ACTA
STOMATOLOGICA
CROATICA
www.ascro.hr
OPEN ACCESS

Acta stomatol Croat. 2026;60(1):19-42.
DOI: 10.15644/asc60/1/2
ORIGINAL SCIENTIFIC PAPER
IZVORNI ZNANSTVENI RAD

Cristiana Palmela Pereira[1,4], Beatriz Serra[2,4], João Paulo Martins[3,4]

Pharmacological Interventions in the Management of Temporomandibular Disorders: A Systematic Review and Meta-analysis

Farmakološke intervencije u liječenju temporomandibularnih poremećaja: sistematizirani pregled i metaanaliza

[1] School of Dental Medicine, University of Lisbon, Portugal
Sveučilište u Lisabonu, Stomatološki fakultet, Portugal
[2] Master's Student, Faculty of Dental Medicine, University of Lisbon, Portugal
Stomatološki fakultet – student magistarskog studija, Sveučilište u Lisabonu, Portugal
[3] School of Health, Polytechnic Institute of Porto, Portugal
Zdravstveni fakultet, Politehnički institut u Portu, Portugal
[4] Center of Statistics and its Applications University of Lisbon (CEAUL), Portugal.
Sveučilište u Lisabonu, Centar za statistiku i njezinu primjenu (CEAUL), Portugal

Abstract

Introduction: Temporomandibular Disorders (TMDs) encompass a set of conditions affecting the masticatory muscles and the temporomandibular joint (TMJ), with an impact on both functionality and individuals' quality of life. Myalgia is a diagnosis of TMD with multifactorial etiology, and treatment strategies aim primarily to relieve pain and restore function. Pharmacological therapy is commonly considered a second-line option, thus complementing conservative measures. **Objectives:** Assess the efficacy of pharmacological interventions in the management of **myalgia associated with temporomandibular disorders**, in adolescents and adults, while exploring differential effects across TMD subtypes through subgroup analyses, using a systematic review and meta-analysis of randomized controlled trials (RCTs). **Materials and Methods:** A systematic review with meta-analysis was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and reported following the PRISMA 2020 statement. Seventeen randomized controlled trials (RCTs) published between 2018 and 2024 were included. Pharmacological interventions such as nonsteroidal anti-inflammatory drugs, corticosteroids, muscle relaxants, antidepressants, and intra-articular injectables—were compared with placebo or other active treatments. The primary outcomes were pain intensity (Visual Analog Scale, VAS) and maximum interincisal opening (MIO) unassisted. **Results and Discussion:** A total of 1,128 participants were analyzed across 25 treatment arms. Pharmacological interventions were associated with a significant reduction in pain (SMD = –0.68; 95% CI: –1.09 to –0.26; $p < 0.001$) and an improvement in MIO (SMD = 0.51; 95% CI: 0.20 to 0.82; $p < 0.001$). Subgroup analyses indicated that interventions were more consistent and effective in arthralgia-only populations, showing lower heterogeneity and a more predictable therapeutic response, whereas myalgia-only populations exhibited smaller and less consistent benefits. Conservative therapies demonstrated a consistent advantage, thus aligning with international recommendations that prioritize such approaches. Subgroup analyses demonstrated more consistent and homogeneous effects in arthralgia-dominant populations, whereas myalgia-only studies showed greater heterogeneity and less predictable responses. **Conclusion:** Pharmacological therapy provides a moderate overall beneficial effect in reducing pain and improving mandibular function in TMD, with stronger and more consistent evidence in arthralgia-dominant populations, while myalgia-related outcomes remain more variable, thus indicating the need for tailored treatment strategies. Further high-quality RCTs with standardized protocols are needed.

Received: October 28, 2025
Accepted: January 9, 2026

Address for correspondence
Cristiana Palmela Pereira
Faculdade de Medicina Dentária da Universidade de Lisboa
Cidade Universitária, Rua Professora Teresa Ambrósio
1600-277 Lisboa, Portugal
cpereira@edu.ulisboa.pt

MeSH Terms: Temporomandibular Joint Disorders; Masticatory Muscles; Myalgia; Arthralgia; Intra-Articular Injections; Antidepressive Agents; Adrenal Cortex Hormones
Author Keywords: Temporomandibular Disorders; Myalgia; Arthralgia; Pharmacological Therapy; Anti-inflammatory Drugs; Muscle Relaxants

Cristiana Palmela Pereira https://orcid.org/0000-0002-9164-7189
João Paulo Martins https://orcid.org/0000-0002-0474-1397
Beatriz Serra https://orcid.org/0009-0004-6388-9721

Introduction

Temporomandibular Disorders (TMDs) are a group of musculoskeletal conditions that can affect the masticatory muscles and the Temporomandibular Joint (TMJ) itself (1). TMDs are more common in individuals between 20 and 40 years of age (2-4).

TMDs affect approximately 5 to 12% of the population, being the second most common musculoskeletal condition (5-6). They comprise a wide spectrum of clinical entities that should be approached individually. The 12 common TMDs include arthralgia; myalgia, which can be further classified into subtypes such as: local myalgia, myofascial pain, myofascial pain with referral; disc displacement disorders; degenerative joint disease; subluxation; and headache attributed to TMD (7).

