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Title page

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Authors: M. Al-Baghdadi[1,2 *], J. Durham[1,2], V. Araujo-Soares[2], S. Robalino[2], L. Errington[3], and J. Steele[2,4]

[1]Department of Oral and Maxillofacial Surgery, School of Dental Sciences, Newcastle University;
[2]Institute of Health and Society, Newcastle University;
[3]Walton Library, Newcastle University;
[4]Department of Restorative Dentistry, School of Dental Sciences, Newcastle University, Newcastle upon Tyne, UK.

*Corresponding author: Mohammed Al-Baghdadi, Department of Oral and Maxillofacial Surgery, School of Dental Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4BW, UK. E-mail(s): m.k.s.al-baghdadi@ncl.ac.uk; dr.mk79@yahoo.com

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ABSTRACT

Various interventions have been employed for managing patients with temporomandibular joint (TMJ) disc displacement without reduction (DDwoR), but their clinical effectiveness remains unclear. This systematic review investigated the effects of these interventions and is reported in accordance with the PRISMA guidelines. Electronic and manual searches until 1st/ November/2013 were conducted for English language, peer-reviewed, publications of randomised clinical trials comparing any form of conservative or surgical interventions for patients with clinical and/or radiological diagnosis of acute or chronic DDwoR. Two primary outcomes (TMJ pain intensity and maximum mouth opening) and a number of secondary outcomes were examined. Two reviewers performed data extraction and risk-of-bias assessment. Data collection and analysis were performed according to Cochrane recommendations. Twenty studies involving 1305 patients were included. Data analysis involved 21 comparisons between a variety of interventions, either between interventions, or between intervention and placebo or no intervention. Meta-analysis on homogenous groups was conducted in 4 comparisons. In most comparisons made, there were no statistically significant differences between interventions relative to primary outcomes at short- or long-term follow-up ($p>0.05$). In a separate analysis, however, the majority of reviewed interventions improved primary outcome measures from their baseline levels significantly over time ($p<0.05$). Evidence levels are, however, currently insufficient for definitive conclusions because the included studies were too heterogeneous and at an unclear to high risk-of-bias. In view of the comparable therapeutic effects, paucity of high-quality evidence, and the greater risks and costs associated with more complex interventions, patients with symptomatic DDwoR should be initially treated using the simplest and least invasive intervention.

INTRODUCTION

Temporomandibular joint (TMJ) disc displacement without reduction (DDwoR) is a specific temporomandibular disorder (TMD) that can cause TMJ pain and limited mouth opening (painful locking), sometimes called a "closed lock" (Okeson, 2007). DDwoR can be acute or chronic depending on the duration of locking (Sembronio *et al.*, 2008; Saitoa *et al.*, 2010). Its incidence amongst TMD patients is estimated at 2-8% (Manfredini *et al.*, 2011; Poveda-Roda *et al.*, 2012).

Various interventions have been suggested for DDwoR, but to-date, the most efficacious/effective approach is still unclear, which may result in management being based

more on experience than evidence (Durham *et al.*, 2007). The aim of this systematic review was, therefore, to investigate the effects of different conservative and surgical interventions used in the management of TMJ DDwoR.

METHODS

Protocol and Registration

This systematic review was conducted in accordance with the Cochrane Collaboration (Higgins and Green, 2011) and the Centre for Reviews and Dissemination (Akers *et al.*, 2009) guidance, and reported according to the PRISMA statement (Moher *et al.*, 2009). All the methods of data collection/analysis and inclusion/exclusion criteria were pre-specified and documented in the review protocol (Al-Baghdadi *et al.*, 2012).

Criteria for Considering Studies (PICOS, Appendix-1)

- **Participants:** Any age, gender with clinical and/or radiological diagnosis of acute or chronic DDwoR.
- **Interventions:** Any form of conservative or surgical interventions.
- **Comparators/Control:** Any alternative intervention, placebo, or no treatment.
- **Outcomes:** Primary outcomes: TMJ pain intensity and unassisted/active maximum mouth opening (MMO). Secondary outcomes: other mandibular movements, mandibular function or patient's quality-of-life, therapy cost, operation/admission duration in surgical trials, and adverse events. The outcomes were evaluated over short-term (≤3months) and long-term (>3months) follow-up periods.
- **Studies:** Randomised and quasi-randomised clinical trials (RCTs and q-RCTs).

Search Strategy (Appendix-2)

Four databases were electronically-searched: CENTRAL; MEDLINE; EMBASE; Scopus till 1st/November/2013. Other sources were manually-searched: citation search and reference lists of included studies, reference lists of relevant review articles and textbooks' chapters, and seven journals highly likely to contain studies relevant to the review topic.

Data Collection and Analysis

Selection of Studies

Eligible studies were selected according to the inclusion/exclusion criteria. Irrelevant reports were identified by their title/abstract and were excluded by the first reviewer (MA). The full-texts of all potentially eligible studies were retrieved and independently examined in-

duplicate by two reviewers (MA&JD) to establish eligibility. Throughout the whole process of this review, disagreements were resolved by consensus or, when necessary, by a third reviewer (JS). Studies excluded at this stage were identified and reasons for exclusion recorded.

Data Extraction and Management

A standardised, pre-piloted, extraction form based on Cochrane recommendations was employed. Eligible studies' data were extracted and recorded by the first reviewer (MA). The second reviewer (JD), blinded to the authors' names, institutions, and journal, crosschecked all extracted data's validity. Authors of included studies were contacted to clarify study design and/or request missing data as required.

Risk-of-bias Assessment

The methodological quality of included studies was assessed independently and in-duplicate by two reviewers (MA&JD 'blinded') using the Cochrane risk-of-bias tool (Higgins *et al.*, 2011). Each domain in the tool was allocated one of the following judgments: low, unclear, or high risk-of-bias. Sample size calculation was also examined.

Data Analysis

The planned data analysis for this review was performed according to Cochrane statistical guidelines (Higgins and Green, 2011) using the Review Manager Software (version 5.2) (RevMan, 2012) comparing between the effects of different interventions (i.e. between-group statistical differences). For dichotomous data, the estimates of effect of an intervention were expressed as risk ratios (RR) together with 95% confidence intervals (CI). For continuous data, mean differences (MD) with 95% CI were used. Clinical and statistical heterogeneities were assessed across the studies prior to pooling. Clinical heterogeneity was determined by examining each study's clinical characteristics for any diversity/variation in for example: technique/delivery of interventions, severity/chronicity of condition, and treatment outcomes. Statistical heterogeneity was assessed by Chi^2 and I^2 statistics (Higgins and Thompson, 2002). A significant p-value<0.05 for Chi^2 test and an I^2 statistic>50% were considered substantial heterogeneity (Deeks *et al.*, 2011). Pooling of clinically and statistically homogeneous trials was done by a fixed-effect model if there were two studies pooled and by a random-effects model if more than two studies pooled. When there was substantial heterogeneity between studies, meta-analysis was not undertaken and the data were integrated into a narrative analysis of the findings. A test for funnel plot asymmetry to assess

publication bias (Egger *et al.*, 1997) was planned, but was not performed due to insufficient numbers of studies pooled in the meta-analyses. Where possible, a subgroup-analysis based on chronicity of the locking condition (acute or chronic: according to duration of locking threshold for chronic lock where disc recapture much less likely estimated at 4weeks) was conducted. Studies, without soft tissue imaging confirming the DDwoR clinical diagnosis, were excluded in a sensitivity-analysis to identify any effect on primary outcomes in the meta-analysis.

Additional data analysis was also performed examining the change from baseline in primary outcomes for each individual intervention at short- and long-term follow-ups (i.e. within-group statistical difference from baseline). This separate analysis was performed to help readers interpret the potential clinical significance of improvement from baseline for each intervention.

RESULTS

Search

The search strategy identified a total of 3333 records from all databases. Of these, the full-texts of 172 potentially eligible papers were retrieved and examined. Figure-1 illustrates the screening process.

Description of Studies

Twenty studies met the inclusion criteria (Lundh *et al.*, 1992; Petersson *et al.*, 1994; Linde *et al.*, 1995; Fridrich *et al.*, 1996; Schiffman *et al.*, 1996; Goudot *et al.*, 2000; Holmlund *et al.*, 2001; Minakuchi *et al.*, 2001; Yuasa and Kurita, 2001; Maloney *et al.*, 2002; Peroz *et al.*, 2004; Yoshida *et al.*, 2005; Ismail *et al.*, 2007; Politi *et al.*, 2007; Schiffman *et al.*, 2007; Diracoglu *et al.*, 2009; Haketa *et al.*, 2010; Yoshida *et al.*, 2011; Craane *et al.*, 2012; Sahlstrom *et al.*, 2013). Summary characteristics of included studies are available in Appendix-3. The list of excluded studies and reasons for exclusion is available upon request.

Risk-of-bias

None of the included studies were at low risk-of-bias across all domains (Appendix-4). Eight were assessed as at unclear overall risk-of-bias due to insufficient information in the trial report and/or from the contacted authors, or because it was not possible to make a definite judgement in at least one domain of the bias assessment tool. The remaining studies were assessed as at high overall risk-of-bias. Of the twenty studies included, seven presented *a*

priori sample-size calculation and eight had inadequate statistical power (<80%) (Appendix-3).

Effects of Interventions

The reviewed interventions varied widely in invasiveness. For the purpose of this review, the interventions were grouped based on their level of invasiveness into three modalities (Appendix-5):

1) Non-invasive (conservative) including: education, self-management, splint therapy, physiotherapy, and their combinations;
2) Minimally-invasive including: arthrocentesis;
3) Invasive (surgical) including: arthroscopic and open joint surgeries.

Twenty-one comparisons were made between interventions. Data for the 21-comparison (between-group statistical analysis) are presented in the text with the primary outcomes described at short- and long-term follow-up time-points in Table-1. Data examining within-group differences from baseline for primary outcomes (within-group statistical analysis) at short- and long-term follow-ups are tabulated and presented in Appendix-6 to allow readers to assess the potential clinical significance of differences. Data on all secondary outcomes are available upon request.

