitation is the quality of the evidence. The majority of the evidence in this overview is from SRs that synthesize evidence from moderate to poor quality primary studies, and we have low or critically low levels of confidence in the results. Of the 14 SRs that conducted a meta-analysis or a NMA, we had low confidence in the results from one SR[20] as it had one critical flaw, and two non-critical weaknesses. The other 13 SRs with meta-analysis had two or more critical flaws, and therefore we had critically low confidence in the results of these SRs.[18,19,21-31] There were seven other SRs that did not conduct a meta-analysis, and therefore the results are more challenging to interpret, however, we had high confidence in the results from two of these SRs[33,36] as they were only lacking justification for their study designs. We had a low level of confidence in two of the other SRs without meta-analysis,[34,39] and critically low confidence in the other SRs without MA.[35,37,38] One additional SR[32] on orthodontics for TMD did not find any primary studies and did not contribute evidence to the overview, and we have moderate confidence in the findings of this review.

Furthermore, a large proportion of the primary studies within the SRs were assessed by the SR authors as having a high or unclear risk of bias, or to be of low quality (depending on the tool used or the way the authors reported the risk of bias/quality). Although more than half of the SRs used an appropriate tool for assessing the risk of bias of the included studies, the remaining seven either did not use a validated approach, or did not describe their approach.[21,23,26,29-31,35]

Heterogeneity and variability in approaches

The inclusion criteria for the intervention for this report was very broad (any pharmacological or non-pharmacological intervention for TMD) as were the criteria for the comparators (any alternative intervention or no intervention), which ensured that all relevant interventions and comparators were captured, however, this resulted in a very large volume of heterogeneous information, thus making informed conclusions challenging. Within each class of intervention, there were multiple different interventions, for example, psychological interventions included hypnosis, relaxation therapy, habit reversal, cognitive behavioural therapy, and biofeedback, and these interventions were compared against multiple different control groups that were not consistently used across SRs (including no treatment, within class comparators [e.g., an alternative psychological treatment], or a comparator from a different class of intervention [e.g., splints]). Further complicating matters, some SRs chose to use mixed control groups as comparators (e.g., manual therapy versus any other therapy [e.g., splint, self-care, or medication][24]) in MAs or qualitative synthesis, thus making it challenging to form conclusions between treatments, as we could not separate out the

treatments in the control groups. The heterogeneity of comparisons within the primary studies also affected the ability of the SR authors to conduct appropriate MAs. Some of the SRs did not include meta-analysis due to the heterogeneity of the primary studies, while others did conduct a meta-analysis despite the heterogeneity, however, we determined that many of these SRs did not use appropriate methods for combining the primary studies and may have a high risk of bias from combining heterogeneous evidence.

Furthermore, there is a lack of consensus in the literature for the definition of TMD. As described in Table 1, TMD is a general term to describe pain and/or dysfunction of the TMJ, masticatory muscles, and supporting structures. As such, the diagnostic categories in some SRs were very broad or lacked clarity, therefore increasing the heterogeneity of the population in the overview.

A number of SRs reported pooled mean differences in pain (measured on the visual analogue scale), and mouth opening (measured in millimetres), rather than standardized mean differences. For these measures we did not have a consistent and satisfactory approach for designating pooled weighted mean differences and mean differences as neutral (both confidence limits lying close to the null). As a consequence, all results that reported mean difference are either favourable or unfavourable, with no mean differences reported as neutral.

Generalizability

The authors of the SRs were affiliated with institutions from around the world, including two institutions from Canada, however, we do not know the countries in which the 251 primary studies captured by the SRs were conducted, and therefore we cannot be certain whether the findings are generalizable to the Canadian clinical practice, as there may be differences in the manner in which care for patients with TMD is provided between countries.

Given that TMD encompasses multiple different diagnoses, the inclusion criteria for the population of this report was broad — patients of any age with TMD (pain and/or dysfunction of the masticatory apparatus including the TMJ, masticatory muscles, and supporting structures). As such, the SRs included a variety of different populations, including osteoarthritis of the TMJ, articular TMD, muscular TMD, and disc displacement, which may limit the generalizability of the findings.

Evidence gaps

We identified a number of evidence gaps. There was a lack of evidence comparing adverse events between interventions, with adverse events only reported in four classes of intervention (pharmacological injections, pharmacological oral, acupuncture or laser physiotherapy, and surgical interventions). Adverse events were compared between surgical interventions with a meta-analysis, but the other SRs reported their adverse events narratively. There was also a small quantity of evidence on the outcome of TMJ clicking. Four intervention categories reported this outcome (splint, pharmacological injections, acupuncture or laser physiotherapy, and surgical), each with only one or two SRs reporting TMJ clicking, half of which were narrative findings.

There was also a lack of evidence for certain classes of intervention. One SR on orthodontics for treating TMD[32] did not find any relevant RCTs, and therefore there is no evidence for the class of intervention within this overview of SRs. None of the SRs examined occlusal appliances or non-occluding appliances as the intervention of interest, and these

treatments were only used as comparators for splints and needle acupuncture, and therefore there is only limited evidence on occlusal and non-occlusal appliances.

No evidence was identified regarding remote/isolated populations, Indigenous Populations, or populations at risk due to high caries and/or periodontal disease or parafunctional habits.

An inherent methodological challenge of overviews of SRs is that the evidence is only as recent as the search date of the most recent SR. Therefore, this overview may have missed emerging evidence (i.e., primary studies) published since the most recent included SR was published. We did not update the included SRs as there is currently no way to systematically investigate whether an update in the context of overviews is necessary.[41]

Literature from 2000 to 2008 was reviewed and of nine potentially relevant SRs, three SRs were identified as potentially eligible[42-45] with few unique studies and minimal additional information. One SR reported limited evidence from three RCTs of unclear and high risk of bias that examined occlusal adjustments for treating TMD.[42] This SR found that occlusal adjustment did not significantly reduce pain when compared with placebo, reassurance, or no treatment (one RCT per comparator).[42] A SR[44] on intra-articular injections of hyaluronate both alone or in combination with surgery for TMD had three unique studies. One RCT reported a favourable but inconclusive reduction in pain for sodium hyaluronate versus placebo, and which is similar to the results reported in Table 14.[44] The other two RCTs reported on combinations of surgery plus hyaluronate injections, which are unique comparisons that preclude any definitive conclusions from being made from this evidence. The other SR[45] on stabilization splints had three unique studies that reported distinctive comparisons; however, the evidence is limited to single RCTs per comparison.

Conclusions and Implications for Decision or Policy-Making

This overview includes 22 SRs covering 252 primary studies published between 1983 and 2017 on the effectiveness and safety of interventions for TMD in adults and children.

Psychological Interventions

For psychological interventions, limited evidence from one SR[19] with critically low confidence in the results, and one SR[20] with low confidence in the results, reported statistically significant favourable findings for pain improvement for long-term (more than three months) cognitive behavioural therapy alone or in combination with biofeedback, and hypnosis or relaxation therapy, however, the evidence was associated with unclear or high risk of bias. With regard to MMO, one SR[19] identified one RCT which the authors considered to be low quality, which found that hypnosis or relaxation therapy had unfavourable results for MMO, but we had critically low confidence in the results of this SR.

Acupuncture or Laser Therapies

For acupuncture or laser physiotherapies, much of the evidence had unclear or high risk of bias, and there was a lot of heterogeneity, and our level of confidence in each of the SRs was critically low. Evidence from one SR[21] suggests that LLLT may be associated with improvements in pain and MMO (versus placebo). Evidence from two SRs,[22,37] suggests that needle acupuncture may be associated with improvements in pain (versus sham acupuncture). There is limited, inconclusive evidence[37] that acupuncture (versus sham or wait list) may have favourable results for TMJ clicking. Limited information regarding

adverse events was reported. None of the comparisons yielded statistically significantly unfavourable results.

Manual Physiotherapies

For manual physiotherapies, our level of confidence in the results of each of the SRs was critically low. One SR[24] reported statistically significant favourable evidence of moderate quality that manual therapy with and without jaw exercises can reduce pain intensity (versus a mixed control). This SR also reported statistically significant favourable findings with regards to MMO from moderate quality evidence for manual therapy plus jaw exercises (versus a mixed control) and posture correcting exercises (versus no treatment). The mixed control group used in these comparisons combined alternative interventions (i.e., splint, medication) with no treatment options (i.e., wait list, self-care), thus limiting the conclusions that can be drawn from the evidence. One SR[23] reported a statistically significant unfavourable pain outcome for musculoskeletal manual therapy, and a statistically significant improvement in MMO from musculoskeletal manual therapy (compared with an active control). This SR reported its evidence as high quality, however, it is unclear whether the risk of bias tool was appropriate, and the active control groups used conventional conservative treatment, usual care, or home exercises, thus increasing the risk of bias in the results.

Splint Therapy

For splint therapy, we had critically low levels of confidence in the results from the SRs. Much of the evidence was from one SR[26] that mainly reported findings from individual RCTs of low quality with high heterogeneity between treatments and controls, which could not be combined in a meta-analysis. Statistically significantly favourable findings for pain improvement for stabilization splints and hard stabilization appliances (versus non-occluding appliances) from evidence determined to be low to high quality were reported by two SRs.[25,26] Another SR[28] reported improvements in pain and MMO for splints versus a mixed control group; however, the evidence had a very high risk of bias. Statistically significantly unfavourable results were reported in one moderate quality SR[25] for MMO for stabilization splint compared with a mixed control group with mostly low-quality evidence. Limited evidence was available for TMJ clicking and adverse events.

Orthodontic Interventions

No evidence was found for orthodontic interventions.