According to the Diagnostic Criteria for TMD (DC/TMD), myalgia is defined as muscle-origin pain affected by jaw movement, function, or parafunction, and replication of this pain occurs with provocation testing of the masticatory muscles (7). Myalgia is further subdivided into three mutually exclusive types, such as: local myalgia, defined as pain localized to the site of palpation; myofascial pain, defined as pain spreading beyond the site of palpation but within the boundary of the muscle being palpated and myofascial pain with referral, defined as pain at a site beyond the boundary of the muscle being palpated. The three types of myalgia can be differentiated by palpation testing (2). The diagnostic criteria for myalgia include pain on jaw movements and palpation of the temporalis and masseter muscles, provided that the provoked pain replicates the patient's complaint (7).

In 2024, the International Network for Orofacial Pain and Related Disorders Methodology, supported by the International Association for Dental Research (INfORM/IADR), published a set of ten key points for good clinical practice in the field of TMDs, thus representing a summary of the current standard of care in TMD treatment and patient needs (8).

TMD treatment may include surgical and non-surgical approaches. Most surgical therapies do not present sufficient scientific evidence (1, 8-9). Within the scope of non-surgical treatment, the first-line approach involves promoting assisted self-management of the condition and conservative strategies, such as cognitive-behavioral therapy and kinesiotherapy. This type of intervention is effective for approximately 90% of individuals. As a second-line treatment to support self-management, the combination with pharmacological therapy and the use of interocclusal appliances may be considered (1, 10-11).

Pain associated with TMD is the main reason why patients with this type of condition seek healthcare. It is known that most patients with TMD are able to cope with the pain, however, there are cases of chronic TMD with periods of acute exacerbation (1). Pharmacotherapy helps manage dysfunction and discomfort by controlling pain and inflammation. However, this type of therapy does not cure the dysfunction (9, 12-14).

Various drugs can be used as pharmacological therapy in the treatment of TMD. Among the most commonly used

Uvod

Temporomandibularni poremećaji (TMD) skupina je mišićno-koštanih stanja koja mogu utjecati na žvačne mišiće i sam temporomandibularni zglob (TMZ) (1). TMD je češći kod osoba u dobi između 20 i 40 godina (2 – 4).

TMD pogađa otprilike od 5 do 12 % populacije, što ga čini drugim najčešćim mišićno-koštanim stanjem (5 – 6). Obuhvaća širok spektar kliničkih entiteta kojima treba pristupati individualno. Dvanaest uobičajenih TMD-ova obuhvaća artralgiju i mijalgiju koja se dalje može klasificirati u podtipove kao što su lokalna mijalgija, miofascijalni bolovi i miofascijalni bolovi s prijenosom, zatim poremećaje pomaka diska, degenerativnu bolest zglobova, subluksaciju i glavobolju koja se pripisuje TMD-u (7).

Prema dijagnostičkim kriterijima za TMD (DC/TMD), mijalgija se definira kao bolovi mišićnoga podrijetla na koju utječu pokreti čeljusti, funkcija ili parafunkcija, a replikacija tih bolova pojavljuje se s provokacijskim testiranjem žvačnih mišića (7). Mijalgija se dalje dijeli na tri uzajamno isključive vrste, kao što su lokalna mijalgija – definirana kao bolovi lokalizirani na mjestu palpacije, miofascijalni bolovi – definirani kao bolovi koji se šire izvan mjesta palpacije, ali unutar granica mišića koji se palpira te miofascijalni bolovi s prijenosom – definirani kao bolovi na mjestu izvan granice mišića koji se palpira. Tri vrste mijalgije mogu se razlikovati palpacijskim testiranjem (2). Dijagnostički kriteriji za mijalgiju uključuju bolove pri pokretima čeljusti i palpaciji temporalnoga i maseternoga mišića, pod uvjetom da izazvani bolovi repliciraju pacijentovu tegobu (7).

Godine 2024. Međunarodna mreža za metodologiju orofacijalnih bolova i srodnih poremećaja, koju podupire Međunarodno udruženje za stomatološka istraživanja (INfORM/IADR), objavila je skup od deset ključnih točaka za dobru kliničku praksu u području temporomandibularnog poremećaja (TMD) koje su zapravo sažetak trenutačnog standarda za skrb u liječenju TMD-a i potreba pacijenata (8).

Liječenje TMD-a može obuhvaćati kirurške i nekirurške pristupe. Za većinu kirurških terapija nema dovoljno znanstvenih dokaza (1, 8 – 9). U sklopu nekirurškoga liječenja, pristup prve linije uključuje promicanje potpomognutog samoliječenja stanja i konzervativnih strategija, poput kognitivno-bihevioralne terapije i kineziterapije. Ta vrsta intervencije učinkovita je kod otprilike 90 % pojedinaca. Kao terapija druge linije, kao potpora u samoliječenju, može se razmotriti kombinacija s farmakološkom terapijom i korištenjem interokluzalnih aparata (1, 10 – 11).