Comparisons of non-invasive interventions

- **Mandibular manipulation (MM) versus control**

MM was compared against control in two studies with the main difference being the delivery of manipulation: by clinicians (Yoshida *et al.*, 2005) or by patients (Yoshida *et al.*, 2011). No extractable numerical data were available from the former study but the authors reported that 172/204 (84%) patients in the MM group showed reduced pain and increased opening at 1week. Of 172 improvers, 170 had 'acute' (≤4weeks) and 2 had 'chronic' (>4weeks) DDwoR. In Yoshida *et al.* (2011), the number of patients with MMO>38mm was significantly greater 10minutes after self-MM and these ‘improvers’ also had a short duration of locking (Mean=35days) (Table-1, Comparison-1).

- **Jaw exercises versus education**

Craane *et al.* (2012) compared jaw manipulation by physiotherapists to education in DDwoR with/without limited opening. Jaw exercises demonstrated no additional effect over education alone on all measured outcomes over the short- or long-term (Table-1, Comparison-2).

- **Self-management versus control**

Two studies compared self-management (self-exercise+self-care/medication) to no active treatment over the short-term (Minakuchi *et al.*, 2001; Yuasa and Kurita, 2001). No statistically significant differences in all measured outcomes between self-management and education were demonstrated by Minakuchi *et al.* (2001) (Table-1, Comparison-3). In Yuasa and Kurita (2001), a greater number of patients experienced decreased pain and increased opening in the self-management group, but the difference was not statistically significant. In a subgroup-analysis, however, self-management demonstrated a statistically significant difference over no treatment with 'chronic' (>4weeks) DDwoR (Table-1, Comparison-4).

- **Self-management versus splint**

Haketa *et al.* (2010) compared self-management involving self-exercises (+self-care/NSAIDs) to splint (+self-care/NSAIDs). Although there was greater reduction in pain intensity in the self-management group over the short-term, the difference was not statistically significant. For MMO, however, self-management demonstrated a statistically significant difference in effect over splint (Table-1, Comparison-5).

- **Splint versus control**

Lundh *et al.* (1992) made this comparison on patients diagnosed by arthrography and given information and pain medication as needed. The number of patients with reduced pain was significantly greater in untreated than those treated with splints over the long-term (Table-1, Comparison-6).

- **Splint versus transcutaneous electric nerve stimulation (TENS)**

In Linde *et al.* (1995), the number of patients with ≥50% pain reduction was significantly greater in the splint group than TENS group, but there was no statistically significant difference between the interventions on MMO over the short-term (Table-1, Comparison-7). TENS caused mild transient hypersensitivity preauricular skin reaction.

- **Combination therapy versus education**

Minakuchi *et al.* (2001) compared the short-term effect of combined splint plus exercises (+self-care/medication/education) to education only with no statistically significant differences in effect between the interventions on all measured outcomes (Table-1, Comparison-8).

- **Combination therapy versus self-management**

Two studies compared combination therapy including splint plus exercises (+self-care/medication/education±CBT) to self-management (self-care/medication/education±self-exercises) (Minakuchi *et al.*, 2001; Schiffman *et al.*, 2007) with no statistically significant differences between the effects of the interventions on all measured outcomes over the longest follow-up (Table-1, Comparison-9). Pooling the data demonstrated no statistically significant differences between the short-term effects of the interventions on pain intensity (standardized mean differences (SMD)=0.22, 95%CI: -0.19 to 0.62, p=0.29) (Figure-2).

- **Combination of splint plus jaw exercises versus splint**

Two studies made this comparison on patients with "disc displacement" or osteoarthritis with the main difference being the delivery of jaw exercises: by clinicians (Ismail *et al.*, 2007) or by patients using either a mechanical device (Therabite) or wooden tongue depressors (WTDs) (Maloney *et al.*, 2002). Pooling the data showed no statistically significant difference in effects between the combined splint+exercises versus splint alone on pain over the short-term (MD=0.90, 95%CI: -12.28 to 14.07, p=0.89). For MMO, however, the meta-analysis showed a statistically significant difference in effect in favour of the combined treatment (MD=4.67mm, 95%CI: 1.80 to 7.55, p<0.01) (Figure-3 and Table-1, Comparison-10).

- **Active pulsed electromagnetic fields (PEMF) versus placebo PEMF**

In Peroz *et al.* (2004), active PEMF did not demonstrate additional effect over placebo on all measured outcomes in DDwoR patients over both short- and longer-term (Table-1, Comparison-11).

- **Active iontophoresis versus placebo iontophoresis**

In Schiffman *et al.* (1996), active iontophoresis by dexamethasone+lidocaine demonstrated greater short-term effects over placebo iontophoresis by normal saline on all measured outcomes but the differences were not statistically significant (Table-1, Comparison-12). Iontophoresis caused two types of mild transient adverse events (skin erythema and dizziness).

Comparisons of minimally-invasive versus non-invasive interventions

- **Arthrocentesis versus control**

Two studies evaluated the short-term effect of arthrocentesis to a control group: diagnostic arthrography (Petersson *et al.*, 1994); auriculotemporal nerve (ATN) block as sham treatment (Sahlstrom *et al.*, 2013). In both, arthrocentesis did not demonstrate statistically significant effect over the control groups on all measured outcomes (Table-1, Comparisons-13&-14). Pooling the data to evaluate the overall effect of arthrocentesis was not possible due to clinical (incomparable 'controls') and statistical (chi^2<0.05; I^2>50%) heterogeneity.

- **Arthrocentesis versus combination therapy**

Diracoglu *et al.* (2009) compared arthrocentesis to a combination of splint plus self-care/self-exercises on patients with 'acute' DDwoR (≤4weeks). In this q-RCT, arthrocentesis demonstrated a statistically significant difference in effect over the combined treatment on pain over both short- and longer-term, but there was no statistically significant difference between the interventions on MMO (Table-1, Comparison-15).

Comparisons of invasive versus non-invasive interventions

- **Arthroscopy versus conservative treatments**

Schiffman *et al.* (2007) compared arthroscopic surgery to two conservative treatment strategies: self-management (self-care/medication/education); combination of splint plus exercises (+self-care/medication/education+CBT). Arthroscopy did not demonstrate statistically significant differences in effect over conservative interventions on all measured outcomes over the short- or long-term (Table-1, Comparisons-16&-17).

- **Open surgery versus conservative treatments**

Schiffman *et al.* (2007) also compared open surgery with the same conservative interventions: self-management; combination therapy. Open surgery did not demonstrate statistically significant differences in effect over self-management on all measured outcomes over the short- or long-term (Table-1, Comparison-18). When compared with the combination therapy, open surgery demonstrated a statistically significant difference in effect on pain over the short-term, but not over the long-term (Table-1, Comparison-19).

Comparison of invasive versus minimally-invasive interventions

- **Arthroscopy versus arthrocentesis**

Two studies made this comparison on patients with disc displacement with/without reduction (Fridrich *et al.*, 1996; Goudot *et al.*, 2000). In Goudot *et al.* (2000), no statistically significant

difference in effects between the interventions on pain over the long-term was demonstrated. For MMO, pooling the data resulted in a statistically significant difference in favour of arthroscopy over the long-term (MD=5.13mm, 95%CI: 3.20 to 7.06, $p<0.001$) (Figure-4 and Table-1, Comparison-20). Four surgical complications were reported by Goudot *et al.* (2000): two intra-operative complications in arthrocentesis group (2 severe reversible bradycardias) and two post-operative complications in arthroscopic group (transient frontal palsy and prolonged cervico-facial oedema).

Comparison of invasive interventions

- **Open surgery versus arthroscopy**

Three studies made this comparison with no statistically significant differences between the effects of the two surgeries on all measured outcomes over the longest follow-up (Holmlund *et al.*, 2001; Politi *et al.*, 2007; Schiffman *et al.*, 2007). When combined in meta-analysis, a significant overall effect for open surgery over arthroscopy on reducing the pain intensity over the long-term was demonstrated (SMD=-0.50, 95%CI: -0.95 to -0.06, $p=0.03$). However, sensitivity-analysis by excluding the study without confirmatory diagnostic imaging (Holmlund *et al.*, 2001), showed no statistically significant difference between the surgical procedures (SMD=-0.43, 95%CI: -0.93 to 0.08, $p=0.10$). Furthermore, pooling the data from two studies (Holmlund *et al.*, 2001; Politi *et al.*, 2007) showed no statistically significant difference between the long-term effects of surgeries on number of patients with MMO>35mm (RR=1.07, 95%CI: 0.76 to 1.49, $p=0.71$) (Figure-5 and Table-1, Comparison-21). Open surgery caused one transient motor nerve injury (Schiffman *et al.*, 2007) and a number of transient sensory nerve injuries (Holmlund *et al.*, 2001; Politi *et al.*, 2007).

DISCUSSION

Summary of Main Findings

There was high clinical heterogeneity amongst the studies included, which was unsurprising given the differing interventions employed, and the considerable variations in techniques applied, combinations, and/or delivery, of interventions. In most comparisons, therefore, there was only one trial and only four meta-analyses could be performed on trials of homogenous comparable groups.

In this review, analysis was conducted between- and within-group. When the interventions were compared with each other (between-group), the least invasive conservative interventions including patient education and self-management seem to exert comparable

effects to more ‘active’ (combined splint plus physiotherapy) or ‘invasive’ (TMJ surgery) treatment approaches. Splints as a solitary treatment approach seem, however, to have no additional effect over other active interventions or no treatment, although as an adjunct to others, they may help to alleviate symptoms.

Among the physiotherapeutic interventions, early mandibular manipulation seems to exert an immediate effect, increasing MMO in patients with ‘acute’ DDwoR. Jaw ‘stretching’ exercises, either alone or in combination with others, also increased MMO but its effect was inconsistent between studies whilst the electro-physical modalities had, in general, no significant effect over placebo treatment or splints and could be associated with transient adverse events.