Pharmacological Injections

For pharmacological injections, evidence of low to medium risk of bias from a NMA[18] suggests that cyclobenzaprine hydrochloride, botulinum toxin, and ping-on have statistically significantly favourable effects for pain improvement (compared with a placebo); however, our level of confidence in this SR is critically low. One SR[27] reported that statistically significantly favourable improvements in pain and MMO for inferior or double spaces injections of hyaluronate or prednisolone versus superior space injections of the same drug, from evidence they determined to be moderate risk of bias. Statistically significantly unfavourable changes in MMO were reported in one SR[31] for intra-articular injections of corticosteroids (versus a placebo injection) after arthrocentesis, from evidence they reported as low risk of bias, although it is unclear whether their risk of bias assessment was accurate. However, our level of confidence in the results from both of these SRs[27,31] was critically low.

Additional evidence from SRs that did not perform any MAs,[34,35,38] with low and critically low levels of confidence in the results, contributed inconclusive findings from RCTs with high and unclear risk of bias. Limited evidence was available for TMJ clicking and adverse events.

Oral Pharmacological Interventions

For oral pharmacological interventions, mostly neutral results were reported for pain and MMO when compared with placebos from two SRs[33,36] that did not include a meta-analysis, and included with low to high-quality evidence. Our overall level of confidence in the results from these SRs was high, as there was only one non-critical weakness. No statistically significantly favourable or unfavourable results were reported. No evidence was found for TMJ clicking, and only limited evidence was reported for adverse events.

Surgical Interventions

For surgical studies, there is limited evidence from two SRs[29,30] to suggest that open surgery is better than arthroscopic surgery and that arthroscopy is better than arthrocentesis for pain improvement, and that arthroscopy is better than arthroscopic lysis and lavage for MMO. However, in these MAs, low to moderate risk of bias evidence from RCTs, CCTs, and retrospective studies with high heterogeneity were combined in the meta-analysis, which may not have been appropriate, and we have critically low confidence in these results. Limited evidence was identified for TMJ clicking and adverse events.

Very limited evidence was identified regarding adverse events for TMD interventions, and therefore no conclusions can be made.

Overall, it is difficult to draw clear conclusions regarding the optimal interventions for the treatment of TMD. The quality of the evidence is low and the risk for bias was high. Additionally, the absence of direct comparisons between most interventions limits the ability to determine which intervention is optimal. Long-term cognitive behavioural therapy, LLLT, manual therapy targeted to the orofacial region (with and without jaw exercises), some splint therapies, cyclobenzaprine hydrochloride, botulinum toxin, inferior space injection or double spaces injection of hyaluronate or prednisolone, and ping-on ointment, and open surgery seem to show the most favourable results compared with various other treatments and placebo. Some manual therapies, intra-articular injections of corticosteroids, and hypnosis seemed to show the most unfavourable results compared with various other interventions. Most oral and topical therapies did not seem to have a favourable or unfavourable effect. The results for occlusal adjustment were limited and no evidence was found suggesting that it is associated with favourable or unfavourable results; this is further corroborated by an SR published in 2003.[42]

Considerations for future research should include SRs that focus on one specific treatment compared with a different specific treatment, and avoid grouping multiple different treatment options as a general control. This would reduce the heterogeneity of the evidence, and allow for stronger conclusions to be drawn from the data. There appears to be a paucity of high-quality RCTs on interventions for TMD, and future work is needed to design and conduct high-quality RCTs. SRs and RCTs should strive for better reporting of adverse events. Additional research is needed on orthodontic, occlusal, and non-occlusal interventions for TMD.

References

1. Diagnosis and management of temporomandibular disorders [draft]. Toronto (ON): Royal College of Dental Surgeons of Ontario; 2018.
2. Prevalence of TMJD and its signs and symptoms. Bethesda (MD): National Institute of Dental and Craniofacial Research; 2018: https://www.nidcr.nih.gov/research/data-statistics/facial-pain/prevalence. Accessed Aug 10, 2018.
3. Armijo-Olivo SL, Gadotti IC. Chapter 4: Temporomandibular disorders. In: Magee DJ, Zachazewski JE, Quillen WS, Manske RC, eds. *Pathology and Intervention in musculoskeletal rehabilitation*. 2nd ed. Maryland Heights (MO): Elsevier; 2016:119-156.
4. Østensjø V, Moen K, Storesund T, Rosén A. Prevalence of painful temporomandibular disorders and correlation to lifestyle factors among adolescents in Norway. *Pain Res Manag.* 2017:2164825. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5468573/. Accessed Aug 10, 2018.
5. Temporomandibular joint syndrome. London (UK): BMJ Publishing Group; 2018: https://bestpractice.bmj.com/topics/en-gb/429. Accessed Aug 10, 2018.
6. Mayo-Wilson E, Golozar A, Cowley T, et al. Methods to identify and prioritize patient-centered outcomes for use in comparative effectiveness research. *Pilot Feasibility Stud.* 2018;4:95.
7. TMD (Temporomandibular joint disorder). Ottawa (ON): Canadian Dental Association; 2018: https://www.cda-adc.ca/en/oral_health/talk/complications/temporomandibular_disorder/. Accessed Aug 10, 2018.
8. Scrivani SJ. Tempromandibular disorders in adults. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2018: www.uptodate.com. Accessed Aug 10, 2018.
9. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
10. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
11. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. *J Clin Epidemiol.* 2009;62(4):380-386.e381.
12. Total prosthetic replacement of the temporomandibular joint: a rapid evidence assessment and economic analysis. Edmonton (AB): Institute of Health Economics; 2013.
13. Pieper D, Antoine SL, Mathes T, Neugebauer EA, Eikermann M. Systematic review finds overlapping reviews were not mentioned in every other overview. *J Clin Epidemiol.* 2014;67(4):368-375.
14. Dosenovic S, Jelicic Kadic A, Miljanovic M, et al. Interventions for neuropathic pain: an overview of systematic reviews. *Anesth Analg.* 2017;125(2):643-652.
15. Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. *Am Psychol.* 2012;67(6):446-462.
16. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed Aug 10, 2018.
17. Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health.* 2011;14(4):417-428.
18. Haggman-Henrikson B, Alstergren P, Davidson T, et al. Pharmacological treatment of oro-facial pain - health technology assessment including a systematic review with network meta-analysis. *J Oral Rehabil.* 2017;44(10):800-826.
19. Zhang Y, Montoya L, Ebrahim S, et al. Hypnosis/relaxation therapy for temporomandibular disorders: a systematic review and meta-analysis of randomized controlled trials. *J Oral Facial Pain Headache.* 2015;29(2):115-125.
20. Aggarwal VR, Lovell K, Peters S, Javidi H, Joughin A, Goldthorpe J. Psychosocial interventions for the management of chronic orofacial pain. *Cochrane Database Syst Rev.* 2011(11):CD008456.
21. Xu GZ, Jia J, Jin L, Li JH, Wang ZY, Cao DY. Low-level laser therapy for temporomandibular disorders: a systematic review with meta-analysis. *Pain Res Manag.* 2018;2018:4230583.
22. Jung A, Shin BC, Lee MS, Sim H, Ernst E. Acupuncture for treating temporomandibular joint disorders: a systematic review and meta-analysis of randomized, sham-controlled trials. *J Dent.* 2011;39(5):341-350.
23. Martins WR, Blasczyk JC, Aparecida Furlan de Oliveira M, et al. Efficacy of musculoskeletal manual approach in the treatment of temporomandibular joint disorder: a systematic review with meta-analysis. *Manual Ther.* 2016;21:10-17.
24. Armijo-Olivo S, Pitance L, Singh V, Neto F, Thie N, Michelotti A. Effectiveness of manual therapy and therapeutic exercise for temporomandibular disorders: systematic review and meta-analysis. *Phys Ther.* 2016;96(1):9-25.
25. Kuzmanovic Pficer J, Dodic S, Lazic V, Trajkovic G, Milic N, Milicic B. Occlusal stabilization splint for patients with temporomandibular disorders: meta-analysis of short and long term effects. *PLoS ONE.* 2017;12(2):e0171296.