Bolovi povezani s temporomandibularnim poremećajem (TMD) glavni su razlog zbog kojeg pacijenti s tom vrstom stanja traže zdravstvenu skrb. Poznato je da se većina oboljelih od TMD-a može nositi s bolovima, no postoji i kronični TMD s razdobljima akutnoga pogoršanja (1). Farmakoterapija, kontroliranjem bolova i upale, pomaže u upravljanju disfunkcijom i nelagodom. No ta vrsta terapije ne liječi disfunkciju (9, 12 –14).

Različiti lijekovi mogu se upotrijebiti kao farmakološka terapija u liječenju TMD-a. Među najčešće korištenima su nesteroidni protuupalni lijekovi (NSAID), mišićni relaksan-

drugs are non-steroidal anti inflammatory drugs (NSAIDs), muscle relaxants, opioid analgesics, and anxiolytics (9, 15-16). However, the evidence base for the use of pharmacological agents to manage myalgia in people with TMD is limited and empiric (17).

Justification of the study

Despite the increasing number of clinical studies, the evidence regarding pharmacological management of myalgia associated with temporomandibular disorders remains scarce, fragmented, and mostly empirical. Previous reviews, including the Cochrane Review on pharmacological interventions for painful persistent TMD (2021) (1), have highlighted the lack of robust and consistent data. In 2024, the International Network for Orofacial Pain and Related Disorders Methodology (INfORM/IADR) (10) reinforced the priority of conservative management, recognizing pharmacological therapy as a supportive second-line option. In this context, an updated systematic review with meta-analysis is warranted to synthesize the most recent randomized clinical trials and to clarify the effectiveness of pharmacological strategies.

Objective of the study

The objective of this study was to systematically review and quantitatively analyze the efficacy of pharmacological interventions in the management of myalgia associated with temporomandibular disorders in adults, as defined in the registered protocol, with secondary subgroup analyses examining differential responses across TMD phenotypes, including arthralgia, based on randomized controlled trials published between 2018 and 2024.

Methods

This systematic review and meta-analysis were conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (18) and reported according to the PRISMA 2020 statement (19). The review protocol was registered in PROSPERO (registration number CRD42024554300).

Eligibility criteria

Eligibility was defined using the Population, Exposure, Comparator, and Outcomes (PECO) framework:

- Population (P): adolescents and adults (≥12 years) diagnosed with myalgia related to TMD (local myalgia, myofascial pain, or myofascial pain with referral);
- Exposure (E): pharmacological interventions including nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, antidepressants, centrally acting muscle relaxants, anticonvulsants, benzodiazepines, local anesthetics, other analgesics, or combination therapies;
- Control Group (C): placebo or other active interventions (e.g., saline, occlusal splints, intra-articular injectables), provided they were clearly defined;
- Outcomes (O): primary outcomes were pain intensity and maximum interincisal opening (MIO).

Inclusion criteria were restricted to randomized controlled trials (RCTs) that reported at least one quantitative outcome related to myalgia using validated pain scales. Ex-

ti, opioidni analgetici i anksiolitici (9, 15 – 16). Međutim, baza dokaza za upotrebu farmakoloških sredstava za liječenje mijalgije kod osoba s temporomandibularnim poremećajem (TMD) ograničena je i empirijska (17).

Opravdanost istraživanja

Unatoč sve većem broju kliničkih istraživanja, dokazi o farmakološkom liječenju mijalgije povezane s temporomandibularnim poremećajima ostaju oskudni, fragmentarni i uglavnom empirijski. U dosadašnjim pregledima, uključujući Cochraneov pregled farmakoloških intervencija za bolni perzistentni TMD (2021.) (1), istaknut je nedostatak robusnih i dosljednih podataka. Godine 2024. Međunarodna mreža za metodologiju orofacijalnih bolova i srodnih poremećaja (INfORM/IADR) (10), prepoznajući farmakološku terapiju kao potpornu opciju druge linije, kao prioritet istaknula je konzervativno liječenje. U tom kontekstu potreban je ažurirani sistematizirani pregled s metaanalizom kako bi se sintetizirala najnovija randomizirana klinička istraživanja i razjasnila učinkovitost farmakoloških strategija.

Cilj istraživanja

Cilj ovog istraživanja bio je napraviti sistematizirani pregled i kvantitativno analizirati učinkovitost farmakoloških intervencija u liječenju mijalgije povezane s temporomandibularnim poremećajima kod odraslih, kako je definirano u registriranom protokolu, sa sekundarnim podskupinskim analizama kojima se ispituju različiti odgovori među fenotipovima TMD-a, uključujući artralgiju, na temelju randomiziranih kontroliranih istraživanja objavljenih između 2018. i 2024. godine.

Metode

Ovaj sustavni pregled i metaanaliza provedeni su u skladu s Cochraneovim priručnikom za sistematizirane preglede intervencija (18) i prijavljeni prema izjavi PRISMA 2020. (19). Protokol pregleda registriran je u PROSPERO-u (registracijski broj CRD42024554300).