Minimally-invasive arthrocentesis and invasive arthroscopic and open joint surgical interventions did not, in general, demonstrate significant differences in effects over non-invasive conservative interventions and could be associated with complications. Nevertheless, in one study, arthrocentesis reduced pain intensity more than conservative treatment in 'acute' DDwoR (Diracoglu *et al.*, 2009). The study, however, used quasi-randomization based on alternate allocation to intervention groups and if excluded from this review, arthrocentesis is not proven to have additional effects over conservative interventions. When compared with each other, arthroscopy increased MMO more than arthrocentesis and open surgery reduced pain intensity more than arthroscopy. In the latter comparison, sensitivity-analysis did not confirm this finding suggesting the result is unstable and the evidence is not robust. The surgical procedures also suffered from clinical heterogeneity in: anaesthetic modality; lavage volumes (50-150ml) sometimes less than recommended (100-400ml) (Zardeneta *et al.*, 1997; Kaneyama *et al.*, 2004); surgical techniques; intra-articular medications injected; intra- and/or post-operative jaw manipulation, making circumstances incomparable and any direct comparison difficult. Previous Cochrane reviews for arthrocentesis (Guo *et al.*, 2009) or arthroscopy (Rigon *et al.*, 2011) included 7 studies which were either included within the present review (5 studies), or did not meet our inclusion criteria (2 studies). The current review’s findings concur with these reviews in that: non-invasive conservative interventions need to be applied first; there is insufficient evidence to support or refute the use of minimally-invasive and invasive surgical interventions; there is a need for higher-quality RCTs.

Overall, the between-group analysis shows no statistically significant differences in effects between most of the compared interventions. The differences in effect between interventions seem to be minimal thereby replicating/confirming results from a previous review (Kropmans

et al., 1999). In contrast, the within-group analysis for difference from baseline caused by each individual intervention shows that most interventions caused a statistically significant improvement in primary outcomes over the short- and long-term. Most analysed interventions, therefore, seem to be effective in alleviating DDwoR symptoms (decreased pain and increased opening) to a greater or lesser degree. These findings, however, highlight three issues:

Firstly: The improvement in patients' symptoms regardless of treatment-specific effects could be due to placebo effects (Greene *et al.*, 2009) or the 'favourable' natural course of DDwoR (Sato *et al.*, 1997; Kurita *et al.*, 1998; Yura, 2012). In this review, most studies did not have a 'true' untreated control group and therefore the estimate of the intervention's effect should be interpreted with caution as it may be due to placebo effects and/or adaptation over time.

Secondly: Some included studies were found to be underpowered to detect statistically significant differences between the compared interventions. Insufficient power usually indicates 'poor' methodological quality, for example Petersson *et al.* (1994) would have needed a reasonable sample size (~48 patients in each treatment group) to achieve adequate power. It also, however, can confirm the minimal therapeutic difference between interventions' effects, for example Holmlund *et al.* (2001) would have needed a very large, and unrealistic, sample size (~132 patients in each treatment group) to achieve adequate power. This would have been highly impractical in a single-centre study of a low incidence condition (DDwoR).

Thirdly: Despite the absence of statistically significant differences between interventions, most interventions caused statistically significant improvement from baseline thereby posing the question: is this improvement clinically meaningful? To answer such a question we must understand the minimal clinically important difference (MCID) determined from the patient's perspective (Copay *et al.*, 2007) for the primary outcomes. For pain intensity, the MCID has been defined as a reduction from baseline of approximately one third (~30%): 2-point on an 11-point numerical rating scale (Farrar *et al.*, 2001); 20mm on a 100mm visual analogue scale (Jensen *et al.*, 2003). In this review, however, pain intensity was measured using different instruments (tools/scales), which may not be directly comparable. For MMO, Kropmans *et al.* (2000) suggests an increase of at least 9mm to demonstrate a statistical and clinical improvement in MMO. Kropmans *et al.*'s study had several methodological flaws and the 9mm threshold was based on the smallest detectable difference in measurements for assisted/passive MMO in untreated patients with "painfully restricted TMJ disorders". This is as opposed to a MCID in MMO, which would require assessment from the patient's

perspective as a result of therapeutic intervention (Dworkin *et al.*, 2008). There is, therefore, no currently agreed MCID for MMO and further studies using biopsychosocially representative samples of subjects with DDwoR are needed to address this. Nevertheless, if the 9mm for assisted/passive MMO improvement is taken as perhaps indicative of MCID, one could estimate an increase from baseline of about 6.5mm or more for unassisted/active MMO (~2.5mm difference between unassisted and assisted MMO for DDwoR patients (Hesse *et al.*, 1996) due to joint laxity and passive stretch force). The suggested values can be used as an approximate to help readers interpret the clinical significance of change from baseline reported in Appendix-6.

The study samples included in this review also had limitations. Most subjects included were female (87%) with a mean age of 35years thereby mirroring closed lock reviews (Al-Belasy and Dolwick, 2007; Monje-Gil *et al.*, 2012) but they were: mostly recruited from specialised university clinics/hospitals as opposed to other first-point contact clinical-settings; differed in the presence/absence of comorbid disorders; differed in duration of DDwoR symptoms (one day to several years). All these factors may have affected the magnitude of treatment effect due to possible variation in the level of pathological changes in the intra-articular tissues (Stiesch-Scholz *et al.*, 2002; Emshoff and Rudisch, 2004; Machon *et al.*, 2012) amongst other variables. To investigate this, a threshold of 4weeks locking duration was estimated for acute/chronic DDwoR subgroup analysis. Few analyses could be conducted using this threshold and the effect of locking duration on effectiveness of interventions could not be established.

Most included studies had methodological flaws in their design and used different methods to assess subjective outcomes. This made comparisons of the effect-size of interventions difficult. Furthermore, none of them captured the broad multidimensional nature of patients' quality-of-life (Locker and Allen, 2007) and only one evaluated the therapy cost (Schiffman *et al.*, 2014). Future trials need to address these outcomes and should follow the IMMPACT recommendations for outcomes assessment in pain clinical trials (Dworkin *et al.*, 2005) and CONSORT guidelines for RCT conduct and reporting (Schulz *et al.*, 2011).

Despite the aforementioned limitations, one issue has become apparent from the results of this review: most interventions appear to alleviate DDwoR symptoms with no significant differences between non-invasive conservative interventions and minimally-invasive or invasive surgical interventions. Given the paucity of evidence and the difficulty in interpreting the minimal clinically important difference, this finding suggests that patients with DDwoR probably should be initially managed with the most minimal and least invasive

intervention. Escalation to more invasive treatment should only occur in the face of objective clinical need. This, however, should be interpreted in the context of a review based mostly on single studies of unclear to high risk-of-bias. Future well-conducted research may change or confirm this.

CONCLUSIONS

Implications for Practice

The comparable therapeutic effects of reviewed interventions suggest using the simplest, least costly, and least invasive interventions to initially manage DDwoR. Of the variety of non-invasive conservative interventions reviewed, the least invasive were patient education, self-management, and early mandibular manipulation. Currently, there is insufficient evidence to support or refute the use of minimally-invasive and invasive surgical interventions for DDwoR. There may well be, however, specific clinical cases where a surgical intervention may help, but the body of evidence does not give a clear indication of when this may be.

Implications for Research

There is weak evidence to support the initial use of simple, minimal, non-invasive conservative interventions, in particular patient education, self-management, and early mandibular manipulation, for DDwoR. Future research needs to specifically examine these interventions to provide more robust evidence of their efficacy or lack of it. The evidence for the effectiveness of minimally-invasive surgical intervention through arthrocentesis and lavage is contradictory. Given its less invasive nature, future high-quality pragmatic RCTs are required to compare the effects of arthrocentesis with conservative interventions. Detailed descriptions about recommended research design are available upon request.

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Tables and figure legends:

Table 1: Summary of findings for the primary outcomes (pain at jaw function and unassisted/active maximum mouth opening).