26. Fricton J, Look JO, Wright E, et al. Systematic review and meta-analysis of randomized controlled trials evaluating intraoral orthopedic appliances for temporomandibular disorders. *J Orofac Pain.* 2010;24(3):237-254.
27. Li C, Zhang Y, Lv J, Shi Z. Inferior or double joint spaces injection versus superior joint space injection for temporomandibular disorders: a systematic review and meta-analysis. *J Oral Maxillofac Surg.* 2012;70(1):37-44.
28. Zhang C, Wu JY, Deng DL, et al. Efficacy of splint therapy for the management of temporomandibular disorders: a meta-analysis. *Oncotarget.* 2016;7(51):84043-84053.
29. Al-Moraissi EA. Open versus arthroscopic surgery for the management of internal derangement of the temporomandibular joint: a meta-analysis of the literature. *Int J Oral Maxillofac Surg.* 2015;44(6):763-770.
30. Al-Moraissi EA. Arthroscopy versus arthrocentesis in the management of internal derangement of the temporomandibular joint: a systematic review and meta-analysis. *Int J Oral Maxillofac Surg.* 2015;44(1):104-112.
31. Liu Y, Wu J, Fei W, et al. Is there a difference in intra-articular injections of corticosteroids, hyaluronate, or placebo for temporomandibular osteoarthritis? *J Oral Maxillofac Surg.* 2018;76(3):504-514.
32. Luther F, Layton S, McDonald F. Orthodontics for treating temporomandibular joint (TMJ) disorders. *Cochrane Database Syst Rev.* 2010(7):CD006541.
33. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. *Cochrane Database Syst Rev.* 2010(10):CD004715.
34. Machado E, Machado P, Wandscher VF, Marchionatti AME, Zanatta FB, Kaizer OB. A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. *Int J Oral Maxillofac Surg.* 2018;22:22.
35. Goiato MC, da Silva EV, de Medeiros RA, Turcio KH, Dos Santos DM. Are intra-articular injections of hyaluronic acid effective for the treatment of temporomandibular disorders? A systematic review. *Int J Oral Maxillofac Surg.* 2016;45(12):1531-1537.
36. Melo G, Casett E, Stuginski-Barbosa J, et al. Effects of glucosamine supplements on painful temporomandibular joint osteoarthritis: A systematic review. *J Oral Rehabil.* 2018;45(5):414-422.
37. Cho SH, Whang WW. Acupuncture for temporomandibular disorders: a systematic review. *J Orofac Pain.* 2010;24(2):152-162.
38. Bousnaki M, Bakopoulou A, Koidis P. Platelet-rich plasma for the therapeutic management of temporomandibular joint disorders: a systematic review. *Int J Oral Maxillofac Surg.* 2018;47(2):188-198.
39. Nagori SA, Roy Chowdhury SK, Thukral H, Jose A, Roychoudhury A. Single puncture versus standard double needle arthrocentesis for the management of temporomandibular joint disorders: a systematic review. *J Oral Rehabil.* 2018;11:11.
40. Stoustrup P, Kristensen KD, Verna C, Kuseler A, Pedersen TK, Herlin T. Intra-articular steroid injection for temporomandibular joint arthritis in juvenile idiopathic arthritis: a systematic review on efficacy and safety. *Semin Arthritis Rheum.* 2013;43(1):63-70.
41. Pollock A, Campbell P, Brunton G, Hunt H, Estcourt L. Selecting and implementing overview methods: implications from five exemplar overviews. *Syst Rev.* 2017;6(1):145.
42. Koh H, Robinson PG. Occlusal adjustment for treating and preventing temporomandibular joint disorders. *Cochrane Database Syst Rev.* 2003(1):CD003812.
43. Medlicott MS, Harris SR. A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. *Phys Ther.* 2006;86(7):955-973.
44. Shi Z, Guo C, Awad M. Hyaluronate for temporomandibular joint disorders. *Cochrane Database Syst Rev.* 2003(1):CD002970.
45. Turp JC, Komine F, Hugger A. Efficacy of stabilization splints for the management of patients with masticatory muscle pain: a qualitative systematic review. *Clin Oral Investig.* 2004;8(4):179-195.
46. Young KA, Wise JA, DeSaix P, et al. Anatomy and physiology. Houston (TX): OpenStax College; 2013.
47. Paco M, Peleteiro B, Duarte J, Pinho T. The effectiveness of physiotherapy in the management of temporomandibular disorders: a systematic review and meta-analysis. *J Oral Facial Pain Headache.* 2016;30(3):210-220.
48. Randhawa K, Bohay R, Cote P, et al. The effectiveness of noninvasive interventions for temporomandibular disorders: a systematic review by the Ontario Protocol for Traffic Injury Management (OPTIMa) Collaboration. *Clin J Pain.* 2016;32(3):260-278.
49. Gross A, Langevin P, Burnie SJ, et al. Manipulation and mobilisation for neck pain contrasted against an inactive control or another active treatment. *Cochrane Database Syst Rev.* 2015(9):CD004249.
50. Calixtre LB, Moreira RF, Franchini GH, Alburquerque-Sendin F, Oliveira AB. Manual therapy for the management of pain and limited range of motion in subjects with signs and symptoms of temporomandibular disorder: a systematic review of randomised controlled trials. *J Oral Rehabil.* 2015;42(11):847-861.
51. Chen YW, Chiu YW, Chen CY, Chuang SK. Botulinum toxin therapy for temporomandibular joint disorders: a systematic review of randomized controlled trials. *Int J Oral Maxillofac Surg.* 2015;44(8):1018-1026.
52. Chen J, Huang Z, Ge M, Gao M. Efficacy of low-level laser therapy in the treatment of TMDs: a meta-analysis of 14 randomised controlled trials. *J Oral Rehabil.* 2015;42(4):291-299.

53. Januzzi E, Nasri-Heir C, Grossmann E, Leite FM, Heir GM, Melnik T. Combined palliative and anti-inflammatory medications as treatment of temporomandibular joint disc displacement without reduction: a systematic review. *Cranio.* 2013;31(3):211-225.

54. Vos LM, Huddleston Slater JJ, Stegenga B. Lavage therapy versus nonsurgical therapy for the treatment of arthralgia of the temporomandibular joint: a systematic review of randomized controlled trials. *J Orofac Pain.* 2013;27(2):171-179.

55. de Souza RF, Lovato da Silva CH, Nasser M, Fedorowicz Z, Al-Muharraqi MA. Interventions for the management of temporomandibular joint osteoarthritis. *Cochrane Database Syst Rev.* 2012(4):CD007261.

56. Petrucci A, Sgolastra F, Gatto R, Mattei A, Monaco A. Effectiveness of low-level laser therapy in temporomandibular disorders: a systematic review and meta-analysis. *J Orofac Pain.* 2011;25(4):298-307.

57. Rigon M, Pereira LM, Bortoluzzi MC, Loguercio AD, Ramos AL, Cardoso JR. Arthroscopy for temporomandibular disorders. *Cochrane Database Syst Rev.* 2011(5):CD006385.

58. La Touche R, Angulo-Diaz-Parreno S, de-la-Hoz JL, et al. Effectiveness of acupuncture in the treatment of temporomandibular disorders of muscular origin: a systematic review of the last decade. *J Altern Complement Med.* 2010;16(1):107-112.

59. Guo C, Shi Z, Revington P. Arthrocentesis and lavage for treating temporomandibular joint disorders. *Cochrane Database Syst Rev.* 2009(4):CD004973.

60. Aggarwal VR, Tickle M, Javidi H, Peters S. Reviewing the evidence: can cognitive behavioral therapy improve outcomes for patients with chronic orofacial pain? *J Orofac Pain.* 2010;24(2):163-171.

61. Moldez MA, Camones VR, Ramos GE, Padilla M, Enciso R. Effectiveness of intra-articular injections of sodium hyaluronate or corticosteroids for intracapsular temporomandibular disorders: a systematic review and meta-analysis. *J Oral Facial Pain Headache.* 2018;32(1):53-66.

62. Vier C, Almeida MB, Neves ML, Santos A, Bracht MA. The effectiveness of dry needling for patients with orofacial pain associated with temporomandibular dysfunction: a systematic review and meta-analysis. *Braz J Phys Ther.* 2018.

63. Davoudi A, Khaki H, Mohammadi I, et al. Is arthrocentesis of temporomandibular joint with corticosteroids beneficial? A systematic review. *Med Oral Patol Oral Cir Bucal.* 2018;23(3):e367-e375.

64. Dickerson SM, Weaver JM, Boyson AN, et al. The effectiveness of exercise therapy for temporomandibular dysfunction: a systematic review and meta-analysis. *Clin Rehabil.* 2017;31(8):1039-1048.

65. Roldan-Barraza C, Janko S, Villanueva J, Araya I, Lauer HC. A systematic review and meta-analysis of usual treatment versus psychosocial interventions in the treatment of myofascial temporomandibular disorder pain. *J Oral Facial Pain Headache.* 2014;28(3):205-222.

66. Liu HX, Liang QJ, Xiao P, Jiao HX, Gao Y, Ahmetjiang A. The effectiveness of cognitive-behavioural therapy for temporomandibular disorders: a systematic review. *J Oral Rehabil.* 2012;39(1):55-62.

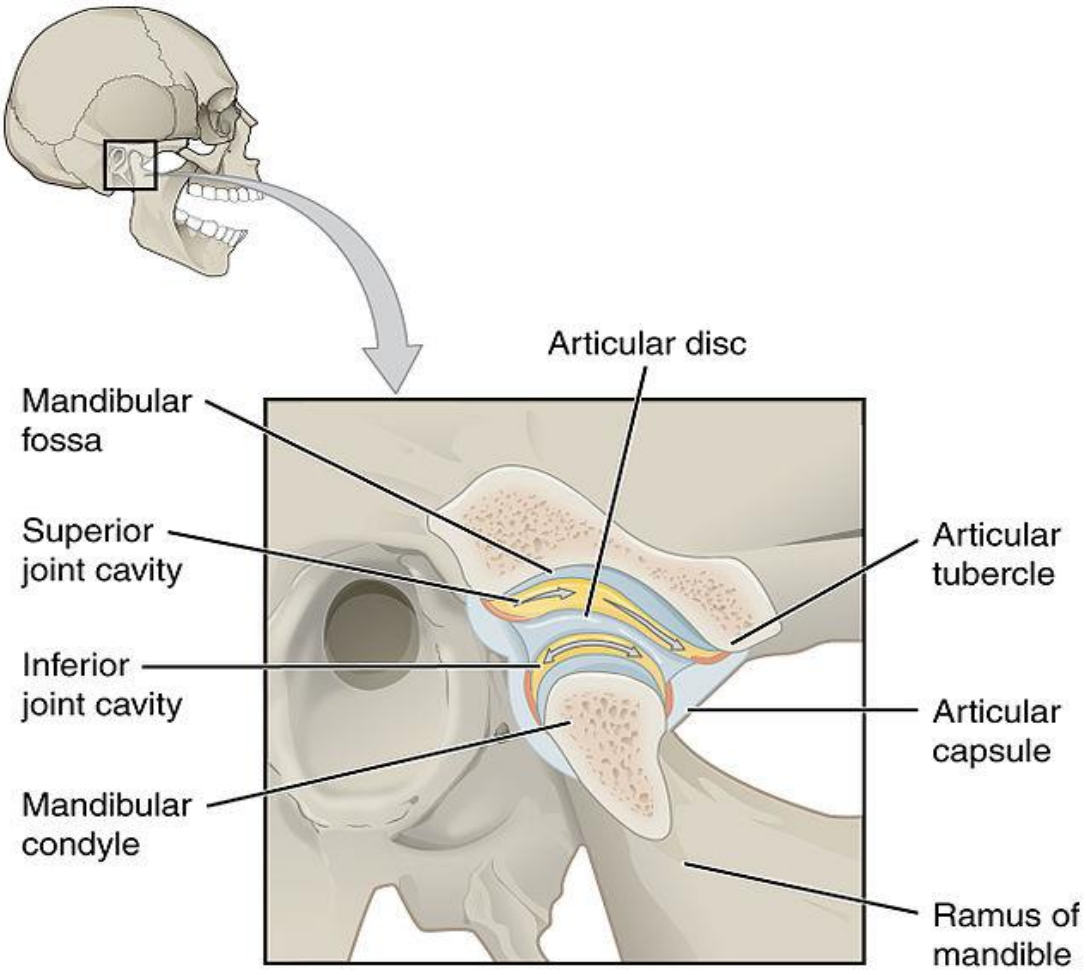
67. Al-Baghdadi M, Durham J, Araujo-Soares V, Robalino S, Errington L, Steele J. TMJ disc displacement without reduction management: a systematic review. *J Dent Res.* 2014;93(7 Suppl):37S-51S.