Kriteriji prihvatljivosti

Prihvatljivost je definirana korištenjem okvira populacije, izloženosti, usporedbe i ishoda (PECO):

- populacija (P): adolescenti i odrasli (≥ 12 godina) s dijagnozom mijalgije povezane s temporomandibularnim poremećajem (TMD) (lokalna mijalgija, miofascijalni bolovi ili miofascijalni bolovi s prijenosom)
- izloženost (engl. *exposure* – E): farmakološke intervencije, uključujući nesteroidne protuupalne lijekove (NSAID), kortikosteroide, antidepresive, centralno djelujuće mišićne relaksante, antikonvulzive, benzodiazepine, lokalne anestetike, druge analgetike ili kombinirane terapije
- usporedba (engl. *control group* – C): placebo ili druge aktivne intervencije (npr., fiziološka otopina, okluzalne udlage, intraartikularne injekcije), pod uvjetom da su jasno definirane
- ishodi (engl. *outcomes* – O): primarni ishodi bili su intenzitet bolova i maksimalno interincizalno otvaranje (MIO).

clusion criteria included: history of trauma to the TMJ; inflammatory, rheumatic, or neoplastic conditions; fibromyalgia; congenital anomalies; animal studies; reviews; case reports; and studies without full-text access.

Uključivanje je bilo ograničeno na nasumična kontrolirana istraživanja (RCT) u kojima su autori, korištenjem validiranih ljestvica za bolove, izvijestili o barem jednom kvantitativnom ishodu povezanom s mijalgijom. Kriteriji za isključivanje obuhvaćali su povijest traume temporomandibularnog zgloba (TMJ), upale, reumatska ili neoplastična stanja, fibromijalgiju, kongenitalne anomalije, studije na životinjama, preglede, prikaze slučajeva i studije bez pristupa punom tekstu.

Information sources and search strategy

A comprehensive electronic search was performed in PubMed, Scopus, the Cochrane Library, and Google Scholar from inception to September 19, 2024, including articles published between 2018 and 2024. The complete search strategies for each database are provided in Table 1. Reference lists of included articles and relevant reviews were handsearched to identify additional studies.

Izvori informacija i strategija pretraživanja

Sveobuhvatno elektroničko pretraživanje provedeno je u PubMedu, Scopusu, Cochraneovoj knjižnici i Googlevu Scholaru od početka do 19. rujna 2024., uključujući radove objavljene između 2018. i 2024. Potpune strategije pretraživanja za svaku bazu podataka navedene su u tablici 1. Popisi literature uključenih radova i relevantnih pregleda ručno su pretraženi kako bi se identificirale dodatne studije.

Table 1 Search protocol used in the systematic review
Tablica 1. Protokol pretraživanja primijenjen u sistematiziranom pregledu

Applied filters and MeSH terms	Database/Results
((myalgia related to TMD) OR (myalgia related to temporomandibular disorders) OR (temporomandibular joint disorders) OR (TMD)) AND ((drugs) OR (Nonsteroidal antiinflammatory drugs) OR (corticosteroids) OR (antidepressant drugs) OR (centrally acting muscle relaxants) OR (anticonvulsants) OR (benzodiazepines))	PubMed: 1371 results Cochrane Library: 112 results Google Scholar: 1260 results
((myalgia related to TMD) OR (myalgia related to temporomandibular disorders)) AND ((drugs) OR (Nonsteroidal antiinflammatory drugs) OR (corticosteroids) OR (antidepressant drugs) OR (centrally acting muscle relaxants) OR (anticonvulsants) OR (benzodiazepines))	Scopus: 849 results

Study selection

Two reviewers independently screened titles and abstracts, followed by full-text assessment of potentially eligible articles. Disagreements were resolved by discussion or by consulting a third reviewer. The selection process was documented in a PRISMA flow diagram.

Odabir studija

Dva recenzenta neovisno su pregledala naslove i sažetke, poslije čega je slijedila procjena cjelovitih tekstova potencijalno odgovarajućih radova. Neslaganja su riješena raspravom ili konzultacijama s trećim recenzentom. Postupak odabira dokumentiran je u dijagramu toka PRISMA.

Data Extraction and Management

Data were extracted independently by two reviewers using a standardized data extraction form. Extracted information included: author, year, country, study design, sample size, demographic characteristics (mean age, % female), TMD diagnosis, intervention details (drug, dosage, frequency, route of administration), comparator type, pain scale used, time points, baseline and follow-up mean pain scores (with standard deviations and/or confidence intervals), and adverse events. If necessary, units of drug dosage were converted to ensure comparability. In cases of disagreement, a third reviewer adjudicated.

Ekstrakcija i upravljanje podatcima

Koristeći se standardiziranim modelom za ekstrakciju podataka, dva su ih recenzenta izdvajala neovisno. Izdvojene informacije uključivale su autora, godinu, zemlju, studijski dizajn, veličinu uzorka, demografska obilježja (prosječna dob, postotak žena), dijagnozu temporomandibularnog poremećaja (TMD), detalje intervencije (lijek, doza, učestalost, put primjene), vrstu komparatora, korištenu ljestvicu bola, vremenske točke, prosječne ocjene bola na početku i tijekom praćenja (sa standardnim devijacijama i/ili intervalima pouzdanosti) i nuspojave. Prema potrebi jedinice doze lijeka pretvorene su kako bi se osigurala usporedivost. U slučaju neslaganja, presuđivao je treći recenzent.

