

# Hyaluronic acid injections for temporomandibular disorders: an overview of systematic reviews

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## ABSTRACT

**Purpose:** To summarise the evidence on the effectiveness of intra-articular injections of hyaluronic acid (HA) in patients with temporomandibular disorders (TMDs). Outcomes of interest were measurable pain scales and functional outcomes.

**Methods:** A systematic search of the literature was conducted in three electronic databases (Pubmed, Cochrane Database of Systematic Reviews and PEDro) to identify all the systematic reviews and meta-analyses that met the inclusion criteria.

**Results:** Twenty-one articles were included, 11 of which reported a meta-analysis. In 16 articles, the administration HA injections (with or without arthrocentesis/arthroscopy) was the main intervention being evaluated. Five studies compared other injection therapies with intra-articular injections of HA.

**Conclusions:** The included studies revealed an upward trend in the use of minimally invasive techniques in TMDs. The majority of these studies supported the use of HA injections, with or without arthrocentesis/arthroscopy.

## KEYWORDS

Hyaluronic acid, injection therapy, temporomandibular disorders, temporomandibular joint.

## Introduction

Temporomandibular disorders (TMDs), which occur in 5–12% of the population, are a common cause of pain affecting the mouth and face. The term TMDs refers to a set of conditions involving the temporomandibular joint (TMJ), masticatory muscles and/or the surrounding structures<sup>[1,2]</sup>. The aetiology of TMDs is multifactorial, involving biological, environmental, social and psychological factors. Hormones have also been studied as risk factors<sup>[3,4]</sup>.

TMDs are frequently associated with symptoms such as facial pain, headache, clicks, ear discomfort, jaw discomfort or dysfunction, bruxism and dizziness, and with signs such as abnormal movements, malocclusion and tenderness of masticatory muscles<sup>[5,6]</sup>.

The classification of TMDs has evolved over the years<sup>[7]</sup>. TMDs can be classified into three groups: 1) muscle disorders; 2) disc disorders; 3) joint disorders<sup>[8]</sup>. The Diagnostic Criteria for TMDs (DC/TMD) standard summarises the main stages in the diagnostic workup of TMDs, and provides a more recent classification of the included diseases<sup>[9]</sup>.

Intra-capsular disorders can be approached using non-invasive treatments, such as behavioural changes, splinting, pharmacotherapy, physiotherapy and physical therapies. Moreover, minimally invasive treatments, such as intra-articular (IA) injections, arthrocentesis, arthroscopy and surgical treatments,

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may be suitable for patients who did not respond to conservative treatments<sup>[10,11]</sup>.

Commonly used pharmacological agents in TMDs are analgesics, myorelaxants, corticosteroids (CSs), anticonvulsants and antidepressants, but the efficacy of these drugs is still limited<sup>[12]</sup>.

Injection therapy has the advantage of directly reaching the articular space, with hyaluronic acid (HA) showing some beneficial effects on the possible regeneration of a degenerated TMJ. However, some studies do not support these restorative effects, and the effectiveness of HA in improving symptoms is still being explored<sup>[10,13,14]</sup>.

This overview of systematic reviews was therefore conducted with the aim of summarising the evidence on the effectiveness of IA injections of HA in patients with TMDs, considering pain and functional outcomes as the main therapeutic targets.

## Methods

### Search strategy

To conduct this overview of systematic reviews, a thorough search of the literature was performed in three different databases: Pubmed, Cochrane Database of Systematic Reviews and PEDro, from their inception up to December 2023. References of the included articles were screened for further articles meeting our inclusion criteria.

All systematic reviews and meta-analyses written in English and focusing on the effectiveness of IA injections of HA in patients affected by TMDs were evaluated.

TMDs are a broad group of pathological conditions, and the use of IA injections has been suggested in intra-capsular disorders <sup>[10]</sup>. In more detail, we here focused on the administration of IA injections of HA, performed alone or in association with arthrocentesis or arthroscopy.. All measurable pain and functional scales were considered as eligible outcomes for assessing the effectiveness of the injections.

Two of the authors performed an initial screening by title and abstract. Duplicates were manually removed. Articles meeting the inclusion criteria were obtained; the same two authors evaluated all these articles by full-text assessment, and the articles were included when there was consensus between the two reviewers.

Whenever they failed to agree on the inclusion of an article, a third author was consulted.