68. Fernandes AC, Duarte Moura DM, Da Silva LGD, De Almeida EO, Barbosa GAS. Acupuncture in temporomandibular disorder myofascial pain treatment: a systematic review. *J Oral Facial Pain Headache.* 2017;31(3):225-232.

69. Chang WD, Lee CL, Lin HY, Hsu YC, Wang CJ, Lai PT. A meta-analysis of clinical effects of low-level laser therapy on temporomandibular joint pain. *J Phys Ther Sci.* 2014;26(8):1297-1300.

Appendix 1: Anatomical Structures

Figure 1: The Osteology of the Temporomandibular Joint[46]



Source: Young KA, Wise JA, DeSaix P, et al. Anatomy & physiology. Houston (TX): OpenStax College; 2013.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2018 July 09 Ovid MEDLINE All 1946 to July 09, 2018 PsycINFO 1806 to July Week 1 2018 **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	July 10 2018
Alerts:	Monthly search updates began July 11, 2018, bi-weekly search updates will run until project completion
Study Types:	Systematic reviews; meta-analyses; technology assessments
Limits:	Publication years: 2008 to present Language limit: English

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.rn	CAS registry number
.dq	Candidate term word (Embase)
.id	Key concepts (PsycINFO)
.jw	Journal word
.hw	Heading word
.mp	Multi-purpose
.md	Methodology (PsychINFO)

CLINICAL DATABASE SEARCH STRATEGY	
1	exp Temporomandibular Joint Disorders/ or exp Temporomandibular Joint/
2	(Temporomandibular or temporo-mandibular or craniomandibular or cranio-mandibular or Costen syndrome or TMJ or TMD or TMJD).ti,ab,kf.
3	exp Temporomandibular Joint Disorder/ or exp Temporomandibular Joint Disc/
4	(Temporomandibular or temporo-mandibular or craniomandibular or cranio-mandibular or Costen syndrome or TMJ or TMD or TMJD).ti,ab,kw,dq.
5	Jaw/ or (jaw or jaws or jawbone*).ti,ab,id.
6	Joint Disorders/ or joint*.ti,ab,id.
7	(Temporomandibular or temporo-mandibular or craniomandibular or cranio-mandibular or Costen syndrome or TMJ or TMD or TMJD).ti,ab,id.
8	1 or 2
9	8 use medall
10	3 or 4
11	10 use oemezd
12	11 not conference abstract.pt.
13	(5 and 6) or 7
14	13 use psyh
15	meta-analysis.pt.
16	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
17	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
18	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
19	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
20	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
21	(handsearch* or hand search*).ti,ab,kf,kw.
22	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
23	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
24	(meta regression* or metaregression*).ti,ab,kf,kw.
25	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
26	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
27	(cochrane or (health adj2 technology assessment) or evidence report).jw.
28	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
29	(outcomes research or relative effectiveness).ti,ab,kf,kw.
30	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
31	(meta-analysis or systematic review).md.
32	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
33	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
34	umbrella review*.ti,ab,kf,kw.
35	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
36	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.

CLINICAL DATABASE SEARCH STRATEGY	
37	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
38	or/15-37
39	9 or 12 or 14
40	39 and 38
41	limit 40 to english language
42	limit 41 to yr="2008 -Current"
43	remove duplicates from 42

OVERVIEW	
PubMed	A limited PubMed search will be performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 7, 2018	Same MeSH, keywords, and date limits were used as per the MEDLINE search. Syntax was adjusted for Cochrane Library databases. Study types searched included: Reviews and technology assessments

Grey Literature

Dates for Search:	July 10-13, 2018
Keywords:	Included terms temporomandibular joint, temporomandibular disorder
Limits:	Publication years 2008-2018

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Databases (free)
- Internet Search.

The following sites were also searched:

- Canadian Dental Association (CDA)

http://www.cda-adc.ca/en/index.asp

- ADA. Center for Evidence-Based Dentistry. Evidence Database

http://ebd.ada.org/en/evidence/evidence-by-topic

Appendix 3: Classification Scale for Summarizing Evidence from SRs

Scale for Summarizing the Evidence From SRs Without Meta-Analysis

Favourable: all of the evidence shows positive effects for the interventions versus comparator
Favourable, inconclusive: most of the evidence shows positive effects for the interventions versus comparator, but some evidence is neutral or negative
Neutral: no difference observed between the effects of the interventions
Unfavourable, inconclusive: most of the evidence is shows negative effects for the interventions versus comparator, but some evidence is neutral or positive
Unfavourable: all of the evidence is shows negative effects for the interventions versus comparator

No evidence: there is no evidence from RCTs (empty reviews).

Scale for Summarizing the Evidence From Meta-Analysis (relative risk, odds ratios)

Favourable, statistically significant: there is an effect in favour of the intervention, CI does not cross 1, or *P* value < 0.05
Favourable, non-statistically significant: there is an effect in favour of the intervention, CI crosses 1, or *P* value > 0.05
Neutral: effect size between 0.95 and 1.05 and the confidence interval (CI) crosses 1
Unfavourable, non-statistically significant: there is an effect in favour of the comparator, CI crosses 1, or *P* value > 0.05
Unfavourable, statistically significant: there is an effect in favour of the comparator, CI does not cross 1, or *P* value < 0.05

Scale for Summarizing the Evidence from Meta-Analysis (standardized mean difference, mean difference)

Favourable, statistically significant: there is an effect in favour of the intervention, CI does not cross 0, or *P* value < 0.05
Favourable, non-statistically significant: there is an effect in favour of the intervention, CI crosses 0, or *P* value > 0.05
Neutral: effect size between –0.05 and +0.05 and the confidence interval (CI) crosses 0 (applies to standardized mean difference only)
Unfavourable, non-statistically significant: there is an effect in favour of the comparator, CI crosses 0, or *P* value > 0.05
Unfavourable, statistically significant: there is an effect in favour of the comparator, CI does not cross 0, or *P* value < 0.05

References: (based off of scales from the following articles):

1. Dosenovic S, Jelicic Kadic A, Miljanovic M, et al. Interventions for neuropathic pain: an overview of systematic reviews. *Anesth Analg*. 2017 Aug;125(2):643-652.
2. Tricco AC, Tetzlaff J, Pham B, Brehaut J, Moher D. Non-Cochrane vs. Cochrane reviews were twice as likely to have positive conclusion statements: cross-sectional study. *J Clin Epidemiol*. 2009 Apr;62(4):380-386.e1

Appendix 4: AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews

1	**Did the research questions and inclusion criteria for the review include the components of PICO?** For yes: • Population • Intervention • Comparator Group • Outcome Optional (recommended): • Time frame for follow-up
2	**Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? [Critical domain]** For Partial Yes: The authors state that they had a written protocol or guide that included ALL the following: • review question(s) • a search strategy • inclusion/exclusion criteria • risk of bas assessment For Yes: As for partial yes, plus the protocol should be registered and should also have specified: • meta-analysis/synthesis plan, if appropriate, AND • a plan for investigating causes of heterogeneity • justification for any deviations from the protocol
3	**Did the review authors explain their selection of the study designs for inclusion in the review?** For Yes, the review should satisfy ONE of the following: • Explanation for including only RCTs • OR explanation for including only NRSI • OR explanation for including both RCTS and NRSI
4	**Did the review authors use a comprehensive literature search strategy? [Critical domain]** For Partial Yes (all of the following): • searched at least 2 databases (relevant to question) • provided key word and/or search strategy • justified publication restrictions (i.e., language) For Yes, should also have (all of the following): • searched the reference lists of included studies • searched trial/study registries • included/ consulted content experts in the field • where relevant, searched for grey literature • conducted search within 24 months of completion of the review
5	**Did the review authors perform study selection in duplicate?** For yes, either ONE of the following: • at least 2 reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include • OR 2 reviewers selected a sample of eligible studies and achieved good agreement (> 80%), with the remainder selected by one reviewer
6	**Did the review authors perform data extraction in duplicate?** For Yes, either ONE of the following: • at least 2 reviewers achieved consensus on which data to extract from included studies • OR 2 reviewers extracted data from a sample of eligible studies and achieved good agreement (> 80%), with the remainder extracted by one reviewer