Comparison (Study)	Primary outcome	Follow-up (short-term & long-term)	No. of Patients (Trials)	Relative effect (95% CI)[a]	*p*-value for between-group difference[b]	Overall Risk-of-Bias	Outcome measuring tool/scale[c]
1. MM *vs.* No treatment (Yoshida *et al.*, 2011)	MMO	10 min (ST)	148 (1 RCT)	RR 16.67 (5.44 to 51.06)	*p*<0.0001 favours MM	High	MMO>38mm
2. Jaw exercises *vs.* Education only (Craane *et al.*, 2012)	Pain[d]	3 mo (ST)	42 (1RCT)	MD 3.81 (-6.15 to 13.77)	NS	Unclear	VAS (0-100)
	Pain[d]	13 mo (LT)	42 (1 RCT)	MD 0.62 (-5.46 to 6.70)	NS	Unclear	VAS (0-100)
	MMO	3 mo (ST)	45 (1 RCT)	MD -3.10 (-6.96 to 0.76)	NS	Unclear	aMMO (mm)
	MMO	13 mo (LT)	42 (1 RCT)	MD -3.80 (-7.68 to 0.08)	NS (*p*=0.05 towards Educ)	Unclear	aMMO (mm)
3. Self-management *vs.* Education only (Minakuchi *et al.*, 2001)	Pain	2 mo (ST)	44 (1 RCT)	MD -4.40 (-19.54 to 10.74)	NS	Unclear	VAS (0-100) on chewing
	MMO	2 mo (ST)	44 (1 RCT)	MD -1.40 (-6.90 to 4.10)	NS	Unclear	aMMO (mm)
4. Self-management *vs.* No treatment (Yuasa and Kurita, 2001)	Pain & MMO	1 mo (ST)	60 (1 RCT)	RR 1.80 (1.00 to 3.23)	NS (*p*=0.05 towards SM)	Unclear	No. improved patients for: VAS pain & MMO
	Subgroup analysis	1 mo (ST)	15 Acute	RR 1.05 (0.57 to 1.94)	NS		
			45 Chronic	RR 2.51 (1.06 to 5.95)	*p*<0.05 favours SM		
5. Self-management *vs.* Splint (Haketa *et al.*, 2010)	Pain	2 mo (ST)	44 (1 RCT)	MD -15.20 (-31.55 to 1.15)	NS (*p*=0.07 towards SM)	Unclear	VAS (0-100)
	MMO	2 mo (ST)	44 (1 RCT)	MD 6.00 (2.67 to 9.33)	*p*<0.001 favours SM	Unclear	MMO with pain (mm)
6. Splint *vs.* Control (Lundh *et al.*, 1992)	Pain	12 mo (LT)	51 (1 RCT)	RR 0.49 (0.26 to 0.92)	*p*<0.05 favour Control	High	No. reduced pain
7. Splint *vs.* TENS (Linde *et al.*, 1995)	Pain	6 wk (ST)	31 (1 RCT)	RR 8.53 (1.21 to 60.33)	*p*<0.05 favours Splint	High	Reduction in pain≥50%
	MMO	6 wk (ST)	31 (1 RCT)	MD -0.16 (-4.07 to 3.75)	NS	High	Change from baseline mm
8. Combination therapy[e] *vs.* Education only (Minakuchi *et al.*, 2001)	Pain	2 mo (ST)	46 (1 RCT)	MD -2.80 (-16.12 to 10.52)	NS	Unclear	VAS (0-100) on chewing
	MMO	2 mo (ST)	46 (1 RCT)	MD 1.40 (-3.94 to 6.74)	NS	Unclear	aMMO (mm)
9. Combination therapy *vs.* Self-management (Minakuchi *et al.*, 2001; Schiffman *et al.*, 2007)	Pain	2-3 mo (ST)	97 (2 RCTs)	SMD 0.22 (-0.19 to 0.62)	NS	Unclear	VAS & SSI
	Pain	60 mo (LT)	50 (1 RCT)	MD 0.00 (-0.13 to 0.13)	NS	Unclear	SSI (0-1)
	MMO	2 mo (ST)	48 (1 RCT)	MD 2.80 (-2.95 to 8.55)	NS	Unclear	aMMO (mm)
10. Jaw exercise + splint *vs.* Splint[f] (Maloney *et al.*, 2002; Ismail *et al.*, 2007)	Pain	1-3 mo (ST)	50 (2 RCTs)	MD 0.90 (-12.28 to 14.07)	NS	High	VAS & NRS (0-100)
	MMO	1-3 mo (ST)	50 (2 RCTs)	MD 4.67 (1.80 to 7.55)	*p*<0.01 favours Ex+Sp	High	aMMO (mm)
11. Active PEMF *vs.* Placebo PEMF (Peroz *et al.*, 2004)	Pain[d]	6 wk (ST)	31 (1 RCT)	MD 0.23 (-17.96 to 18.42)	NS	Low	VAS (0-100)
	Pain[d]	4 mo (LT)	30 (1 RCT)	MD 19.49 (0.97 to 38.01)	*p*<0.05 favour placebo	Unclear	VAS (0-100)
	MMO[d]	6 wk (ST)	31 (1 RCT)	MD -2.47 (-8.23 to 3.29)	NS	Low	aMMO (mm)
	MMO	4 mo (LT)	30 (1 RCT)	MD -1.00 (-6.09 to 4.09)	NS	Unclear	aMMO (mm)
12. Active iontophoresis *vs.* Placebo iontophoresis[g] (Schiffman *et al.*, 1996)	Pain	1 wk (ST)	18 (1 RCT)	MD -0.03 (-0.21 to 0.15)	NS	Unclear	SSI (0-1)
	MMO	1 wk (ST)	18 (1 RCT)	MD 1.90 (-5.70 to 9.50)	NS	Unclear	aMMO (mm)
13. Arthrocentesis *vs.* Arthrography only (Petersson *et al.*, 1994)	Pain[h]	2 mo (ST)	33 (1 RCT)	MD -16.02 (-34.79 to 2.75)	NS (*p*=0.09 towards AC)	High	VAS (0-100) after chewing
	MMO	2 mo (ST)	33 (1 RCT)	MD -3.00 (-9.54 to 3.54)	NS	High	mm
14. Arthrocentesis *vs.* ATN LA block (Sahlstrom *et al.*, 2013)	Pain[d] (no ITT)	3 mo (ST)	37 (1 RCT)	MD 24.60 (6.06 to 43.14)	*p*<0.01 favours LA	Unclear	VAS (0-100) at movements
	Pain (ITT)	3 mo (ST)	45 (1 RCT)	RR 0.72 (0.46 to 1.14)	NS	Unclear	Reduced pain≥30%
	MMO[d]	3 mo (ST)	37 (1 RCT)	MD -4.90 (-10.00 to 0.20)	NS (*p*=0.06 towards LA)	Unclear	aMMO (mm)
15. Arthrocentesis *vs.* Combination therapy (Diracoglu *et al.*, 2009)	Pain	3 mo (ST)	110 (1 qRCT)	MD -19.3 (-28.54 to -10.06)	*p*<0.0001 favours AC	High	VAS (0-100)
	Pain	6 mo (LT)	110 (1 qRCT)	MD -28.80 (-36.56 to -21.04)	*p*<0.0001 favours AC	High	VAS (0-100)
	MMO	3 mo (ST)	110 (1 qRCT)	MD 1.93 (-0.75 to 4.61)	NS	High	mm
	MMO	6 mo (LT)	110 (1 qRCT)	MD 2.35 (-0.07 to 4.77)	NS (*p*=0.06 towards AC)	High	mm
16. Arthroscopy *vs.* Self-management (Schiffman *et al.*, 2007)	Pain	3 mo (ST)	50 (1 RCT)	MD 0.01 (-0.12 to 0.14)	NS	Unclear	SSI (0-1)
	Pain	60 mo (LT)	51 (1 RCT)	MD 0.03 (-0.09 to 0.15)	NS	Unclear	SSI (0-1)
17. Arthroscopy *vs.* Combination therapy (Schiffman *et al.*, 2007)	Pain	3 mo (ST)	43 (1 RCT)	MD -0.08 (-0.24 to 0.08)	NS	Unclear	SSI (0-1)
	Pain	60 mo (LT)	47 (1 RCT)	MD 0.03 (-0.09 to 0.15)	NS	Unclear	SSI (0-1)
18. Open surgery *vs.* Self-management (Schiffman *et al.*, 2007)	Pain	3 mo (ST)	48 (1 RCT)	MD -0.07 (-0.20 to 0.06)	NS	Unclear	SSI (0-1)
	Pain	60 mo (LT)	50 (1 RCT)	MD 0.05 (-0.09 to 0.19)	NS	Unclear	SSI (0-1)
19. Open surgery *vs.* Combination therapy (Schiffman *et al.*, 2007)	Pain	3 mo (ST)	41 (1 RCT)	MD -0.16 (-0.32 to -0.00)	*p*<0.05 favours OS	Unclear	SSI (0-1)
	Pain	60 mo (LT)	46 (1 RCT)	MD 0.05 (-0.09 to 0.19)	NS	Unclear	SSI (0-1)
20. Arthroscopy *vs.* Arthrocentesis (Fridrich *et al.*, 1996; Goudot *et al.*, 2000)	Pain	12 mo (LT)	62 (1 RCT)	MD 10.00 (-1.20 to 21.20)	NS (*p*=0.08 towards AC)	High	VAS (0-100)
	MMO	6-24 mo (LT)	81 (2 RCTs)	MD 5.13 (3.20 to 7.06)	*p*<0.0001 favours AS	High	mm
21. Open surgery *vs.* Arthroscopy (Holmlund *et al.*, 2001; Politi *et al.*, 2007; Schiffman *et al.*, 2007)	Pain	3 mo (ST)	42 (1 RCT)	MD -0.08 (-0.23 to 0.07)	NS	Unclear	SSI (0-1)
	Pain	12 mo (LT)	81 (3 RCTs)	SMD -0.50 (-0.95 to -0.06)	*p*<0.05 favours OS	High	VAS & SSI
	Sensitivity analysis	12 mo (LT)	61 (2 RCTs)	SMD -0.43 (-0.93 to 0.08)	NS	High	VAS & SSI
	MMO	12 mo (LT)	40 (2 RCTs)	RR 1.07 (0.76 to 1.49)	NS	High	MMO>35mm

Abbreviations: AC: arthrocentesis, aMMO: active (unassisted) maximum mouth opening, AS: arthroscopy, ATN LA block: auriculotemporal nerve local anaesthesia block, CI: confidence interval, Educ: education, Ex+Sp: exercises plus splint, ITT: intention-to-treat analysis, LT: long-term, MD: mean difference, min: minutes, MM: mandibular manipulation, mm: millimetres, MMO: maximum mouth opening, mo: months, No.: number of patients, NRS: numerical rating scale, NS: non-significant, OS: open surgery, PEMF: pulsed electromagnetic fields, qRCT: quasi-randomised clinical trial, RCT: randomised clinical trial, RR: risk ratio, SM: self-management, SMD: standardised mean difference, SSI: symptoms severity index, ST: short-term, TENS: transcutaneous electric nerve stimulation, VAS: visual analogue scale, wk: weeks.

[a] The risk ratio (RR) is the ratio of the chance of experiencing a particular event that occurs with use of the intervention to that occurs with the use of control. The mean difference (MD) is the difference in means values between two groups in a clinical trial. It estimates the amount by which an intervention changes the outcome on average compared with the control. It can be used as a summary statistic in meta-analysis when outcome measurements in all studies are made on the same scale. The standardized mean difference (SMD) is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it on different scales. It expresses the size of the intervention effect in each study relative to its variance (SD). Further details about the statistical analysis used to measure the relative effects of interventions in clinical trials are available in the Cochrane handbook for systematic reviews of interventions which is accessible online: http://handbook.cochrane.org/.

[b] Statistical significance (p-value<0.05) for between-group statistical differences.