A qualitative (narrative) synthesis of the included articles was then conducted, highlighting the strengths and weaknesses of single articles, and the most critical issues regarding the effectiveness of this treatment.

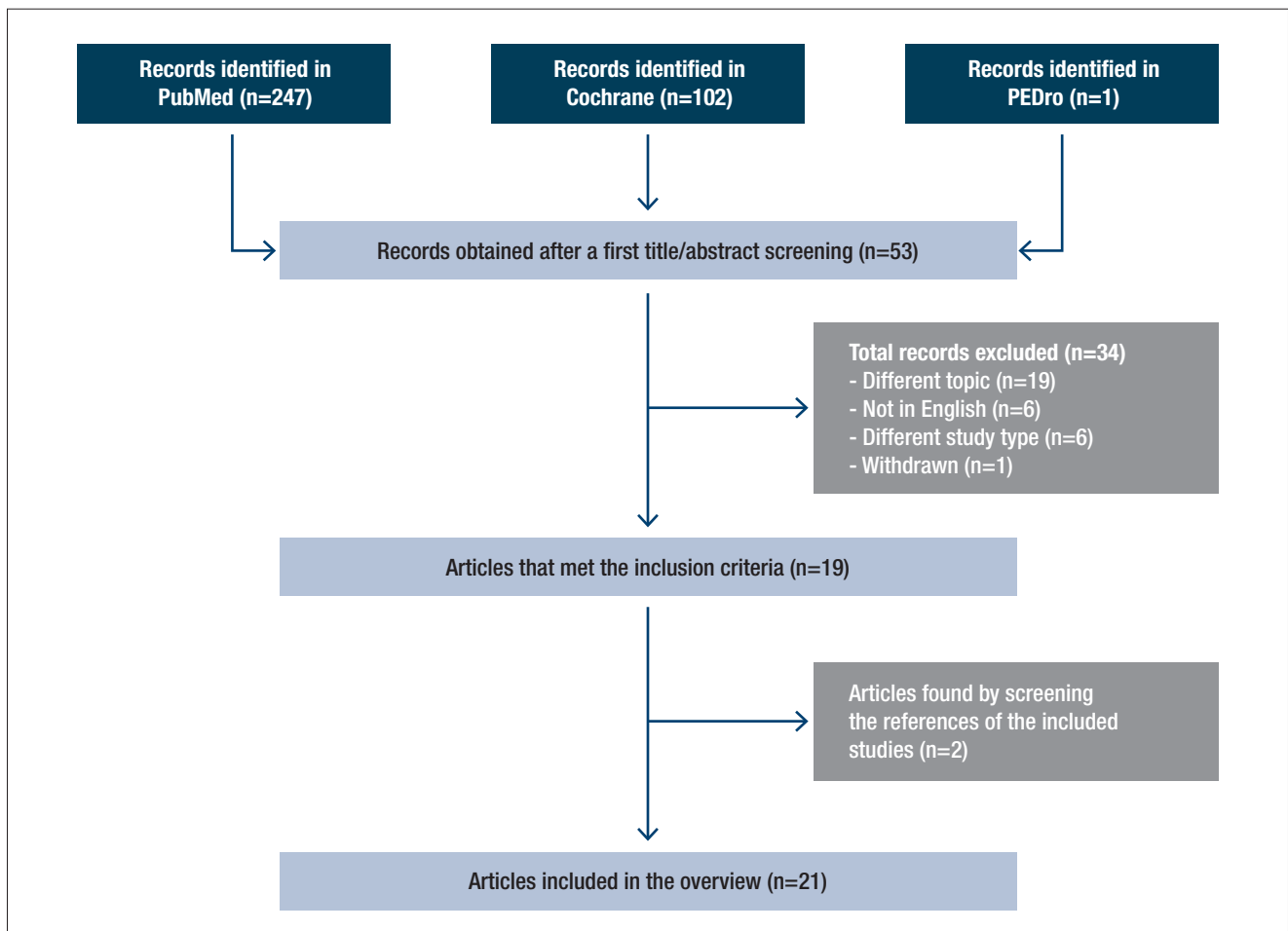
## Results

Our search yielded 350 results. Duplicates (n=103) were removed, and after title and abstract screening, a total of 53 articles were obtained for full-text assessment. Of these, 34 articles were excluded for the following reasons: not written in English (n=6), focused on a different topic (n=19), withdrawn by the authors (n=1), did not meet the inclusion criteria (n=6). A further two articles were obtained by screening the references of the included studies. Figure 1 summarises the selection process.