7	**Did the review authors provide a list of excluded studies and justify the exclusions? [Critical domain]**	
	For Partial yes: • provided a list of all potentially relevant studies that were read in full-text form but excluded from the review	For Yes, must also have: Justified the exclusion from the review of each potentially relevant study
8	**Did the review authors describe the included studies in adequate detail?**	
	For Partial Yes (ALL the following): • described populations • described interventions • described comparators • described outcomes • described research designs	For Yes, should also have ALL the following: • described population in detail • described intervention in detail (including doses where relevant) • described comparator in detail (including doses where relevant) • described study's setting • time frame for follow-up
9	**Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? [Critical domain]**	
	RCTs For Partial Yes, must have assessed RoB from: • unconcealed allocation, and • lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)	**RCTs** For Yes, must also have assessed RoB from: • allocation sequence that was not truly random, and • selection of the reported result from among multiple measurements or analyses of a specified outcome
	NRSI For Partial Yes, must have assessed RoB: • from confounding, and • from selection bias	**NRSI** For Yes, must also have assessed RoB: • methods used to ascertain exposures and outcomes, and • selection of the reported result from among multiple measurements or analyses of a specified outcome
10	**Did the review authors report on the sources of funding for the studies included in the review?**	
	For Yes: Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies	
11	**If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results? [Critical domain]**	
	RCTs For Yes: • The authors justified combining the data in a meta-analysis • AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. • AND investigated the causes of any heterogeneity	
	For NRSI For Yes: • The authors justified combining the data in a meta-analysis • AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present • AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available • AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review	

12	**If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**
	For Yes: • included only low risk of bias RCTs • OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect.
13	**Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review? [Critical domain]** For Yes: • included only low risk of bias RCTs • OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results
14	**Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?** For Yes: • There was no significant heterogeneity in the results • OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review
15	**If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review? [Critical domain]** For Yes: Performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias
16	**Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?** For Yes: • The authors reported no competing interests OR • The authors described their funding sources and how they managed potential conflicts of interest

NRSI = non-randomized studies of interventions; PICO = population, intervention, control group and outcome; RCT = randomized controlled trial; RoB = risk of bias.

Rating overall confidence in the results of the review

High

No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest

Moderate

More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review

Low

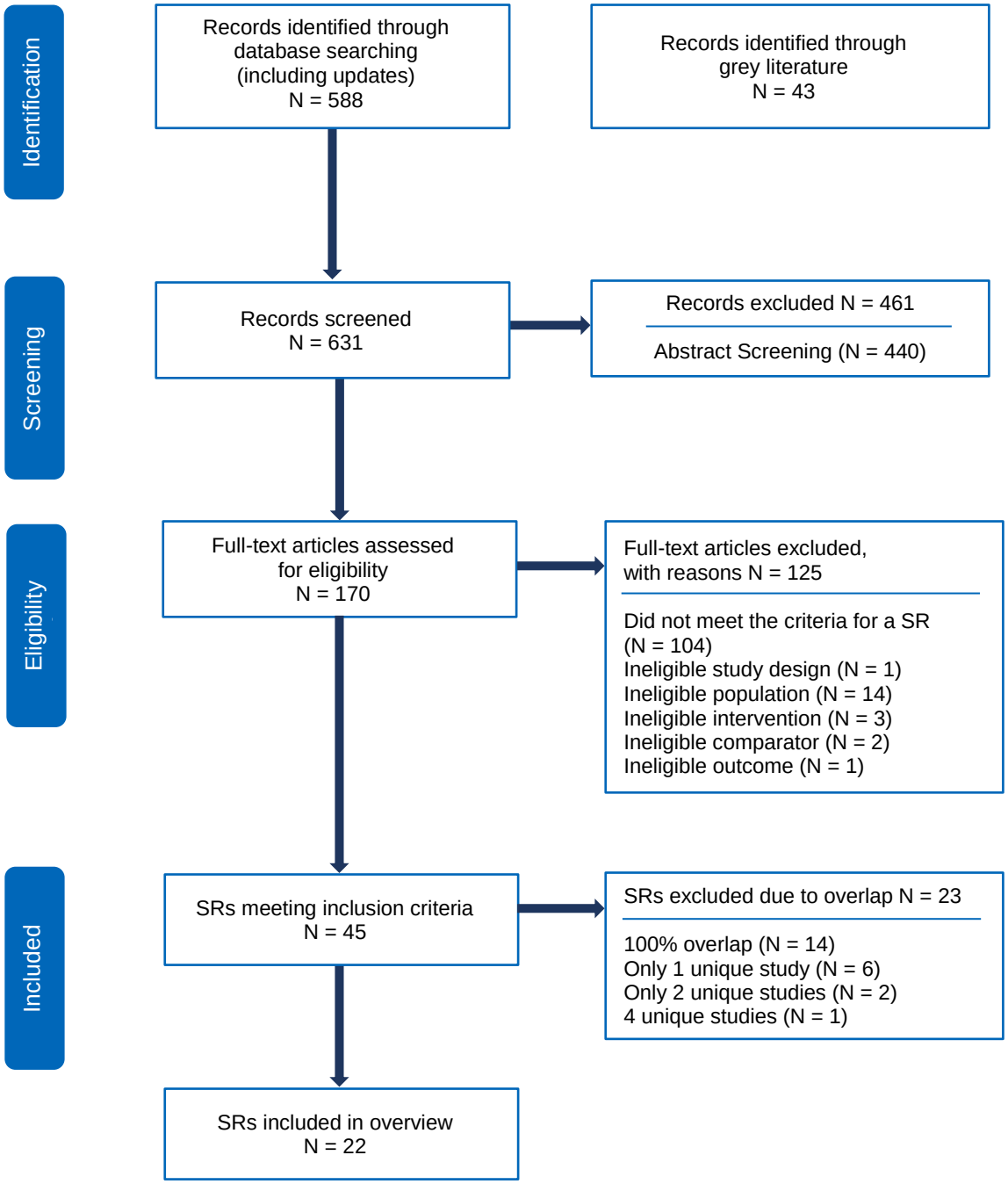
One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

Critically low

More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence

Appendix 5: Selection of Included Studies



Appendix 6: SRs excluded due to overlapping primary studies

Author Year	Unique Studies	Overlap (%)	Primary Studies	Type of Intervention	Reason for Exclusion
Paco 2016[47]	0	100	7	Physiotherapy	100% overlap
Randhawa 2016[48]	0	100	8	Multiple	100% overlap
Gross 2015[49]	0	100	1	Physiotherapy	100% overlap
Calixtre 2015[50]	0	100	8	Physiotherapy	100% overlap
Chen 2015[51]	0	100	5	Pharmacological	100% overlap
Chen 2015[52]	0	100	14	Physiotherapy	100% overlap
Januzzi 2013[53]	0	100	1	Pharmacological	100% overlap
Vos 2013[54]	0	100	3	Surgical	100% overlap
de Souza 2012[55]	0	100	3	Multiple	100% overlap
Petrucci 2011[56]	0	100	6	Physiotherapy	100% overlap
Rigon 2011[57]	0	100	6	Surgical	100% overlap
La Touche 2010[58]	0	100	4	Physiotherapy	100% overlap
Guo 2009[59]	0	100	2	Surgical	100% overlap
Aggarwal 2010[60]	0	100	6	Psychological	100% overlap
Moldez 2018[61]	1	86	7	Pharmacological	Only 1 study not included in the others (Bertolami 1993), but it doesn't report pain in a usable fashion.
Vier 2018[62]	1	86	7	physiotherapy	Only 1 unique study
Davoudi 2018[63]	1	83	6	Pharmacological	Only 1 study (Olsen-Bergen and Bjornland 2014) not covered; intervention is arthrocentesis with VitB12 + physiological salt water + triamcinolone
Dickerson 2016[64]	1	83	6	Physiotherapy	Only 1 study not overlapping (Canuli 2011), with a very specific population: TMD with sleep apnea, receiving mandibular advancement therapy with or without support therapy.
Roldan-Barraza 2014[65]	2	83	12	Splint	1 study not captured by a more recent or Cochrane review, but doesn't have a specific control group (Ferrand 2012). Another primary study was orofacial pain not TMD (Alencar 2009)
Liu 2012[66]	1	80	5	Psychological	The one non-included primary study is Mishra 2000 is not an RCT.
Al-Baghdadi 2014[67]	4	80	20	Multiple	Only 4 studies not reported elsewhere but each with a unique intervention/comparators (Peroz 2004 [pulsed electromagnetic fields], Petersson 1994 [arthrocentesis vs. arthrography], Sahlstrom 2013 [arthrocentesis vs. nerve block], Schiffman 1996 [active Iontophoresis])
Fernandes 2017[68]	1	75	4	Physiotherapy	Only one study (Itoh 2012) not captured by other studies (acupuncture)
Chang 2014[69]	2	71	7	Physiotherapy	Two studies no captured elsewhere, one study (Cetiner 2006) in the meta-analysis, on not included in the meta-analysis (Fikackova 2007). SR does not don't provide any details of the included studies, so meta-analysis is highly biased.