Risk of bias assessment

The risk of bias was assessed independently by two reviewers using the Cochrane RoB 2.0 tool (Cochrane Risk of Bias tool for randomized trials). Disagreements were resolved by consensus or by consulting a third reviewer. The level of agreement between reviewers was quantified using Cohen's Kappa coefficient (20).

Rizik od pristranosti u procjeni

Rizik od pristranosti neovisno su procijenila dva recenzenta koristeći se alatom Cochrane RoB 2.0 (Cochranov alat za procjenu rizika od pristranosti za randomizirana istraživanja). Neslaganja su riješena konsenzusom ili konzultacijama s trećim recenzentom. Razina slaganja između recenzenata kvantificirana je s pomoću Cohenova koeficijenta kappa (20).

Outcome measures

Primary outcomes: Change in pain intensity, assessed by validated scales (e.g., Visual Analog Scale, VAS). Change in maximum interincisal opening unassisted, measured in millimeters.

Secondary outcomes: Adverse events associated with pharmacological interventions, such as gastrointestinal discomfort, drowsiness or fatigue, dry mouth and allergic reactions, among others.

Data synthesis and statistical analysis

The effect size was expressed as standardized mean difference (SMD, Cohen's d) with 95% confidence intervals (CI). Values of 0.2, 0.5, and 0.8 were interpreted as small, medium, and large effects, respectively. Cohen's d and corresponding standard errors were calculated for each study based on reported means, standard deviations, and sample sizes for intervention and control groups.

For studies with multiple post-baseline time points, a multilevel random-effects meta-analysis model was fitted using maximum likelihood estimation, with random intercepts for each study to account for within-study correlations among repeated measurements. Best linear unbiased predictions (BLUP) were extracted as the study-specific estimates for these studies. For studies with only one post-baseline time point, a conventional random-effects meta-analysis was applied.

All study-specific SMD were combined in a meta-analysis using an inverse-variance weighted random-effects model. Heterogeneity was assessed using the I^2 statistic.

Subgroup-specific pooled effects were estimated using separate random-effects meta-analyses within each subgroup. To formally test for differences between subgroups, mixed-effects meta-regression models were fitted with the subgroup variable as a categorical moderator, and the likelihood ratio test was used to assess statistical significance. Pairwise comparisons between subgroups were conducted, with p-values adjusted using the Holm method to account for multiple testing. Publication bias was evaluated with funnel plots and the trim-and-fill method. All analyses were performed in R (metafor package) (21). Forest plots and funnel plots were generated using package ggplot2.

A two-sided significance level of 5% was used for all statistical tests.

Results

Study selection

A total of 572 records were retrieved through database searches (PubMed, Scopus, Cochrane Library, and Google Scholar). After removal of 9 duplicates, 563 unique records were screened by title and abstract. Of these, 521 were excluded for not meeting eligibility criteria. Of the 41 articles selected for full-text review, only 37 were available. The full texts of 37 articles were assessed, and 20 were excluded for the following reasons: not a randomized controlled trial (n =

Mjerenje ishoda

Primarni ishodi: promjena intenziteta bolova procijenjena je validiranim ljestvicama (npr., vizualna analogna ljestvica – VAS); promjena maksimalnoga interincizalnog otvora bez pomoći mjerena je u milimetrima.

Sekundarni ishodi: nuspojave povezane s farmakološkim intervencijama, kao što su gastrointestinalne tegobe, pospanost ili umor, suha usta i alergijske reakcije.

Sinteza podataka i statistička analiza

Veličina učinka izražena je kao standardizirana srednja razlika (Cohenov d – SMD) s 95-postotnim intervalima pouzdanosti (CI). Vrijednosti od 0,2, 0,5 do 0,8 interpretirane su kao mali, srednji i veliki učinci. Cohenov **d** i odgovarajuće standardne pogreške izračunate su za svaku studiju na temelju prijavljenih srednjih vrijednosti, standardnih devijacija i veličina uzorka za intervencijsku i kontrolnu skupinu.

Za studije s više vremenskih točaka nakon početnog razdoblja, model metaanalize s više razina slučajnih učinaka prilagođen je korištenjem procjene maksimalne vjerojatnosti, sa slučajnim odsječcima za svaku studiju kako bi se uzele u obzir korelacije unutar studije među ponovljenim mjerenjima. Najbolja linearna nepristrana predviđanja (BLUP) izdvojena su kao procjene specifične za te studije. Za studije sa samo jednom vremenskom točkom nakon početnog razdoblja, primijenjena je konvencionalna metaanaliza slučajnih učinaka.

Svi SMD-ovi specifični za studiju kombinirani su u metaanalizi korištenjem modela slučajnih učinaka ponderiranog inverznom varijancom. Heterogenost je procijenjena korištenjem statistike I^2.