[c] For uniformity, data were analysed and presented by rescaling pain scales (VAS and NRS) on 0-10 cm (Goudot *et al.*, 2000; Holmlund *et al.*, 2001; Maloney *et al.*, 2002; Politi *et al.*, 2007; Diracoglu *et al.*, 2009) to a 0-100 mm scale.

[d] Unpublished statistical data provided by the contacted authors (personal e-mail communication).

[e] Combination therapy of splint plus jaw exercises (± self-care/education/medication ± cognitive behavioural therapy 'CBT') conservative interventions.

[f] In Maloney *et al.* (2002), Therabite devise + splint group and wooden tongue depressors (WTDs) + splint group were merged as one group: jaw exercises plus splint.

[g] In Schiffman *et al.* (1996), three groups were compared (active iontophoresis by dexamethasone + lidocaine, control iontophoresis by lidocaine only, and placebo iontophoresis by normal saline). In this review, however, only the comparison between active and placebo iontophoresis was considered and reported.

[h] Estimated from figure 2 in the published trial.

Figure legends:

Figure 1: Study flow diagram.

Figure 2: Forest plot* of pooled data regarding pain outcome for combination therapy versus self-management.

* Guidance for interpreting forest plots can be found in (Lewis and Clarke, 2001).

Figure 3: Forest plot of pooled data regarding pain and mandibular movements outcomes for combination of splint plus jaw exercises versus splint only.

Figure 4: Forest plot of pooled data regarding maximum mouth opening outcome for arthroscopy versus arthrocentesis.

Figure 5: Forest plot of pooled data regarding pain, mandibular movements, and function outcomes for open joint surgery versus arthroscopic surgery.

Title: TMJ Disc Displacement without Reduction Management: A Systematic Review

APPENDICES

Systematic Review Methods (Details)*

Appendix 1 (Table). Inclusion/Exclusion Criteria

Inclusion criteria	Exclusion criteria
Types of studies	**Types of studies**
Randomised clinical trials (RCTs) that involve patients with TMJ DDwoR and comparing any form of conservative (non-surgical) or surgical interventions against each other, placebo or no treatment. Quasi-randomised studies, such as those allocating patients by using alternate days of the week, birth date, or consecutive attendance considered only if the baseline demographic details (e.g., severity of condition) of each comparable group were approximately similar. Included quasi-random trials were, however, subject to a sensitivity analysis. Studies which involve other heterogeneous groups of TMD patients (e.g. osteoarthritis, myofacial pain, disc displacement with reduction) in addition to patients with DDwoR were considered only if separate data were provided for DDwoR patients. If the separate data had not been provided but the percent of DDwoR patients in the study sample was more than 70%, the study was examined to be included.	Studies comparing different types or techniques of similar intervention group (such as trials comparing different techniques of arthroscopy, different techniques of arthrocentesis, or those comparing between different types of occlusal splints). Studies evaluating a treatment modality after an initial surgical intervention (such as trials evaluating different medications or splints after arthroscopy or arthrocentesis).
Types of participants	**Types of participants**
Patients of any age, gender, and of all degree of severity with clinical and/or radiological diagnosis of TMJ DDwoR as diagnosed according to: American Association of Orofacial Pain (AAOP) guidelines for acute or chronic DDwoR (de Leeuw, 2008); research diagnostic criteria for temporomandibular disorders (RDC/TMD) for DDwoR with (IIb) or without (IIc) limited mouth opening (Dworkin and LeResche, 1992); Wilkes staging for internal derangement (stage III or IV) (Wilkes, 1989); or any other compatible criteria for DDwoR diagnosis. Confirming the disc position by soft tissue imaging was not a prerequisite to include the study. Studies which involve participants with confirmed diagnosis of DDwoR disorder with comorbid disorders.	Patients with systemic diseases.
Types of interventions	**Types of interventions**
Different forms of conservative (non-surgical) and surgical therapeutic interventions such as: patient education, self-management, psychosocial therapy, pharmacological therapy, physiotherapy, splint therapy, intra-articular medication injection, arthrocentesis, arthroscopic surgery, and open joint surgery. Studies that evaluate these therapeutic interventions against each other, placebo or no treatment were included. Standardized combinations of treatments were also included.	Studies comparing different types or techniques of similar intervention group. Studies evaluating a treatment modality after an initial surgical intervention.

* Further details about the review methods are available in the study protocol registered at PROSPERO-CRD database (Al-Baghdadi *et al.*, 2012).

Appendix 2. Search Strategy

Electronically-searched databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL) via Cochrane Library (November/2013 issue);
2. MEDLINE via Ovid (1966-November/2013);
3. EMBASE via Ovid (1980-November/2013);
4. Scopus via SciVerse (1966-November/2013).

Limits: English-language, peer-reviewed, publications.

The search strategy was primarily developed for the MEDLINE (see below) and was revised appropriately for each database searched to take account of differences in controlled vocabulary and syntax rules.

Ovid MEDLINE(R) <1966 to October Week 4 2013>

1. exp Temporomandibular Joint disorders/
2. exp Temporomandibular Joint/
3. 1 or 2
4. (temporomandibular joint or tmj).tw.
5. (derangement adj6 (disorder$ or condition$)).tw.
6. (derangement adj2 internal).tw.
7. (lock$ adj2 (closed or jaw)).tw.
8. ((displace$ or dislocat$ or unreduc$ or nonreduc$ or un-reduc$ or non-reduc$ or derange$) adj6 (disc or disk or meniscus)).tw.
9. or/4-8
10. 3 and 9

The above subject search was linked to the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised controlled trials (RCTs) in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0 (updated March 2011) (Higgins and Green, 2011):

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp animals/ not humans.sh.
11. 9 not 10

Hand-searched Journals:

1. Journal of Oral and Maxillofacial Surgery (from 2010 to October 2012).
2. Cranio: The journal of craniomandibular practise (from 1996 to October 2012).
3. Journal of Prosthetic Dentistry (from 1999 to September 2012).
4. Journal of Oral Rehabilitation (from 2004 to October 2012).
5. Journal of Orofacial Pain (from 1987 to December 2012).
6. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology (from 2004 to February 2012).
7. International Journal Oral and Maxillofacial Surgery (from 2003 to October 2012).

These journals were hand-searched by the first reviewer (MA) according to dates not already have been hand-searched by the Cochrane worldwide hand-searching programme (according to Master List of journals completed search by the Cochrane Oral Health Group to October 2012).

Systematic Review Results

Appendix 3 (Table). Characteristics of Included Studies (Studies in Chronological Order)

Study (year)	Study design				Participants						Interventions	Follow-up time-points	Main assessed outcomes	Adverse events	Dropouts (groups)
	Allocation	Blinding	Setting, Country	Fund	Sample size (PA used?)[a]	Age (years)	Gender	Locking duration	Diagnostic criteria	ST imaging					
Lundh *et al.* (1992)	Random	NR	University, Sweden	Yes	51 (No)	Mean 29	5m,46f	NR	Eriksson criteria[b]	Arthrogr.	Splint, N=25 Control, N=26	6, 12 mo	Pain	NR	No
Petersson *et al.* (1994)	Random	Single-blind	University, Sweden	NR	34 (No)	Mean 33	5m,29f	NR	Eriksson criteria[b]	Arthrogr.	Arthrocentesis, N=16/17 Arthrography, N=17	2 mo	Pain, MMO, LM, PM, Self-questionnaire	No	Total=1 (AC=1)
Linde *et al.* (1995)	Random	NR	University, Sweden	Yes	33 (2 exc) (No)	Median 37	5m,26f	Median 6mo (range 2wk-16yr)	Own study criteria	No	TENS, N=16/17 Splint, N=15	6 wk	Pain, MMO, LM, PM, Frequency and severity of complaints	Yes (TENS: unclear)	Total=2: (TENS=1, unclear=1)
Fridrich *et al.* (1996)	Random	NR	University, USA	NR	19 (15 DDwoR) (No)	Mean 31	19f	NR	Own study criteria	MRI	Arthroscopy, N=11 Arthrocentesis, N=8	1 wk, 1, 3, 6, 12, 24 mo	Pain, MMO, LM, PM, dietary alterations	No	Total=15 at 24 mo (unclear)
Schiffman *et al.* (1996)	Random	Double-blind	University, USA	Yes	27 (No)	Mean 29	3m,24f	NR	AACMDs and own criteria[c]	None	Active iontoph., N=9 Control iontoph., N=9 Placebo iontoph., N=9	1 wk	Pain (SSI), Function (CMI), MMO, LM	Yes (N: unclear)	None
Goudot *et al.* (2000)	Random	NR	University, France	NR	62 (54 DDwoR) (No)	Mean 38	75%f	> 6mo	Own study criteria	MRI	Arthroscopy, N=33 Arthrocentesis, N=29	12 mo	Pain, MMO	Total=4: (As=2, Ac=2)	None
Holmlund *et al.* (2001)	Random	NR	University, Sweden	NR	22 (2 exc) (No)	Mean 34.5	2m,18f	Mean 14.5mo (range 2-60mo)	Own study criteria	None	Open surgery (Discectomy), N=10 Arthroscopy, N=10/12	3, 12 mo	Pain, MMO, PM, MFIQ	Yes (N: unclear, As=1)	Total=2: (AS=2)
Minakuchi *et al.* (2001) **Report: Minakuchi *et al.* (2004)**	Random	Single-blind	University, Japan	Yes	69 (No)	Mean 34	7m,62f	Mean 98dy ±SD 156.8dy	Own study criteria	MRI	Education, N=21 Self-management, N=23 Combination therapy, N=25	2, 4, 8 wk	Pain, MMO, DAL, self-questionnaire	NR	Total=10 (Educ=2; SM=2; Comb=4; Unclear=2) (ITT used)
Yuasa and Kurita (2001) **Report: Yuasa *et al.* (2003)**	Random	NR	University, Japan	NR	60 (Yes)	Median 28	12m,48f	Median 84dy (range 16-1254dy)	AAOMS & IAOMS criteria[d]	MRI	Self-management, N=30 No treatment, N=30	2, 4 wk	Pain, MMO, interference with daily life	None	Yes (unclear) (LOCF use)
Maloney *et al.* (2002)[e]	Random	NR	University, USA	Yes	24 DDwoR (No)	NR	NR	NR	RDC/TMD	MRI	Therabite+Splint, N=10 WTDs+Splint, N=7 Splint, N=7	4 wk	Pain, MMO, LM, PM	NR	No
Peroz *et al.* (2004)[e]	Random	Double-blind	University, Germany	Yes	31 DDwoR (No)	Mean 44	83%f	≥ 6mo	RDC/TMD	MRI in some patients	Active PEMF, N=13/14 Placebo PEMF, N=17	9 dy, 6 wk, 4 mo	Pain, MMO, LM, PM, RDLA	NR	Total=1: (Active PEMF=1)