Appendix 7: Study Characteristics of Included Systematic Reviews

Table 25: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
Zhang 2015[19] Canada No funding obtained	SR with MA of RCTs June 30 2014 MEDLINE, EMBASE, PsycINFO, AMED, Cochrane Library, CENTRAL, DARE, NHS Economic Evaluation Database Cochrane RoB	3 RCTs ranging from 2002 to 2008	25 to 80 TMD with: • myofascial pain • internal derangement of the joint • degenerative joint disease. (Included TMD, craniomandibular dysfunction, myofascial pain dysfunction syndrome, myofascial pain, facial arthromyalgia, masticatory myalgia, and mandibular dysfunction) Adults and Pediatrics	*Psychological* • Hypnosis • Relaxation therapy • Hyporelaxation • Therapy	No treatment (or minimal therapy [e.g., a clinician visit without treatment, or brief information])	Pain (orofacial, craniofacial, headaches) (2 weeks to 6 months) MMO or ease of opening (2 to 6 months)	None
Aggarwal 2011[20] UK National Institute of Health Research (NIHR), UK Clinician Scientist Award, NIHR. British Orthodontic Society (BOS), UK.	SR with MA of RCTs October 25 2010 Embase, MEDLINE, PsychINFO, CENTRAL, Cochrane Oral Health Group's Trials Register Cochrane RoB	15 RCTs ranging from 1986 to 2010	20 to 185 Chronic orofacial pain due to TMD Adults	*Psychological* • Hypnosis • Physical Self-regulation • Biofeedback • Enhanced progressive relaxation programme • TENS CBT • Habit reversal treatment • Education • Self-Management or home exercises • Dental Programme	Placebo or Sham No treatment Hypnosis or relaxation therapy	Pain (orofacial, craniofacial, headaches) (NR) MMO or ease of opening (NR)	Populations at risk due to high caries and/or periodontal disease, parafunctional habits

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
				• Supportive Counselling			
Xu 2018[21] China National Natural Science Foundation of China; Shaanxi Province Natural Science Basic Research Foundation of China; Key discipline foundation of Xi'an Medical University	SR with MA of RCTs May 16 2017 Cochrane Library, PubMed, Embase, Web of Science, PEDro, CINAHL, Scopus, Allied and Complementary Medicine (AMED), ClinicalTrials.gov, Toxline, ProQuest, PsycBite, Current Contents Connect, WHO Trial Registry for RCTs Modified Jadad scale, GRADE	31 RCTs ranging from 1997 to 2017	14 to 99 General TMD and myogenous or arthrogenous temporomandibular pain Adults and Pediatrics	*Laser Therapy* LLLT (3 to 20 treatment sessions)	Placebo or Sham	Pain (orofacial, craniofacial, headaches) (Immediately to 3 months after last treatment) MMO or ease of opening (Immediately to 3 months after last treatment) TMJ clicking or noise (Immediately to 1 month) Adverse events (NR)	None
Jung 2011[22] South Korea Pusan National University Research Grant	SR with MA of RCTs July 2010 Cochrane Library, PubMed, Embase, MEDLINE, CINAHL, DBPIA, OASIS, Korea Institute of Science and Technology Information, National Assembly Library, Korean Studies	7 RCTs ranging from 2002 to 2010	7 to 28 Articular and/or muscular TMD Adults	*Physiotherapy* Acupuncture and methods of stimulating acupuncture points that do not involve needle insertion (e.g., laser, acupressure, moxibustion)	Placebo or Sham	Pain (orofacial, craniofacial, headaches) (NR) MMO or ease of opening (NR)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
	Information, China Academic Journals Full-text Database Cochrane RoB						
Cho 2010[37] South Korea Funding source NR	SR of RCTs (no MA) July 2008 Cochrane Library, Embase, MEDLINE, CINAHL, PsychINFO, AMED, CENTRAL, DBPIA, Korea Institute of Science and Technology Information, National Assembly Library, Korean Studies Information, China Academic Journals Full-text Database (CJFD), KoreaMed, Japan Science and Technology Information Aggregator Electronic Cochrane RoB	14 RCTs ranging from 1985 to 2008	15 to 170 Myogenous TMD Adults and Pediatrics	*Physiotherapy* Traditional and contemporary acupuncture (including electroacupuncture)	Placebo or Sham No treatment Splint therapy Physiotherapy Ultrasound therapy Vitamin B1 Indomethacin	Pain (orofacial, craniofacial, headaches) (NR) MMO or ease of opening (NR) TMJ clicking or noise (NR) Adverse events (NR)	None
Martins 2016[23] Brazil Funding source NR	SR with MA of RCTs August 2014 Cochrane Library, PubMed, Web of Science, PEDro	8 RCTs ranging from 1994 to 2012	26 to 122 General TMD Adults and Pediatrics	*Physiotherapy* Musculoskeletal Manual Approach	Placebo or Sham No treatment Education Splint therapy	Pain (orofacial, craniofacial, headaches) MMO or ease of opening Follow-up: 1 day to	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
	Physiotherapy Evidence Database (PEDro) Scale				Manual therapy Home exercises	24 weeks	
Armijo-Olivo 2015[24] Canada Banting Fellowship, CIHR Incentive Award, Alberta Innovates Health Solution STIHR Training Program of Knowledge Translation (KT) Canada Music and Motion Fellowship from the Faculty of Rehabilitation Medicine of the University of Alberta	SR with MA of RCTs April 7 2015 Cochrane Library, Embase, MEDLINE, Web of Science, CINAHL, CENTRAL Cochrane RoB	48 RCTs ranging from 1985 to 2014	12 to 305 Diagnosis of TMD according to the research diagnostic criteria for temporomandibular disorders (RDC/TMD) established by Dworkin and LeResche or any clinical diagnosis involving signs and symptoms of TMD Adults	*Pharmacological* *Splint* *Physiotherapy* • Any manual therapy intervention (e.g., mobilization, manipulation, soft tissue mobilization, TB jaw motion device) or exercise therapy (e.g., chewing protocol exercise, intraoral myofascial therapy) alone or in combination with other therapies *Psychological* • Education • Self-management • Home exercises	Placebo or Sham No treatment Education Splint therapy Arthrocentesis Exercise Therapy Acupuncture Therapy Self-care/management Electric Stimulation EMG Biofeedback Botulinum toxin injections Physiotherapy Arthroscopy Arthroplasty	Pain (orofacial, craniofacial, headaches) (1 day to 12 months) MMO or ease of opening (1 day to 12 months)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
					Manual Therapy Bupivacaine injection NSAIDs Home exercises		
Kuzmanovic Pficer 2017[25] Serbia No funding obtained	SR with MA of RCTs October 2016 Embase, MEDLINE, Web of Science Cochrane RoB, Jadad Scale	33 RCTs ranging from 1985 to 2014	8 to 200 TMD with more than one of the following symptoms/signs: myofascial pain and /or pain in the TMJ, myofascial pain and/or pain in the TMJ on palpation, muscles tenderness, limitation or deviation in mandibular range of motion, limited mouth opening with/ without reduction, presence of sound effects in TMJ, headache or earache Adults and Pediatrics	*Splint* • Stabilization Splint (Michigan splint, Tanner appliance, the Fox appliance, centric relation appliance) • Education	Non-occluding appliances Occlusal appliances Behavioural treatment Exercise Counselling No treatment	Pain (orofacial, craniofacial, headaches) (< 3 months to > 3 months) MMO or ease of opening(< 3 months to > 3 months)	None
Zhang 2016[28] China No funding obtained	SR with MA of RCTs and NRS March 31, 2016 PubMed, Embase, MEDLINE, CENTRAL (Cochrane Central Register of Controlled	13 RCTs and CCTs ranging from 1985 to 2012	17 to 76 General TMD Adults	*Splint* Splint (hard, soft, stabilization, flat, anterior repositioning)	Placebo or Sham No treatment Arthrocentesis Self-care/management	Pain (orofacial, craniofacial, headaches) (2.5 months to 6 months) MMO or ease of opening (2.5 months to 6 months)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
	Trials), ClinicalTrials.gov Cochrane RoB				EMG Biofeedback Physiotherapy	TMJ clicking or noise (NR)	
Fricton 2010[26] USA AAOP; US National Institute of Dental and Craniofacial Research's TMJ Implant Registry and Repository	SR with MA of RCTs March 2006 Cochrane Library, MEDLINE, CENTRAL Cochrane RoB, CONSORT, Modified Cochrane RoB	45 RCTs ranging from 1983 to 2006	14 to 200 TMJ disorder Not reported	*Orthodontics* • Intraoral appliances, including soft and hard stabilization appliances • Anterior positioning appliances • Anterior bite appliances • Soft resilient appliances for TMJ disease	No treatment Acupuncture Non-occluding appliances	Pain (orofacial, craniofacial, headaches) (7 days to 12 months) MMO or ease of opening (7 days to 12 months) TMJ clicking or noise (7 days to 12 months)	None
Luther 2010[32] UK University of Leeds, UK; United Lincolnshire Hospitals NHS Trust, UK; King's College London, UK	SR of RCTs (no MA) April 13 2010 Embase, MEDLINE, CENTRAL, Cochrane Oral Health Group's Trials Register Cochrane RoB	0 RCTs included	0 patients TMD exhibiting 2 or more clinical symptoms Adults	*Orthodontics* Orthodontic appliances	Placebo or Sham No treatment	NR	None
Liu 2018[31] China No funding obtained	SR of RCTs and NRS, with MA of RCTs only June 30 2016 Cochrane Library, PubMed, Embase, MEDLINE, Web of	13 RCTs, 2 qRCTs, 1 cohort study ranging from 1985 to 2017	14 to 564 TMJ osteoarthritis, TMJ arthritis(excluding TMJ rheumatic arthritis), or TMJ internal degenerative diseases[b] Adults[c]	*Pharmacological and Surgical* Intra-articular injection with corticosteroids alone compared with other drugs, with or without basic treatment procedures such	Arthrocentesis Ringer lactate injection Saline injection, Corticosteroid	Pain (orofacial, craniofacial, headaches) (1 week to 8 years) MMO or ease of opening (1 weeks to 8 years)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
	Science, CBM (Chinese Biomedical Literature Database), China National Knowledge Infrastructure, Wanfang Database Cochrane RoB[a]			as arthrocentesis	injection Bupivacaine injection	TMJ clicking or noise (1 week to 6 months) Adverse events (1 week to 8 years)	
Machado 2018[34] Brazil No funding obtained	SR of RCTs (no MA) January 2018 Cochrane Library, PubMed, Embase, Web of Science, Scopus, CENTRAL, LILACS, CAPES Cochrane RoB	18 RCTs ranging from 1997 to 2016	12 to 50 Clinical diagnosis of temporomandibular myofascial pain Adults and Pediatrics	*Pharmacological and Physiotherapy* Dry needling or wet needling (with injection of substances as local anaesthetics, botulinum toxin, corticosteroids or other drugs)	Placebo or Sham (false needling, saline injection, false laser) Acupuncture (Dry needling) Manual Therapy (e.g., mobilization, manipulation) Combination drug therapy Laser therapy Pharmacological	Pain (orofacial, craniofacial, headaches) (5 minutes to 6 months) MMO or ease of opening (5 minutes to 6 months) Adverse events (NR)	None
Häggman-Henrikson 2017[18] Sweden No funding obtained	SR with NMA of RCTs March 1 2017 Cochrane Library, PubMed, Embase, National Health Service Economic Evaluation Database (NHS EED)	24 RCTs ranging from 1985 to 2017	20 to 102 Chronic (equal to greater than 3 months) orofacial pain (TMD-muscle mainly associated with myalgia, TMD-joint mainly associated with TMJ pain, excluded trigeminal neuralgia or	*Pharmacological* Any pharmacological treatment (topical, local, or general): • HA injection • corticosteroid injection • Tenoxicam HA injection • dexamethasone injection	Placebo or Sham Splint therapy Corticosteroid injection Arthroscopy Arthroplasty	Pain (orofacial, craniofacial, headaches) (2 weeks to 6 months)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
	Swedish Agency for Health Technology Assessment and Assessment of Social Services RoB tool, GRADE		rheumatic disorders) Adults	• PEA capsules • Diclofenac tablets • NSAIDs tablets • Celecoxib tablets • Naproxen tablets • glucosamine sulphate • ibuprofen • TZA capsules • CYC capsules • Granisetron injection • Botox injection • propranolol tablets • clonazepam tablets • clonazepam capsules • Ping-on ointment	(e.g., reconstruction, interpositional) PRGF injection Ibuprofen		
Bousnaki 2018[38] Greece Greek State Scholarship Foundation (IKY), which was funded by the action ''Enhancing Human Research Potential through Doctoral Research'' from the resources of the European Program ''Development of Human Potential, Education and Lifelong Learning'',	SR of RCTs (no MA) May 2017 MEDLINE, Scopus Cochrane RoB, Jadad Scale	6 RCTs ranging from 2015 to 2017	20 to 100 TMJ-OA; or anterior disc displacement with or without reduction, together with degenerative changes in the articulating structures of the TMJ Adults[c]	*Pharmacological and Surgical* Arthrocentesis and PRP (platelet-rich plasma) injections	Arthrocentesis Ringer's lactate injection Hyaluronic acid injection Saline injection	Pain (orofacial, craniofacial, headaches) (1 months to 24 months) MMO or ease of Opening (1 months to 24 months) TMJ clicking or noise (1 month to 24 months)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
2014–2020, with funds from European Social Fund (ESF) and national resources							
Goiato 2016[35] Brazil No funding obtained	SR of RCTs and NRS (no MA) March 2016 MEDLINE, Web of Science Jadad scale	6 RCTs and 1 retrospective study ranging from 1985 to 2014	16 to 100 General TMD Adults	*Pharmacological* Hyaluronic injections (with or without arthrocentesis)	Corticosteroid (CS) injection Saline injections NSAID injection	Pain (orofacial, craniofacial, headaches) MMO or ease of opening (4 weeks to 24 months)	None
Li 2012[27] China National Undergraduates Innovating Experimentation Project	SR with MA of RCTs March 2011 Embase, MEDLINE, CENTRAL, CBM Cochrane RoB, CONSORT	4 RCTs ranging from 2003 to 2010	56 to 104 TMD diagnosis by clinical and/or radiological assessment without limitation in gender, age, race, and social economic status Adults	*Pharmacological* Inferior Space Injection; (ISI): once with hyaluronate . Taking Michigan stabilization splint for 2 months ; 3 times with hyaluronate , once 2 week Double Spaces injection once with prednisolone; 4 times with hyaluronate , once a week. Oral take diclofenac sodium	Splint therapy Hyaluronic acid injection SSI (Superior Space Injection) Oral diclofenac sodium Prednisolone injection	Pain (orofacial, craniofacial, headaches) (1 month to 6 months) MMO or ease of opening (1 month to 6 months)	None
Melo 2018[36] Brazil Coordination for the Improvement of Higher Education	SR of RCTs (no MA) December 15 2017 Cochrane Library, PubMed, Embase, Web of Science,	3 RCTs ranging from 2001 to 2013	39 to 60 TMJ osteoarthritis Adults	*Pharmacological* Oral administration of glucosamine supplements	Placebo or Sham Ibuprofen	Pain (orofacial, craniofacial, headaches) (baseline to 12 weeks) MMO or ease of opening (baseline to	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
Personnel, Ministry of Education, Brazil	LILACS, LIVIVO, Science Direct Cochrane RoB, GRADE					12 weeks) Adverse events (NR)	
Mujakperuo 2010[33] UK University of Aberdeen MSc Programme in Clinical Pharmacology, UK	SR of RCTs (no MA) August 2 2010 Embase, MEDLINE, CINAHL. CENTRAL, Cochrane Oral Health Group's Trials Register Cochrane RoB	11 RCTs ranging from 1983 to 2010	20 to 83 Clinically or radiographically diagnosed to have TMD Adults	*Pharmacological* Pharmacological Agents alone or with other treatments for TMD. NSAIDs (cream and oral) Oral benzodiazepine Cyclobenzaprine Gabapentin Glucosamine hydrochloride/chondroitin sulphate COX-2 inhibitor Capsaicin cream	Placebo or Sham	Pain (orofacial, craniofacial, headaches) (Baseline to 12 months) Adverse events (NR)	None
Nagori 2018[39] India Funding NR	SR of RCTs (No MA) October 2017 PubMed, Scopus, CENTRAL, Google Scholar Cochrane RoB	5 RCTs ranging from 2012 to 2016	12 to 78 Anchored disc phenomenon; anterior disc displacement with or without reduction; capsulitis; synovitis; osteoarthritis; pain and jaw function Age NR	*Surgical* Single puncture arthrocentesis	Arthrocentesis	Pain (orofacial, craniofacial, headaches) (1 months to 6 months) MMO or ease of opening (1 months to 6 months) Adverse events (3 months to 6 months)	None
Al-Moraissi 2014[30] Yemen	SR with MA of RCTs and NRS January 2014	2 RCTs, 2 CCTs, 2 retrospective cohort studies	19 to 62 Anchored disc phenomenon, closed lock, anterior disc	*Surgical* Arthrocentesis	Arthroscopy	Pain (orofacial, craniofacial, headaches) (1 week to 26 months)	None