At the end of this process, 21 articles <sup>[15-35]</sup> were included in our overview of systematic reviews. In 11 of them <sup>[15-18,22,23,25,26,31,33,35]</sup> the authors performed a meta-analysis.

Seven articles <sup>[17,20,21,27,28,30,32]</sup> dealt with all subsets of TMDs, while the others evaluated patients within specific subsets. In particular: eight <sup>[18,19,22,23,25,29,33,35]</sup> included patients with oste-

**Figure 1** Study flowchart.



oarthritis (OA) of the temporomandibular joint (TMJ); one <sup>[16]</sup> included patients with internal derangement; three <sup>[24,31,34]</sup> grouped together patients with TMJ OA and disc displacement; one <sup>[26]</sup> considered both TMJ OA and internal derangement; and the last one <sup>[15]</sup> focused specifically on disc displacement with reduction.

The articles reviewed here are listed by publication date, from the most recent to the least recent. Sixteen <sup>[15-30]</sup> considered HA injections (with or without arthrocentesis/arthroscopy) as the study intervention and are summarised below.

- 1) Al Moraissi *et al.*, 2024 <sup>[15]</sup>, conducted a meta-analysis in patients clinically and radiologically diagnosed with disc displacement with reduction who underwent one of the following treatments: occlusal splints, low-level laser therapy, manual therapy, arthrocentesis alone, arthrocentesis plus HA injection, arthrocentesis plus platelet-rich plasma (PRP) injection, arthrocentesis plus splints, no treatment. They included 20 randomised controlled trials (RCTs) evaluating the effectiveness of these treatments on pain and functional outcome, i.e., maximum mouth opening (MMO), at short- (3 months) and intermediate-term (6 months) follow-ups. They concluded that arthrocentesis plus a co-adjuvant was superior to other treatments.
- 2) Jian Li *et al.*, 2023 <sup>[16]</sup>, conducted a systematic review with meta-analysis of RCTs including patients with internal derangement undergoing arthrocentesis and a subsequent injection (PRP versus HA). Their outcomes were MMO and pain scales assessed at 1, 3 and 6 months of follow-up. They included seven studies in their meta-analysis, but were not able to demonstrate statistically significant differences between PRP and HA injections on any outcome at any of the follow-ups considered.
- 3) In a systematic review and network meta-analysis, Xu *et al.*, 2023 <sup>[17]</sup>, evaluated the effectiveness of IA injections of HA, PRP and platelet-rich fibrin (PRF) in patients with TMDs. The outcomes taken into consideration were pain relief and improvements in MMO at 1, 3 and 6 months of follow-up. Ninety-two patients treated with HA injections were included. They reported that all three treatments were more effective than placebo, and concluded that PRF was most likely to be the best treatment.
- 4) Xie *et al.*, 2022 <sup>[18]</sup>, conducted a systematic review and meta-analysis of nine RCTs evaluating the effectiveness of two or more injections of different drugs in patients diagnosed with TMJ OA. The injectables under study were CSs, HA, PRP and placebo (Ringer's lactate solution). Pain and MMO after at least 3 months of follow-up were the outcomes considered. The results of the network meta-analysis showed that none of the injection treatments produced improvements in pain or MMO. The pairwise meta-analysis revealed no significant differences, on pain, between HA and placebo at both short- and long-term follow-up. PRP was deemed likely to be the best injectable.