Appendix 3 (Table) *(Continued)*

Study (year)	Study design				Participants						Interventions	Follow-up time-points	Main assessed outcomes	Adverse events	Dropouts (groups)
	Allocation	Blinding	Setting, Country	Fund	Sample size (PA used?)[a]	Age (years)	Gender	Locking duration	Diagnostic criteria	ST imaging					
Yoshida *et al.* (2005)	Random	NR	University, Japan	NR	305 (No)	Range (18-74)	76m,229f	(range 1dy-<1yr)	Own study criteria	None	MM+NSAID, N=204 NSAID, N=101	Unclear (1 wk)	Pain, MMO	NR	NR
Ismail *et al.* (2007)	Random	only data analyst	University, Germany	NR	26 (21 DDwoR) (Yes)	Mean 43	3m,23f	< 6mo	RDC/TMD	MRI	Exercises+Splint, N=13 Splint, N=13	1 wk, 1, 2, 3 mo	Pain, MMO, PM	NR	No
Politi *et al.* (2007)	Random	NR	University, Italy	NR	20 (No)	Mean 43	6m,14f	Mean 14.9mo (range 6-27mo)	Own study criteria	MRI	Open surgery (Condylectomy), N=10 Arthroscopy, N=10	12 mo	Pain, MMO, PM, MFIQ	Yes (N: unclear)	No
Schiffman *et al.* (2007) **Report: Schiffman *et al.* (2014)**	Random	Single-blind	University, USA	Yes	108 (2 exc) (Yes)	Mean 32	8m,98f	< 6mo and ≥ 6mo	Wilkes (III or IV)	MRI	Self-management, N=27/29 Combination therapy, N=23/26 Arthroscopy, N=24/27 Open surgery (Arthroplasty), N=24/26	3, 6, 12, 18, 24, 60 mo	Pain (SSI), Function (CMI), Therapy Cost	Total=1 (OS=1)	Total=12: (Comb=3, AS=4, OS=5) (ITT used)
Diracoglu *et al.* (2009)	Alternate[f] (q-RCT)	Single-blind	University, Turkey	NR	120 (No)	Mean 34	16m,104f	≤ 3wk	Own study criteria	MRI	Arthrocentesis, N=54/60 Combination therapy, N=56/60	1, 3, 6 mo	Pain, MMO, LM, PM	NR	Total=10 (unclear)
Haketa *et al.* (2010)[g]	Random	Single-blind	University, Japan	Yes	52 (Yes)	Mean 38	6m,46f	> 2wk	Own study criteria	MRI	Self-management, N=19/24 Splint, 25/28	1, 2 mo	Pain, MMO, LDF	None	Total=14: (SM=9; Splint=5)
Yoshida *et al.* (2011) **Report: Yoshida *et al.* (2013)**	Random	NR	University, Japan	NR	148 (No)	Mean 40	148f	Mean 50dy (range 1-360dy)	Own study criteria	None	Self-MM, N=74 No treatment, N=74	10 min	MMO, LM, PM	NR	NA
Craane *et al.* (2012)[g]	Random	Single-blind	University, Belgium	No	49 (Yes)	Mean 37	2m,47f	several wk to several yr	RDC/TMD (IIb, IIc)	MRI in only 6/49	Jaw exercise, N=20/23 Education, N=22/26	3, 6, 12, 26, 52 wk	Pain, MMO, MFIQ	NR	Total=7: (Exer=3; Educ=4) (ITT used)
Sahlstrom *et al.* (2013)[g]	Random	Single-blind	University, Sweden	No	45 (Yes)	Mean 35	4m,41f	Median 24mo (range 3-360mo)	RDC/TMD	MRI	Arthrocentesis, N=14/20 Extra-articular LA, N=23/25	1, 3 mo	Pain, MMO, JFLS	None	Total=8: (AC=6; LA=2) (ITT used)

Abbreviations: AC: arthrocentesis, Arthrogr: arthrography, AS: arthroscopy, CMI: craniomandibular index, Comb: combination therapy of splints + physiotherapy + medication/education, C: control, DAL: daily activity limitations, Dx: diagnosis, dy: days, Educ: education, exc: excluded; exer: exercises, f: female, FOC: frequency of complaints, iontoph.: iontophoresis, ITT: intention-to-treat analysis, JFLS: jaw functional limitation scale, LA: local anaesthetic, LDF: limitation of daily functions, LM: lateral movement, LOCF: last observation carried forward, m: male, MM: mandibular manipulation, MFIQ: mandibular function impairment questionnaire, MMO: maximum mouth opening, min: minutes, mm: millimetres, mo: months, MRI: magnetic resonance imaging, N: number, NA: not applicable, NR: not reported, NSAIDs: non-steroidal anti-inflammatory drugs, OS: open surgery, PA: power-analysis, PEMF: pulsed electromagnetic fields, PM: protrusive movement, PT: physiotherapy, q-RCT: quasi-randomised clinical trial, RDC/TMD: research diagnostic criteria of temporomandibular disorders, RDLA: restriction of daily life activities, SD: standard deviation, self-ex: self-exercise, SM: self-management, self-MM: self- mandibular manipulation, SSI: symptoms severity index, TENS: transcutaneous electric nerve stimulation, wk: weeks, WTDs: wooden tongue depressors, yr: years.

[a] *A priori* power-analysis was done in 7 RCTs. In the remaining 13 trials, a *post-hoc* power-analysis was performed using the G*3power statistical software (version 3) and 8 trials were found under-powered (<80%) for their level of significance for the two primary outcomes (pain and MMO) (Petersson *et al.*, 1994; Linde *et al.*, 1995; Schiffman *et al.*, 1996; Holmlund *et al.*, 2001; Minakuchi *et al.*, 2001; Maloney *et al.*, 2002; Peroz *et al.*, 2004; Politi *et al.*, 2007).
[b] Criteria suggested by (Eriksson and Westesson, 1983).
[c] Criteria suggested by American academy of craniomandibular disorders (AACMDs) in addition to own study's authors criteria (Schiffman *et al.*, 1989; McNeill, 1990).
[d] Criteria suggested by American association of oral and maxillofacial surgeons (AAOMS) and international association of oral and maxillofacial surgeons (IAOMS) (surgery, 1984; Goss, 1993).
[e] Separate data for DDwoR patients are available and/or obtained from the contacted authors (personal e-mail communication).
[f] Patients were allocated to undergo either arthrocentesis or conservative treatment (a combination of splint and physiotherapy) according to their admission to the TMJ clinic (consecutively 1 to each group).
[g] Statistical data (unpublished) were provided by the study authors (personal e-mail communication).

Appendix 4 (Figures): Risk of Bias

Figure legends for Appendix 4:

Appendix Figure 4.1. Summary Assessment for the Overall Risk of Bias*

*** Other bias:** represents any other apparent bias in the trial design or conduct other than the already assessed biases in the tool (i.e., selection, performance and detection, attrition, and reporting biases) and it involves any concerns about bias in the included studies such as: baseline imbalance, blocked randomization in un-blinded trials, effects of funding sources ...etc.

Appendix Figure 4.2. The Individual Domain Risk of Bias for Each Study*

Symbols: [+] Low risk-of-bias, [**?**] Unclear risk-of-bias, [**-**] High risk-of-bias.

* Useful information and further clarifications about study design/conduct were obtained in the following studies (Petersson *et al.*, 1994; Schiffman *et al.*, 1996; Holmlund *et al.*, 2001; Yuasa and Kurita, 2001; Schiffman *et al.*, 2007).

Appendix 5 (Table). Description of interventions

Intervention	Description
1. Non-invasive	involves any conservative (non-surgical) interventions.
• Patient education	Includes information, explanation, and reassurance only.
• Self-management	Includes self-care instructions and advice plus medication (e.g., over-the-counter analgesic, NSAIDS, muscle relaxants) ± self-exercises.
• Splint therapy	Includes different types of splints such as: stabilisation splints, repositioning splints, or soft splints.
• Physiotherapy	Includes different approaches of physical therapy such as: - Mandibular manipulation (MM): a 'singular' manual mandibular manipulation technique to 'unlock' the jaw and recapture the displaced disc (disc repositioning). - Jaw exercises: 'repeated' jaw 'stretching' exercises applied either by the patients themselves (home exercise programme 'self-exercises') or by clinicians (professional exercise therapy 'active or passive jaw exercises'). - Electro-physical modalities: ultrasound therapy, short wave diathermy, iontophoresis, transcutaneous electric nerve stimulation (TENS), pulsed electromagnetic fields (PEMF), or low level laser therapy (LLT).
• Combination therapy	Includes splints plus jaw exercises ± (self-care/medication/ education ± psychosocial 'cognitive behavioural' therapy 'CBT').
2. Minimally-invasive	involves any intra-articular intervention by needles only.
• Arthrocentesis	A technique using needles and injections for joint hydraulic pumping and lavage inside the superior joint space.
3. Invasive	involves any surgical interventions.
• Arthroscopic surgery	A technique using an arthroscope for joint hydraulic pumping and lavage and/or any other operative arthroscopic operations inside the superior joint space.
• Open joint surgery	A technique using a skin incision to approach the temporomandibular joint such as discoplasty, discectomy, eminectomy, or condylectomy.