First Author, Publication Year, Country, Funding Source	Review Methods, Including Databases, Date of Last Literature Search, and QA Tools Used	Study Types, Numbers, and Publication Y Range of Primary Studies Included	Number (Range), Type of TMD, Age, of Participants Included in Primary Studies	Intervention	Comparator	Outcomes Reported by Systematic Reviews (Follow-up ranges)	Subgroup Analyses of Interest Conducted
No funding obtained	PubMed, Embase, MEDLINE, CINAHL, CENTRAL Cochrane Database of Systematic Reviews, Electronic Journal Center MOOSE, STROBE statement	ranging from 1995 to 2013	displacement with or without reduction (ADDR/ADDWR), capsulitis, synovitis, and internal derangement with regard to pain and jaw function (MIO, excursive movements, and protrusive movements) Adults and Pediatrics			MMO or ease of opening (1 week to 26 months)	
Al-Moraissi 2015[29] Yemen No funding obtained	SR with MA of RCTs and NRS August 2014 PubMed, MEDLINE, CENTRAL, OVID MOOSE, STROBE statement	3 RCTs, 2 CCTs, 2 retrospective studies ranging from 2001 to 2011	20 to 458 ID-like anchored disc phenomenon, disc displacement with or without reduction, painful click, and closed lock of the TMJ Adults	*Surgical* • Open surgery • Arthroscopic lysis and lavage	Arthroscopy	Pain (orofacial, craniofacial, headaches) (1 year to 5 years) MMO or ease of opening (1 year to 5 years) TMJ clicking or noise (1 year)	None

AAOP = American Academy of Orofacial Pain; AMED = Allied and Complimentary Medicine; CAPES = catalog of dissertations and theses; CBM = Chinese Biomedical Literature Database; CCT = controlled clinical trial; CENTRAL = Central Register of Controlled Trials; CIHR = Canadian Institute of Heath Research; CINAHL = Cumulative Index to Nursing and Allied Health Literature; CONSORT = Consolidated Standards of Reporting Trials; CYC = cyclobenzaprine; DARE = Database of Abstracts of Reviews of Effects; LILACS = Latin American and Caribbean Health Sciences Literature; LIVIVO = ZB MED Search Portal for Life Sciences; LLLT = low level laser therapy; MA = meta-analysis; MIO = maximal interincisal opening; MMO = maximal mouth opening; MOOSE = Meta-analysis of Observational Studies in Epidemiology; NHS = National Health Service; NMA = network meta-analysis; NR = not reported; NRS = non-randomized studies; NSAIDs = nonsteroidal anti-inflammatory drugs; OASIS = Outcome and Assessment Information Set; PEDro = Physiotherapy Evidence Database; qRCT = quasi-randomized controlled trial; RCT = randomized controlled trial; RoB = risk of bias; SR = systematic review; STROBE = Strengthening the Reporting of Observational Studies in Epidemiology; TENS = transcutaneous electrical nerve stimulation; TMD = temporomandibular disorder; TMJ = temporomandibular joint; TZA = tizanidine hydrochloride; QA = quality appraisal.