- 5) In their systematic review Liapaki *et al.*, 2021 <sup>[19]</sup>, evaluated the effectiveness of IA injections of different drugs preceded or not preceded by arthrocentesis/arthroscopy in patients affected by TMJ OA. They included nine RCTs evaluating the effectiveness of these treatments on pain and MMO amelioration at a follow-up of at least 6 months. In injection-only treatments, HA was found to be superior to CSs, and treatment with multiple injections of medium molecular weight (MW) HA was superior to treatment with single injections of high- or medium MW HA. The authors reported improvements in pain and functional outcomes at 12 and 24 months in the studies evaluating arthrocentesis plus HA.
- 6) A systematic review by Sábado-Bundó *et al.*, 2021 <sup>[20]</sup>, evaluated the effectiveness of arthrocentesis or arthroscopy plus HA injections in patients with TMDs. The outcomes under study were pain and MMO, and the follow-up lasted at least 6 months. They included six studies, five using arthrocentesis and one using arthroscopy. All the studies reported improvements in MMO (statistically significant in two of the six); all the studies reported improvements in pain evaluation, with four of them reporting greater improvements in the HA group (in three studies this difference reached statistical significance).
- 7) Sakalys *et al.*, 2020 <sup>[21]</sup>, in a systematic review and meta-analysis, evaluated the effectiveness on pain and function of arthroscopy plus IA injections in patients with TMDs. They included three RCTs in the systematic review (two in the meta-analysis). They reported that arthroscopy plus IA injections was superior to arthroscopy alone. Moreover, the authors reported that HA injections were effective on pain relief in the long term, but the best results were obtained by arthroscopy plus injections of plasma rich in growth factors (PRGF).
- 8) In their meta-analysis, Liu *et al.*, 2020 <sup>[22]</sup>, evaluated the effectiveness of arthrocentesis or arthroscopy plus IA drug injections in patients affected by TMJ OA. They included only RCTs and the outcomes under study, over a short-term follow-up (from 1 to 3 months after the intervention), were pain and MMO. They concluded that morphine and tramadol (in addition to arthrocentesis) were most likely to improve pain: arthrocentesis followed by HA injections obtained significantly better results than arthrocentesis alone. As for the other outcome, arthrocentesis plus HA injections achieved significantly better results on MMO than arthrocentesis alone. However, arthrocentesis plus platelet-derived growth factor was the treatment considered most likely to be the best, followed arthrocentesis + HA.
- 9) Al Moraissi *et al.*, 2020 <sup>[23]</sup>, in their meta-analysis evaluated the effectiveness of 12 different treatments on pain and MMO at short-term ( $\leq 5$  months) or intermediate-term follow-up ( $\geq 6$  months to 4 years) in patients affected by arthrogenous TMDs. The following treatments were evaluated: conservative treatments, physical therapy, IA injections of HA, IA injections of CSs, arthrocentesis alone, arthrocentesis plus HA, arthrocentesis plus PRP, arthrocentesis plus CSs, arthroscopy alone, arthroscopy plus PRP, arthroscopy plus HA and open surgery. They included 36 RCTs. The authors' findings supported the superiority of minimally invasive techniques (IA injections, arthrocentesis, arthroscopy, each in combination with PRP, HA and CSs) over the non-invasive procedures both at short- and intermediate-term follow-up. They reported that IA injec-