Appendix 6 (Tables). Statistical analysis for within-group difference from baseline for primary outcomes of each individual intervention.

Appendix Table 6.1: Change from baseline for TMJ pain intensity (at jaw function) primary outcome.

Study[a] (Year)	Intervention	Follow-up time-point	Pre-treatment	Post-treatment	Change[b] from baseline	*p*-value[c] for within-group difference from baseline	Overall Risk-of-Bias
			Mean ± SD	Mean ± SD	Mean ± SD		
Yoshida *et al.* (2005)	MM	1 wk (ST)	45.5	29	-16.5	NR	High
	NSAID only	1 wk (ST)	NR	NR	NR	NR	High
Yoshida *et al.* (2011)	MM	Outcome not assessed	NA	NA	NA	NA	NA
	No treatment						
Craane *et al.* (2012)[d]	Jaw exercises	3 mo (ST)	51.15 ± 12.91	21.63 ± 16.77	-29.52 ± 14.96	$p<0.05$	Unclear
	Education	3 mo (ST)	54.14 ± 15.93	17.82 ± 16.09	-36.32 ± 16.01	$p<0.05$	Unclear
	Jaw exercises	13 mo (LT)	51.15 ± 12.91	8.10 ± 10.46	-43.05 ± 11.75	$p<0.05$	Unclear
	Education	13 mo (LT)	54.14 ± 15.93	7.48 ± 9.55	-46.66 ± 13.13	$p<0.05$	Unclear
Minakuchi *et al.* (2001)	Combination therapy	2 mo (ST)	47.7 ± 25.2	26.2 ± 19.5	-21.5 ± 22.53	$p<0.001$	Unclear
	Self-management	2 mo (ST)	55.8 ± 25.8	24.6 ± 25.7	-31.2 ± 25.75	$p<0.001$	Unclear
	Education	2 mo (ST)	59.0 ± 24.0	29.0 ± 25.5	-30 ± 24.76	$p<0.001$	Unclear
Yuasa and Kurita (2001)	Self-management	1 mo (ST)	Median 53.5	Median 25.5	Median -20	$p<0.01$	Unclear
	No treatment	1 mo (ST)	Median 57	Median 22	Median -6	$p<0.05$	Unclear
Haketa *et al.* (2010)	Self-management	2 mo (ST)	63.1 ± 21.4	21.3 ± 26.4	-41.8 ± 24.04	$p<0.001$	Unclear
	Splint	2 mo (ST)	58.9 ± 28.2	36.5 ± 28.7	-22.4 ± 28.45	$p<0.001$	Unclear
Lundh *et al.* (1992)	Splint	12 mo (LT)	NR	NR	NR	NR	High
	Control	12 mo (LT)	NR	NR	NR	NR	High
Linde *et al.* (1995)	Splint	6 wk (ST)	51	NR	NR	$p<0.001$	High
	TENS	6 wk (ST)	63	NR	NR	$p<0.001$	High
Maloney *et al.* (2002)[e]	Jaw exercises + Splint	1 mo (ST)	49.41 ± 29.26	32.35 ± 26.37	-17.06 ± 27.85	$p<0.05$	High
	Splint	1 mo (ST)	44.29 ± 32.07	38.57 ± 24.10	-5.72 ± 28.37	NS	High
Ismail *et al.* (2007)	Jaw exercises + Splint	3 mo (ST)	45 ± 20	NR	-28 ± 21	$p<0.05$	Unclear
	Splint	3 mo (ST)	42 ± 22	NR	-23 ± 22	$p<0.05$	Unclear
Peroz *et al.* (2004)[f]	Active PEMF	6 wk (ST)	44.82 ± 22.15	32.64 ± 25.54	-12.88 ± 23.91	$p<0.01$	Low
	Placebo PEMF	6 wk (ST)	48.50 ± 33.58	32.41 ± 25.94	-16.09 ± 30.00	$p<0.01$	Low
	Active PEMF	4 mo (LT)	44.82 ± 22.15	39.08 ± 25.82	-5.74 ± 24.10	$p<0.05$	Unclear
	Placebo PEMF	4 mo (LT)	48.50 ± 33.58	19.59 ± 25.43	-28.91 ± 29.79	$p<0.05$	Unclear
Schiffman *et al.* (1996)[g]	Active iontophoresis	1 wk (ST)	0.57 ± 0.1	0.47 ± 0.2	-0.10 ± 0.16	NS	Unclear
	Placebo iontophoresis	1 wk (ST)	0.52 ± 0.2	0.50 ± 0.2	-0.02 ± 0.20	NS	Unclear
Schiffman *et al.* (2007)	Self-management	3 mo (ST)	0.61 ± 0.23	0.33 ± 0.22	-0.28 ± 0.23	$p<0.0001$	Unclear
	Combination therapy	3 mo (ST)	0.72 ± 0.17	0.42 ± 0.27	-0.30 ± 0.23	$p<0.0001$	Unclear
	Arthroscopy	3 mo (ST)	0.70 ± 0.19	0.34 ± 0.25	-0.36 ± 0.22	$p<0.0001$	Unclear
	Open surgery	3 mo (ST)	0.76 ± 0.22	0.26 ± 0.24	-0.50 ± 0.23	$p<0.0001$	Unclear
	Self-management	60 mo (LT)	0.61 ± 0.23	0.23 ± 0.25	-0.38 ± 0.24	$p<0.0001$	Unclear
	Combination therapy	60 mo (LT)	0.72 ± 0.17	0.23 ± 0.23	-0.49 ± 0.20	$p<0.0001$	Unclear
	Arthroscopy	60 mo (LT)	0.70 ± 0.19	0.26 ± 0.20	-0.44 ± 0.20	$p<0.0001$	Unclear
	Open surgery	60 mo (LT)	0.76 ± 0.22	0.28 ± 0.25	-0.48 ± 0.24	$p<0.0001$	Unclear
Petersson *et al.* (1994)[h]	Arthrocentesis	2 mo (ST)	56.75 ± 20.14	33.63 ± 27.02	-23.12 ± 23.83	$p<0.01$	High
	Arthrography	2 mo (ST)	61.12 ± 18.23	49.65 ± 27.99	-11.47 ± 23.62	NS ($p=0.06$)	High
Sahlstrom *et al.* (2013)[d]	Arthrocentesis	3 mo (ST)	60.6 ± 26.7	55.0 ± 30.7	-5.6 ± 28.77	NS	Unclear
	ATN LA block	3 mo (ST)	58.1 ± 23.2	30.4 ± 22.6	-27.7 ± 22.90	$p<0.0001$	Unclear
Diracoglu *et al.* (2009)	Arthrocentesis	3 mo (ST)	62.6 ± 23.5	31.5 ± 25.2	-31.1 ± 23.3	$p<0.01$	High
	Combination therapy	3 mo (ST)	56.6 ± 24.7	50.8 ± 24.2	-6.2 ± 15.8	$p<0.01$	High
	Arthrocentesis	6 mo (LT)	62.6 ± 23.5	15.1 ± 18.2	-47.4 ± 21.4	$p<0.01$	High
	Combination therapy	6 mo (LT)	56.6 ± 24.7	43.9 ± 23.1	-12.2 ± 17.6	$p<0.01$	High
Fridrich *et al.* (1996)	Arthroscopy	6-24 mo (LT)	64.5	17	-47.5	$p<0.05$	High
	Arthrocentesis	6-24 mo (LT)	66	23	-43	$p<0.05$	High
Goudot *et al.* (2000)	Arthroscopy	12 mo (LT)	57 ± 9	19 ± 24	-38 ± 24	$p<0.0001$	High
	Arthrocentesis	12 mo (LT)	56 ± 8	9 ± 21	-47 ± 21	$p<0.0001$	High
Holmlund *et al.* (2001)	Open surgery	12 mo (LT)	62 ± 28.2	6 ± 12.7	-56 ± 21.87	$p<0.001$	High
	Arthroscopy	12 mo (LT)	71 ± 9.9	25 ± 32.1	-46 ± 23.75	$p<0.01$	High
Politi *et al.* (2007)	Open surgery	12 mo (LT)	80 ± 13.3	13 ± 12.5	-67 ± 13.15	$p<0.01$	High
	Arthroscopy	12 mo (LT)	79 ± 12	19 ± 18.5	-60 ± 15.59	$p<0.01$	High

Abbreviations: ATN LA block: auriculotemporal nerve local anaesthesia block, LT: long-term, MM: mandibular manipulation, mo: months, NA: not-applicable, NR: not-reported, NS: non-significant, NSAID: non-steroidal anti-inflammatory drug, PEMF: pulsed electromagnetic fields, ST: short-term, TENS: transcutaneous electric nerve stimulation, wk: weeks.

[a] Studies are ordered in accordance with the study order in the summary of findings table (Table 1).
[b] Mean change and Standard deviation (SD) for mean change were reported in only three studies (Goudot *et al.*, 2000; Ismail *et al.*, 2007; Diracoglu *et al.*, 2009). In the remaining studies, difference in means and SD for difference were calculated using an Excel sheet (version 14.0) by applying the following formulae: [$Mean_{change\ from\ baseline} = Mean_{post} - Mean_{pre}$], and [$SD_{change\ from\ baseline} = \sqrt{(SD_{pre})^2 + (SD_{post})^2/2}$] (Markiewicz *et al.*, 2008; Fritz *et al.*, 2012; Katsnelson *et al.*, 2012) respectively.
[c] Statistical significance (p-value<0.05) for within-group statistical difference from baseline as reported in the studies. In Petersson *et al.* (1994), the p-value was not reported, but was calculated by the Paired T-Test for summarised data (mean differences) using Minitab statistical package (version 16).
[d] Unpublished statistical data were provided by the study authors (personal e-mail communication).
[e] Therabite + splint group and WTDs + splint group were merged together as one group jaw exercises + splint.
[f] Separate data for DDwoR patients are available and/or obtained from the contacted authors (personal e-mail communication).
[g] Only comparison between active iontophoresis by dexamethasone + lidocaine and placebo iontophoresis by normal saline was considered and reported.
[h] Estimated from Figure 2 in the published trial.