[a] Not explicitly described as the Cochrane RoB, but it can be assumed by the use of the seven bias domains from the Cochrane RoB tool.

[b] According to the Research Diagnostic Criteria for Temporomandibular Disorders.

[c] No age range specified in methods.

Appendix 8: Critical Appraisal of Included Systematic Reviews Using AMSTAR 2

Intervention Type	References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Psychological	Zhang 2015[19]	**X**	**X**	**X**	**O**	**Y**	**Y**	**X**	**Y**	**Y**	**X**	**X**	**X**	**X**	**X**	**X**	**Y**
Psychological	Aggarwal 2011[20]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**X**	**Y**	**Y**	**X**	**Y**
Physiotherapy (acupuncture, laser)	Xu 2018[21]	**Y**	**X**	**X**	**O**	**Y**	**Y**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**Y**
Physiotherapy (acupuncture, laser)	Jung 2011[22]	**Y**	**X**	**Y**	**O**	**X**	**Y**	**X**	**O**	**Y**	**X**	**Y**	**X**	**Y**	**Y**	**X**	**Y**
Physiotherapy (acupuncture, laser)	Cho 2010[37]	**Y**	**X**	**X**	**Y**	**X**	**X**	**X**	**Y**	**Y**	**X**	No MA	No MA	**Y**	**Y**	No MA	**X**
Physiotherapy (manual)	Martins 2016[23]	**Y**	**X**	**X**	**X**	**Y**	**Y**	**X**	**Y**	**O**	**X**	**X**	**X**	**X**	**Y**	**X**	**Y**
Physiotherapy (manual)	Armijo-Olivo 2016[24]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**X**	**Y**	**Y**	**X**	**Y**	**X**	**Y**	**Y**	**X**	**Y**
Splint	Kuzmanovic Pficer 2017[25]	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	**Y**	**O**	**Y**	**X**	**X**	**X**	**X**	**X**	**Y**	**Y**
Splint	Zhang 2016[28]	**X**	**X**	**X**	**O**	**X**	**Y**	**X**	**X**	**Y**	**X**	**X**	**X**	**X**	**X**	**Y**	**Y**
Splint	Fricton 2010[26]	**Y**	**X**	**Y**	**O**	**Y**	**Y**	**X**	**Y**	**O**	**X**	**X**	**X**	**X**	**X**	**Y**	**X**
Orthodontics	Luther 2010[32]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	NA	**Y**	NA	NA	NA	NA	NA	NA	**Y**
Pharmacological (injection)	Liu 2018[31]	**Y**	**X**	**X**	**Y**	**Y**	**Y**	**X**	**Y**	**X**	**X**	**Y**	**X**	**X**	**Y**	**X**	**Y**
Pharmacological (injection)	Machado 2018[34]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**X**	**Y**	**Y**	**X**	No MA	No MA	**Y**	**Y**	No MA	**Y**
Pharmacological (injection)	Häggman-Henrikson 2017[18]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**X**	ISPOR	ISPOR	**X**	**X**	**X**	**Y**
Pharmacological (injection)	Bousnaki 2018[38]	**Y**	**X**	**Y**	**O**	**Y**	**X**	**Y**	**O**	**Y**	**X**	No MA	No MA	**X**	**X**	No MA	**Y**
Pharmacological (injection)	Goiato 2016[35]	**Y**	**X**	**X**	**O**	**X**	**X**	**X**	**X**	**X**	**X**	No MA	No MA	**X**	**X**	No MA	**Y**
Pharmacological (injection)	Li 2012[27]	**Y**	**X**	**X**	**Y**	**Y**	**Y**	**X**	**Y**	**Y**	**X**	**Y**	**X**	**X**	**Y**	**X**	**X**
Pharmacological (oral)	Melo 2018[36]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	No MA	No MA	**Y**	**Y**	No MA	**Y**
Pharmacological (oral)	Mujakperuo 2010[33]	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	No MA	No MA	**Y**	**Y**	No MA	**Y**
Surgical	Nagori 2018[39]	**Y**	**X**	**X**	**Y**	**Y**	**X**	**Y**	**Y**	**Y**	**X**	No MA	No MA	**Y**	**Y**	No MA	**Y**
Surgical	Al-Moraissi 2015[29]	**Y**	**X**	**X**	**Y**	**X**	**X**	**X**	**O**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**Y**

Intervention Type	References	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Surgical	Al-Moraissi 2015[30]	**Y**	**X**	**X**	**Y**	**X**	**X**	**X**	**O**	**X**	**X**	**X**	**Y**	**X**	**X**	**X**	**Y**

Y = yes; N = no; O = partial yes; NA = not applicable (i.e., no primary studies); No MA = no meta-analysis conducted.

Note: Critical domains of the AMSTAR 2 tool (Appendix 4) include: #2 review methods were established a priori and justifications for any significant deviations from the protocol were provided; #4 comprehensive literature search strategy was used; #7 list of excluded studies was provided with justifications; #9 a satisfactory technique for assessing RoB was used; #11 if meta-analysis was performed, appropriate statistical methods were used; #13 review authors accounted for RoB of individual studies when interpreting/ discussing the results; #15 If quantitative synthesis was performed, an adequate investigation of publication bias was conducted and discussed.

Appendix 9: Overlapping Primary Studies Between Included SRs

Class of intervention	Number of Times Cited in Overlap	Psychological		Physiotherapy			Splint	Pharmacological						Surgical								
Reviews		Zhang 2015	Aggarwal 2011	Xu 2018	Jung 2011	Cho 2010	Martins 2016	Armijo-Olivo 2016	Kuzmanovic Pficer 2017	Zhang 2016	Fricton 2010	Liu 2018	Machado 2018	Häggman-Henrikson 2017	Bousnaki 2018	Goiato 2016	Li 2012	Melo 2018	Mujakperuo 2010	Nagori 2018	Al-Moraissi 2015	Al-Moraissi 2015
Total # of studies in SR		3	15	31	7	17	8	49	33	11	45	9	18	24	6	7	4	3	11	5	7	6
# of unique studies		2	10	29	3	8	4	36	15	3	22	6	12	13	6	2	4	2	8	3	5	5
# of overlapping studies		1	5	2	4	9	4	13	18	8	23	3	6	11	0	5	0	1	3	2	2	1
Primary Studies																						
Turk 1993	4		X						X	X	X											
Bjornland 2007	3											X		X		X						
Carlson 2001	3		X						X		X											
Crockett 1986	3		X					X			X											
Ismail 2007	3						X	X	X													
Johansson 1991	3					X			X		X											
Kopp 1985	3											X		X		X						
Truelove 2006	3							X	X		X											
Ekberg 2003	3								X	X	X											
List 1993	3					X			X		X											
Raustia 1985, Raustia 1986, Raustia and Pohjola 1986	3					X		X	X													
Ekberg 1998b	3								X	X	X											
Komiyama 1999	2		X					X														
Magnusson and Syren 1999	2							X			X											
Schiffman 2007	2							X													X	
Gencer 2014	2													X		X						

Class of intervention	Number of Times Cited in Overlap	Psychological		Physiotherapy			Splint	Pharmacological						Surgical								
Reviews		Zhang 2015	Aggarwal 2011	Xu 2018	Jung 2011	Cho 2010	Martins 2016	Armijo-Olivo 2016	Kuzmanovic Pficer 2017	Zhang 2016	Fricton 2010	Liu 2018	Machado 2018	Häggman-Henrikson 2017	Bousnaki 2018	Goiato 2016	Li 2012	Melo 2018	Mujakperuo 2010	Nagori 2018	Al-Moraissi 2015	Al-Moraissi 2015
Manfredini 2012	2															X				X		
Smith 2007	2				X	X																
Von Piekartz 2011	2						X	X														
Carmeli 2001	2							X			X											
Conti 2012	2								X	X												
Cuccia 2010	2						X	X														
da Silva 2012	2			X									X									
Ernberg 2011	2												X	X								
Goddard 2002	2				X	X																
Kopp 1987	2											X				X						
Lundh 1992	2								X		X											
Maloney 2002	2							X		X												
Schmid-Schwap 2006	2				X	X																
Shen and Goddard 2007	2				X	X																
Thie 2001	2													X				X				
Turk 1996	2		X								X											
Al Quran 2006	2								X	X												
Christidis 2015	2												X	X								
Dahlstrom 1985	2								X		X											
Dao 1994	2								X		X											
Gray 1991	2								X		X											
Guarda-Nardini 2008	2												X	X								
Harkins 1991	2													X					X			
Herman 2002	2													X					X			
Hobeich 2008	2																				X	X

Class of intervention	Number of Times Cited in Overlap	Psychological		Physiotherapy			Splint	Pharmacological						Surgical								
Reviews		Zhang 2015	Aggarwal 2011	Xu 2018	Jung 2011	Cho 2010	Martins 2016	Armijo-Olivo 2016	Kuzmanovic Pficer 2017	Zhang 2016	Fricton 2010	Liu 2018	Machado 2018	Häggman-Henrikson 2017	Bousnaki 2018	Goiato 2016	Li 2012	Melo 2018	Mujakperuo 2010	Nagori 2018	Al-Moraissi 2015	Al-Moraissi 2015
Kalamir 2010	2						X	X														
List 1992	2					X					X											
List 1992a	2					X					X											
Lundh 1988	2									X	X											
Rubinoff 1987	2								X		X											
Stiesch-Scholz 2005	2								X		X											
Ta and Dionne 2004	2													X					X			
Uemoto 2013	2			X									X									
Wahlund 2003	2	X									X											
Wassell 2004	2								X		X											
Wright 1995	2									X	X											