Združeni učinci specifični za podskupine procijenjeni su korištenjem zasebnih metaanaliza slučajnih učinaka unutar svake podskupine. Kako bi se formalno testirale razlike između podskupina, modeli metaregresije mješovitih učinaka prilagođeni su varijablom podskupine kao kategoričkim moderatorom, a test omjera vjerojatnosti korišten je za procjenu statističke značajnosti. Provedene su parne usporedbe između podskupina s p-vrijednostima prilagođenima Holmovom metodom kako bi se uzelo u obzir višestruko testiranje. Pristranost objavljivanja procijenjena je ljevkastim dijagramima i metodom obrezivanja i popunjavanja. Sve analize obavljene su u R-u (metafor paket) (21). Prezentirani dijagrami generirani su korištenjem paketa ggplot2.

Za sve statističke testove primijenjena je dvostrana razina značajnosti od 5 %.

Rezultati

Odabir studija

Ukupno su 572 zapisa preuzeta pretraživanjem baza podataka (PubMed, Scopus, Cochrane Library i Google Scholar). Nakon uklanjanja 9 duplikata, 563 jedinstvena zapisa pregledana su prema naslovu i sažetku. Od njih je 521 odbačen jer ni jedan od njih nije ispunjavao kriteriie prihvatljivosti. Od 41 članka odabranog za pregled punog teksta, dostupno je bilo samo 37. Procijenjeni su puni tekstovi 37 radova, a 20 je isključeno iz sljedećih razloga: nije bila riječ o rando-

2) (22-23), insufficient outcome data (n = 11) (24-35), or not focused on pharmacological management of myalgia related to TMD (n = 7) (36-42).

Ultimately, 17 articles met all inclusion criteria and were included in the qualitative synthesis (43-59). Several trials included multiple intervention arms, resulting in a total of 25 comparisons available for quantitative analysis (meta-analysis). The study selection process is illustrated in the PRISMA flow diagram (Figure 1).

The 25 comparisons included in this review were conducted across nine countries between 2018 and 2024. A total of 1,128 participants were included, with a median sample size of 48 (range: 24–199). The proportion of female participants ranged from 40.9% to 100%, and the mean age ranged from 27.1 to 52.0 years.

Pharmacological interventions evaluated included platelet-rich plasma (PRP), sodium hyaluronate, methylprednisolone acetate, tenoxicam, dexamethasone, nimesulide, injectable platelet-rich fibrin (iPRF), ozone, propranolol, clorzoxazone, dextrose with saline solution, azithromycin, lidocaine, duloxetine, and MESNA.

To allow for exploratory analyses, the selected studies were grouped into four geographic categories. The western countries group includes the United States of America (43), Poland (56), Romania (55), Serbia (48), and Sweden (47), comprising five studies; the Muslim countries group includes three studies from Turkey (44, 50, 54) and three from Egypt (46, 57-58), Asia includes three studies from India (45, 52, 59) and South America includes three studies from Brazil (49, 51, 53).

Further details of the included studies can be found in Table 2.

Risk of bias in included studies

Inter-observer validation was calculated using the Cohen's Kappa coefficient (18) to determine agreement between examiners, resulting in 0.893.

The funnel plot displays a relatively symmetrical distribution of studies around the pooled effect size, with no apparent gaps or asymmetry for both pain and maximum interincisal opening. Moreover, the trim and fill method estimated zero potentially missing studies, thus indicating a low likelihood of significant publication bias in the two meta-analysis (Figure 2).

Based on the RoB 2 assessment, four articles were found to have a low risk of bias (low risk – green), ten with a moderate risk (some concerns – yellow), and three with a high risk of bias (high risk – red) (Figure 3).

Effects of interventions

Pain (primary outcome)

Regarding interventions, these were grouped according to treatment strategies into three main categories: conservative treatments (e.g., medications, patient counseling, occlusal splints, physiotherapy, and low-level laser therapy), less invasive treatments (e.g., intra-articular drug injections), and surgical treatment, which includes minimally invasive arthroscopic procedures or invasive open surgeries such as arthroplasty.

miziranom kontroliranom istraživanju (n = 2) (22 – 23), podatci o ishodima bili su nedovoljni (n = 11) (24 – 35) ili nisu bili usmjereni na farmakološko liječenje mijalgije povezane s temporomandibularnim poremećajem (n = 7) (36 – 42).

Na kraju je 17 radova ispunjavalo sve kriterije i uključeno je u kvalitativnu sintezu (43 – 59). U nekoliko istraživanja bilo je uključeno više intervencijskih skupina, što je rezultiralo s ukupno 25 usporedbi dostupnih za kvantitativnu analizu (metaanaliza). Proces odabira studija ilustriran je dijagramom toka PRISMA (slika 1.).

Ukupno 25 usporedbi uključenih u ovaj pregled provedeno je u devet zemalja između 2018. i 2024. godine. Ukupno je bilo uključeno 1128 sudionika, s medijanom veličine uzorka od 48 (raspon: 24 – 199). Udio sudionica kretao se od 40,9 do 100 %, a prosječna dob bila je od 27,1 do 52 godine.