Appendix Table 6.2: Change from baseline for maximum mouth opening (unassisted/active MMO) primary outcome.

Study[a] (Year)	Intervention	Follow-up time-point	Pre-treatment	Post-treatment	Change[b] from baseline	*p*-value[c] for within-group difference from baseline	Overall Risk-of-Bias
			Mean ± SD	Mean ± SD	Mean ± SD		
Yoshida *et al.* (2005)	MM	1 wk (ST)	26.5	33.25	+6.75	NR	High
	NSAID only	1 wk (ST)	28.4	28.4	0	NS	High
Yoshida *et al.* (2011)[d]	MM	10 min (ST)	27 ± 3.83	38 ± 3.83	+11 ± 3.83	$p<0.001$	High
	No treatment	10 min (ST)	29 ± 2.5	30 ± 3.17	+1 ± 2.85	$p<0.01$	High
Craane *et al.* (2012)[e]	Jaw exercises	3 mo (ST)	35.8 ± 7.4	39.4 ± 6.3	+3.6 ± 6.87	$p<0.05$	Unclear
	Education	3 mo (ST)	36.2 ± 7.1	42.5 ± 6.9	+6.3 ± 7.0	$p<0.05$	Unclear
	Jaw exercises	13 mo (LT)	35.8 ± 7.4	42.7 ± 5.7	+7.8 ± 6.2	$p<0.05$	Unclear
	Education	13 mo (LT)	36.2 ± 7.1	46.5 ± 7.1	+10.1 ± 8.2	$p<0.05$	Unclear
Minakuchi *et al.* (2001)	Combination therapy	2 mo (ST)	33.6 ± 9.68	42.4 ± 10.1	+8.8 ± 9.89	$p<0.001$	Unclear
	Self-management	2 mo (ST)	36.1 ± 9.98	39.6 ± 10.2	+3.5 ± 10.09	$p<0.001$	Unclear
	Education	2 mo (ST)	36.7 ± 10.36	41 ± 8.39	+4.3 ± 9.43	$p<0.001$	Unclear
Yuasa and Kurita (2001)	Self-management	1 mo (ST)	Median 29	Median 37.5	Median +7	$p<0.0001$	Unclear
	No treatment	1 mo (ST)	Median 30	Median 33.5	Median +1.5	$p<0.05$	Unclear
Haketa *et al.* (2010)	Self-management	2 mo (ST)	32.2 ± 5.5	41.0 ± 5.4	+8.8 ± 5.45	$p<0.001$	Unclear
	Splint	2 mo (ST)	30.3 ± 7.7	35.0 ± 5.8	+4.7 ± 6.82	$p<0.001$	Unclear
Lundh *et al.* (1992)	Splint	Outcome not assessed	NA	NA	NA	NA	NA
	Control						
Linde *et al.* (1995)	Splint	6 wk (ST)	NR	NR	+5.9 ± 4.18	$p<0.0001$	High
	TENS	6 wk (ST)	NR	NR	+6.06 ± 6.72	$p<0.01$	High
Maloney *et al.* (2002)[f]	Jaw exercises + Splint	1 mo (ST)	28.06 ± 3.51	34 ± 4.61	+5.94 ± 4.1	$p<0.01$	High
	Splint	1 mo (ST)	28.29 ± 6.05	29.86 ± 6.47	+1.57 ± 6.26	NS	High
Ismail *et al.* (2007)	Jaw exercises + Splint	3 mo (ST)	30.1 ± 5.4	40.8 ± 4.1	+10.4 ± 5.4	$p<0.05$	Unclear
	Splint	3 mo (ST)	28.6 ± 5.8	35.9 ± 4.8	+7.3 ± 6.2	$p<0.05$	Unclear
Peroz *et al.* (2004)[g]	Active PEMF	6 wk (ST)	32.25 ± 9.5	36.71 ± 8.36	+4.46 ± 8.95	$p<0.05$	Low
	Placebo PEMF	6 wk (ST)	35 ± 7.7	39.18 ± 7.87	+4.18 ± 7.79	$p<0.05$	Low
	Active PEMF	4 mo (LT)	32.25 ± 9.5	38 ± 7	+5.57 ± 8.34	$p<0.05$	Unclear
	Placebo PEMF	4 mo (LT)	35 ± 7.7	39 ± 7.1	+4.0 ± 7.41	$p<0.05$	Unclear
Schiffman *et al.* (1996)[h]	Active iontophoresis	1 wk (ST)	32.2 ± 6.5	38.2 ± 10.2	+6 ± 8.55	$p<0.05$	Unclear
	Placebo iontophoresis	1 wk (ST)	34 ± 7.8	36.3 ± 5.6	+2.3 ± 6.8	NS	Unclear
Schiffman *et al.* (2007)	Self-management	3 mo (ST)	NR	NR	NR	$p<0.0001$	Unclear
	Combination therapy	3 mo (ST)	NR	NR	NR	$p<0.0001$	Unclear
	Arthroscopy	3 mo (ST)	NR	NR	NR	$p<0.0001$	Unclear
	Open surgery	3 mo (ST)	NR	NR	NR	$p<0.0001$	Unclear
	Self-management	60 mo (LT)	NR	NR	NR	$p<0.0001$	Unclear
	Combination therapy	60 mo (LT)	NR	NR	NR	$p<0.0001$	Unclear
	Arthroscopy	60 mo (LT)	NR	NR	NR	$p<0.0001$	Unclear
	Open surgery	60 mo (LT)	NR	NR	NR	$p<0.0001$	Unclear
Petersson *et al.* (1994)	Arthrocentesis	2 mo (ST)	27.4 ± 6.0	32.6 ± 10.8	+5.2 ± 8.74	$p<0.05$	High
	Arthrography	2 mo (ST)	30.7 ± 8.1	35.6 ± 8.1	+4.9 ± 8.1	$p<0.05$	High
Sahlstrom *et al.* (2013)[e]	Arthrocentesis	3 mo (ST)	34.4 ± 7.2	37.8 ± 7.4	+3.4 ± 7.3	NS	Unclear
	ATN LA block	3 mo (ST)	33.1 ± 9.1	42.7 ± 8.1	+9.6 ± 8.61	$p<0.05$	Unclear
Diracoglu *et al.* (2009)	Arthrocentesis	3 mo (ST)	31.20 ± 7.03	35.13 ± 6.72	+3.92 ± 6.10	$p<0.01$	High
	Combination therapy	3 mo (ST)	29.89 ± 4.82	33.20 ± 7.61	+4.17 ± 7.80	$p<0.01$	High
	Arthrocentesis	6 mo (LT)	31.20 ± 7.03	37.89 ± 6.53	+6.68 ± 6.20	$p<0.01$	High
	Combination therapy	6 mo (LT)	29.89 ± 4.82	35.54 ± 6.41	+6.20 ± 6.50	$p<0.01$	High
Fridrich *et al.* (1996)	Arthroscopy	6-24 mo (LT)	30 ± 8.7	47.5 ± 4.7	+17.5 ± 6.99	$p<0.0001$	High
	Arthrocentesis	6-24 mo (LT)	33 ± 12.2	41 ± 4.9	+8 ± 9.3	$p<0.05$	High
Goudot *et al.* (2000)	Arthroscopy	12 mo (LT)	29 ± 4.8	38.6 ± 4.2	+9.6 ± 5.8	$p<0.0001$	High
	Arthrocentesis	12 mo (LT)	29.4 ± 3.1	33.8 ± 4.4	+4.3 ± 4.4	$p<0.0001$	High
Holmlund *et al.* (2001)	Open surgery	12 mo (LT)	NR	NR	NR	$p<0.001$	High
	Arthroscopy	12 mo (LT)	NR	NR	NR	$p<0.01$	High
Politi *et al.* (2007)	Open surgery	12 mo (LT)	NR	NR	NR	$p<0.01$	High
	Arthroscopy	12 mo (LT)	NR	NR	NR	$p<0.01$	High

Abbreviations: ATN LA block: auriculotemporal nerve local anaesthesia block, LT: long-term, min: minutes, MM: mandibular manipulation, mo: months, NA: not-applicable, NR: not-reported, NS: non-significant, NSAID: non-steroidal anti-inflammatory drug, PEMF: pulsed electromagnetic fields, ST: short-term, TENS: transcutaneous electric nerve stimulation, wk: weeks.

[a] Studies are ordered in accordance with the study order in the summary of findings table (Table 1).

[b] Mean change and Standard deviation (SD) for mean change were reported in five studies (Linde *et al.*, 1995; Goudot *et al.*, 2000; Ismail *et al.*, 2007; Diracoglu *et al.*, 2009; Craane *et al.*, 2012). In the remaining studies, difference in means and SD for difference were calculated using an Excel sheet (version 14.0) by applying the following formulae: [$Mean_{change\ from\ baseline} = Mean_{post} - Mean_{pre}$], and [$SD_{change\ from\ baseline} = \sqrt{(SD_{pre})^2 + (SD_{post})^2/2}$] (Markiewicz *et al.*, 2008; Fritz *et al.*, 2012; Katsnelson *et al.*, 2012) respectively.

[c] Statistical significance (p-value <0.05) for within-group statistical difference from baseline as reported in the studies. In Fridrich *et al.* (1996), the p-value was not reported, but was calculated by the Paired T-Test for summarised data (mean differences) using Minitab statistical package (version 16).
[d] Mean (SD) were calculated from the reported median (range) in the published trial according to (Hozo *et al.*, 2005).
[e] Unpublished statistical data were provided by the study authors (personal e-mail communication).
[f] Therabite + splint group and WTDs + splint group were merged together as one group jaw exercises + splint.
[g] Separate data for DDwoR patients are available and/or obtained from the contacted authors (personal e-mail communication).
[h] Only comparison between active iontophoresis by dexamethasone + lidocaine and placebo iontophoresis by normal saline was considered and reported.

APPENDICES REFERENCES

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