tions of HA were the most effective on pain reduction at short-term follow-up.

- 10) In their systematic review, Ferreira *et al.*, 2018<sup>[24]</sup>, evaluated the effectiveness of IA injections in patients with TMJ OA and/or anterior disc displacement (with or without reduction). The outcomes considered were pain, functional limitation and patients' self-reported discomfort. They included five articles on internal derangement of TMJ, nine on TMJ OA, and four on disc displacement with reduction. The authors noted a high variability in the injection administration protocols. They reported that HA injections alone appeared effective in improving pain, and that the use of arthrocentesis plus HA did not seem to be superior to arthrocentesis alone.
  - 11) In their systematic review and meta-analysis, Liu *et al.*, 2018<sup>[25]</sup>, evaluated the effectiveness of IA injections of CS or other injection drugs on pain and maximal interincisal opening in patients affected by TMJ OA. They included eight articles in the meta-analysis. At short-term follow-up (3–4 weeks), no differences were found between the HA and CS treatments.
  - 12) In their systematic review and meta-analysis, Moldez *et al.*, 2018<sup>[26]</sup>, evaluated the effectiveness, on pain, of HA and CS injections (without arthrocentesis) in patients with TMJ OA or with disc displacement. They included seven studies in the systematic review and four in the meta-analysis. Pain was evaluated with a visual analogue scale at short-term (4 to 6 months) and long-term (6 months to 2 years) follow-up. The articles included in the systematic review reported a greater effectiveness of HA than of placebo. The authors reported no statistically significant differences between CSs and HA at either follow-up.
  - 13) Goiato *et al.*, 2016<sup>[27]</sup>, in their systematic review included seven RCTs and one retrospective study evaluating the effectiveness of HA injections compared with other IA medications in patients affected by TMDs. They reported that HA injections were found to have the best results, with several RCTs unable to demonstrate a statistically significant difference versus CS injections.
  - 14) Machado *et al.*, 2013<sup>[28]</sup>, in their systematic review evaluated the effectiveness of IA injections of CSs and/or HA in patients with TMDs. They included nine RCTs and reported that both CSs and sodium hyaluronate were effective on TMJ internal derangement at short- and medium-term follow-up. The effectiveness of the two treatments was similar in the short term, although HA gave better results in the medium term.
  - 15) de Souza *et al.*, 2012<sup>[29]</sup>, in their Cochrane review, evaluated the effectiveness on pain, MMO, subjective TMJ sounds and other secondary outcomes of any non-surgical or surgical therapy for TMJ OA. They included three RCTs in the qualitative analysis. They compared the effectiveness of HA and CS injections, reporting that both treatments obtained improvements on both outcomes at 6 months of follow-up, with HA showing the better results.
  - 16) In their systematic review, Manfredini *et al.*, 2010<sup>[30]</sup>, evaluated the effectiveness of HA injections in patients with TMDs. They included 19 studies, 12 focusing on disc displacement, and seven on TMJ OA. In both conditions, the authors reported improvements of pain and functional outcomes.
- Five other studies<sup>[31-35]</sup> focused mainly on other drug injection treatments and evaluated the effectiveness of IA injections of HA as comparison. These studies were also included in our overview of systematic reviews. In more detail:
- 17) Al-Hamed *et al.*, 2021<sup>[31]</sup>, in their systematic review and meta-analysis, compared the effectiveness of platelet concentrates (PCs), HA, and saline solution injections in patients affected by TMJ OA or disc displacements. They included nine studies in the systematic review (eight in the meta-analysis) and found pain scale reductions with all three treatment modalities: PCs gave better results than HA at three months, but not at 12 months. Both PCs and HA improved MMO, with no statistically significant differences.
  - 18) Gutierrez *et al.*, 2021<sup>[32]</sup>, in their systematic review, evaluated the effectiveness of arthrocentesis/arthroscopy plus IA injections of PRP, comparing its effectiveness with saline solution, HA and Ringer's lactate solution. The primary outcome was pain, and the secondary outcome MMO. They included eight RCTs, in six of which the authors performed arthrocentesis, and in two arthroscopy. All the studies reported improvements in both outcomes. Seven of the eight studies reported better outcomes in the group treated with PRP, with a statistically significant difference between PRP and HA found in three of them.
  - 19) Li *et al.*, 2020<sup>[33]</sup>, conducted a meta-analysis in patients diagnosed with TMJ OA. They included six RCTs evaluating the effectiveness on pain reduction of IA injections of PRP. Among the studies included, comparisons with IA injections of HA were performed in three. When compared with PRP, the authors reported similar results on pain at 6 months, although PRP showed better results at 12 months of follow-up.
  - 20) Bousnaki *et al.*, 2018<sup>[34]</sup>, in their systematic review, included six RCTs evaluating the effectiveness of IA drug injections after arthrocentesis/arthroscopy on pain and MMO: the drugs in question were PRP (or PRGF), HA and saline/Ringer's solution. Three of the six included studies compared PRP with HA. Of these three studies, two reported better results for PRP injections, while one reported that the two drugs gave similar results.
  - 21) Haigler *et al.*, 2018<sup>[35]</sup>, in their systematic review, focused on the effectiveness of PRP/PRGF after arthrocentesis/arthroscopy in patients affected by TMJ OA. Comparisons were also made with arthrocentesis/arthroscopy followed by saline solution or HA. When compared with HA, PRP injections showed better results in terms of pain improvement (even though both were effective in reducing pain); no statistically significant differences in the effect on MMO were seen respect to the control group.

## Discussion

The treatment of TMDs often requires a complex approach, involving a multidisciplinary group comprising a physiother-

apist, gnathologist, orthodontist and several other figures, depending on the stage of the pathology [36,37]. According to the American Association of Dental Research, the treatment of TMDs should be conservative, unless there are specific and justifiable indications to the contrary [38].

When conservative treatments fail, the minimally invasive techniques should be suggested as a viable alternative in the management of TMDs [39]. New treatment strategies have been explored, such as oxygen-ozone therapy [40]. Injection therapy, arthrocentesis and arthroscopy are the most frequently performed [10,11]. The use of ultrasound guidance for IA injections has been supported in literature [41].

Hyaluronic acid is a glycosaminoglycan discovered in 1934. Found in most connective tissues, it is particularly concentrated in the synovial fluid [42]. HA has multiple physiological properties that depend on its MW and concentration [43,44].