Procjenjivane farmakološke intervencije uključivale su plazmu bogatu trombocitima (PRP), natrijev hijaluronat, metilprednizolon acetat, tenoksikam, deksametazon, nimesulid, injekcijski fibrin bogat trombocitima (iPRF), ozon, propranolol, klorzoksazon, dekstrozu s otopinom soli, azitromicin, lidokain, duloksetin i MESNA-u.

Kako bi se omogućile istraživačke analize, studije su grupirane u četiri geografske kategorije. U skupini zapadnih zemalja bile su Sjedinjene Američke Države (43), Poljska (56), Rumunjska (55), Srbija (48) i Švedska (47) s ukupno pet studija; skupina muslimanskih zemalja obuhvaćala je tri studije iz Turske (44, 50, 54) i tri iz Egipta (46, 57 – 58); Aziju su predstavljale tri studije iz Indije (45, 52, 59), a Južnu Ameriku tri studije iz Brazila (49, 51, 53).

Više detalja o uključenim studijama možete pronaći u tablici 2.

Rizik od pristranosti u uključenim studijama

Validacija između promatrača izračunata je s pomoću Cohenova kappa koeficijenta (18) kako bi se utvrdila suglasnost između ispitivača, što je rezultiralo s 0,893.

Ljevkasti dijagram prikazuje razmjerno simetričnu raspodjelu studija oko združene veličine učinka, bez vidljivih praznina ili asimetrije i za bol i za maksimalni interincizalni otvor. Štoviše, metodom obrezivanja i popunjavanja procijenjena je nula potencijalno nedostajućih studija, što upućuje na nisku vjerojatnost značajne pristranosti u objavljivanju dviju metaanaliza (slika 2.).

Na temelju procjene RoB 2 utvrđeno je da četiri članka imaju nizak rizik od pristranosti (niski rizik – zeleno), deset umjeren (umjereni rizik – žuto) i tri visok (visoki rizik – crveno) (slika 3.).

Učinci intervencija

Bol (primarni ishod)

Kad je riječ o intervencijama, one su grupirane prema strategijama liječenja u tri glavne kategorije: konzervativna terapija (npr., lijekovi, savjetovanje pacijenata, okluzalne udlage, fizioterapija i laserska terapija niskog intenziteta), manje invazivna terapija (npr., intraartikularne injekcije lijekova) i kirurško liječenje koje uključuje minimalno invazivne artroskopske postupke ili invazivne otvorene operacije poput artroplastike.

Table 2 Descriptive information of the twenty five included studies.
Tablica 2. Deskriptivne informacije o dvadeset pet uključenih studija