The number of primary studies on HA injections has shown an upward trend over the years. HA was the most commonly investigated injectable for TMDs during the period 2017–2023, and the number of primary studies on injectable centrifuged blood products has grown comparably [39]. Our study confirms this trend, as 18 of the 21 included studies were published in the last ten years.

The effectiveness of HA injections, administered alone or in association with arthrocentesis/arthroscopy, is supported by several of the included studies [16,17,19–35]. One study [18] did not support its effectiveness. However, no solid conclusions can be drawn when comparing it to other injection treatments, such as platelet derivatives [16,17,31–35] or CSs [22,25–29].

Two compartments can be identified in the TMJ, namely, the superior (or disco-temporal) and the inferior (or disco-mandibular) ones, which are separated by the articular disc. Recent studies analysed the different effectiveness of IA injections in these two compartments [45].

Arthrocentesis involves the introduction of two needles into the upper joint space to perform a lavage with a saline or Ringer's solution under local anaesthesia. Arthrocentesis can be followed by an accessory IA application of different drugs [46]. The included articles support the use of arthrocentesis [15,22,24], but no solid conclusions can be drawn about the possible beneficial effects of the addition of drug injections.

Arthroscopy involves lavage of the TMJ, intracapsular lysis and subsequent accessory IA application of drugs, and it allows, at the same time, examination of the joint with a telescope. It is performed under general anaesthesia [47]. The use of IA drug injection during arthroscopy was supported in the reviewed articles [21] and repositioning and fixation of an anteriorly displaced TMJ disc has been reported in the literature [48].

It is important to note that only seven articles [17,20,21,27,28,30,32] focused on TMDs generally, while all the others focused specifically on single or multiple pathological subsets.

Twelve of the 21 studies focused mainly on patients affected by TMJ OA: eight only on TMJ OA, and the other four on TMJ OA in association with disc displacement or internal derangement. TMJ OA is a common condition whose prevalence ranges from 8% to 60% [49]; it involves dysregulation and degradation of several chemical signalling pathways, with degenerative involvement of the cartilage and subchondral bone [13].

Recognised TMJ disc pathologies are disc structural changes and disc displacement (with functional internal derangement). Five studies focused mainly on patients affected by disc pathologies: one focused on disc displacement with reduction, three on both TMJ OA and disc displacement, and one on both TMJ OA and internal derangement. There is a possible relationship between degenerative changes of the TMJ and internal derangement of the disc [3]. A single or double click during opening or closing of the mouth is also possible and is frequently related to displacement of the intra-articular disc [5]. Internal derangement of the disc is said to have a prevalence of more than 20% [50]. Minimally invasive techniques may improve symptoms, but do not restore the damaged disc. Disc replacement or discopexy (for repositioning an anteriorly displaced disc) are possible in particular cases [48,51].

Despite the importance of management of TMDs for the affected population, this aspect is not always considered with due attention, even in the rehabilitation field. In past years, particular interest has been shown in the diagnosis of these functional problems, but when it comes to conservative treatments, we have always limited ourselves to physiotherapeutic techniques, practised by a small number of therapists and strictly linked to their experience and manual skills, demonstrating a particularly marked operator-dependent variability. In this context and, by virtue of a global approach by the rehabilitation team (which includes all the healthcare professionals of interest for the specific case), IA infiltrations, also using an ultrasound-guided technique, could represent an additional opportunity for patients affected by TMDs, thanks to not only the biological properties closely associated with IA treatments (viscosupplementation and viscoinduction), but also the capsular dilation effects, in addition to the beneficial proprioceptive effects of the needle.

## Study limitations

We are aware that our study is not free from limitations: first, the high variability in the protocols of administration of the drugs might have influenced the results. Moreover, the data were often obtained by comparing different therapies together and not by performing one-to-one comparisons. Last, a quantitative synthesis of the results was not performed, so no solid conclusions can be drawn.

## Conclusion

Taken together, the systematic reviews included in the present overview underlined the upward trend in the use of minimally invasive techniques in TMDs. The majority of the included studies support the use of HA in TMDs, with or without arthrocentesis/arthroscopy. When compared with other injectables, no solid conclusions on HA can be drawn. More studies are needed to evaluate the effectiveness of the treatment, with greater attention to the administration protocols used with injectables.

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