Study characteristics			Population characteristics			Intervention characteristics				
Author Year Country	Age Mean (years)	% Female	TMD Diagnostic	Type of pain	TMD Scale	Intervention (n of cases)	Control (n of controls)	Follow-up (n post-baseline)	Measure of effect (VAS scale)	Measure of effect (MIO scale)
Batabyal et al. 2023 India	37,91	55	TMD Symptoms	Arthralgia		Platelet-Rich Plasma (30)	Lidocaíne + Triamcinolone (30)	2	-1,42 (-2,00; -0,84)	1,49 (0,99; 196)
1.Yapıcı-Yavuz et al. 2018 Turkey		86,36	Non-reducing disc displacement of the TMJ	Arthralgia	*RDC/TMD*	Arthrocentesis + intra-articular injection of sodium hyaluronate (11)	Arthrocentesis (11)	4	-0,19 (-0,73; 0,36)	0,01 (-0,44; 0,46)
2.Yapıcı-Yavuz et al. 2018 Turkey		86,36	Non-reducing disc displacement of the TMJ	Arthralgia	*RDC/TMD*	Arthrocentesis + intra-articular injection of methylprednisolone acetate (11)	Arthrocentesis (11)	4	0,13 (-0,41; 0,68)	-0,11 (-0,57; 0,34)
3.Yapıcı-Yavuz et al. 2018 Turkey		86,36	Non-reducing disc displacement of the TMJ	Arthralgia	*RDC/TMD*	Arthrocentesis + intra-articular injection of tenoxicam (11)	Arthrocentesis (11)	4	-0,01 (-0,55; 0,53)	-0,23 (-0,68; 0,22)
1.Martins et al. 2023 Brasil	34,55	91,6	Sintomas de DTM, *estadios III ou IV de Wilkes*		Wilkes classification	Arthroscopy + intra-articular injection of 2 mg dexamethasone (24)	Arthroscopy (12)	3	-0,47 (-1,05; 0,11)	0,43 (-0,06; 0,92)
2.Martins et al. 2023 Brasil	34,55	91,6	TMD Symptoms, *III ou IV stages of Wilkes*		Wilkes classification	Arthroscopy + intra-articular injection of 4 mg dexamethasone (24)	Arthroscopy (12)	3	-0,88 (-1,47; -0,29)	0,35 (-0,14; 0,84)
1.Dalewski et al. 2019 Poland	30,73	80	Myofascial pain	Myalgia		Interocclusal splint + nimesulide (30)	Interocclusal splint (30)	1	1,02 (0,56; 1,48)	
2.Dalewski et al. 2019 Poland	30,73	80	Myofascial pain	Myalgia		Interocclusal splint + dry needling therapy (30)	Interocclusal splint (30)	1	-0,83 (-1,29; -0,38)	
1.Tepecik et al. 2024 Turkey	36,30	100	Disc displacement without reduction	Arthralgia	*DC/TMD*	Arthrocentesis + intra-articular injection of sodium hyaluronate (29)	Interocclusal splint (30)	2	-0,69 (-1,22; -0,16)	0,11 (-0,33; 0,55)
2.Tepecik et al. 2024 Turkey	36,30	100	Disc displacement without reduction	Arthralgia	*DC/TMD*	Intra-articular injection of iPRF (29)	Interocclusal splint (30)	2	-0,36 (-0,89; 0,17)	-0,12 (-0,55; 0,32)
Pereira et al. 2021 Brasil	43,91	100	Muscular TMD	Myalgia	*DC/TMD*	Ozone therapy (25)	Cyclobenzaprine + nimesulide (23)	2	-3,30 (-4,04; -2,55)	1,34 (0,82; 1,87)
Tchivileva et al. 2020 USA	34,05	77,5	Muscular TMD	Myalgia	*DC/TMD*	Propanolol (100)	Placebo (99)	1	-0,74 (-1,03; -0,45)	-0,02 (-0,30; 0,26)
1.Bechir et al. 2018 Romania	50,50	56,1	Muscular TMD	Myalgia	*DC/TMD*	Low level laser therapy (42)	Fastum gel + Clorzoxazone (40)	7	-0,59 (-1,04; -0,13)	1,04 (0,68; 1,40)
2.Bechir et al. 2018 Romania	50,50	56,1	Muscular TMD	Myalgia	*DC/TMD*	Low level laser therapy + Fastum gel + Clorzoxazone (41)	Fastum gel + Clorzoxazone (40)	7	-0,83 (-1,29; -0,37)	1,63 (1,26; 1,99)
Venepally et al. 2018 India	32,43	50	Myofascial pain	Myalgia	Laskin's criteria, 1969	Transcutaneous Electrical Nerve Stimulation (20)	Aceclofenac + Paracetamol + Tizanidine (20)	4	-0,83 (-1,37; -0,29)	
Gibaly et al. 2024 Egypt	31,78	62,5	Temporomandibular joint anterior disc displacement, Wilkes stage II	Artralgia	Wilkes classification	Deep dry needling + Dextrose (20)	Deep dry needling (20)	4	-0,36 (-0,90; 0,17)	0,99 (0,54; 1,44)
Mosleh et al. 2021 Egypt	27,15	70,83	Anteriorly non reducing disc displacement, Wilkes stage III	Arthralgia + Myalgia	Wilkes classification	Arthrocentesis plus intra-articular injection of azithromycin (12)	Arthrocentesis + intra-articular injection of methylprednisolone acetate ednisolona (12)	2	-0,05 (-0,73; 0,64)	-0,21 (-0,80; 0,38)
Chandra et al. 2021 India	30,50	40,90	TMD Symptoms	Arthralgia		Intra-articular injection of PRP (22)	Arthrocentesis (22)	4	-0,46 (-0,98; 0,07)	0,35 (-0,08; 0,78)
1.Đorđević et al. 2019 Serbia	38,30	84,10	TMD Symptoms	Arthralgia		Interocclusal splint (20)	Ibuprofeno (16)	1	-0,34 (-1,00; 0,32)	
2.Đorđević et al. 2019 Serbia	38,30	84,10	TMD Symptoms	Arthralgia		Interocclusal splint (20)	Diazepam (8)	1	-0,29 (-1,12; 0,53)	
1.Bilici et al. 2018 Turkey			Myofascial pain and Internal Derangement	Arthralgia + Myalgia	*RDC/TMD*	Interocclusal splint plus intra-articular injection of lidocaine (3 times on alternate days) (12)	Interocclusal splint (29)	2	-2,84 (-3,59; -2,10)	
2.Bilici et al. 2018 Turkey			Myofascial pain and Internal Derangement	Arthralgia + Myalgia	*RDC/TMD*	Interocclusal splint plus intra-articular injection of lidocaine (3 times, once a week) (15)	Interocclusal splint (29)	2	0,35 (-0,27; 0,96)	
Isacsson et al. 2018 Sweden	52,00	81,50	TMD Symptoms	Arthralgia	*DC/TMD*	Arthrocentesis + intra-articular injection of methylprednisolone acetate ednisolona (27)	Saline solution (27)	1	-0,25 (-0,78; 0,29)	
Ferreira et al. 2023 Brasil	39,24	96,15	TMD Symptoms	Arthralgia + Myalgia	*DC/TMD*	Duloxetine (40)	Placebo (38)	1	0,63 (0,18; 1,09)	
Mosleh et al. 2024 Egypt		88,33	TMD Symptoms, *II, III ou IV stages of Wilkes*		Wilkes classification	Arthrocentesis plus intra-articular injection of MESNA (30)	Arthrocentesis + intra-articular injection of sodium hyaluronate (30)	4	-3,62 (-4,23; -3,01)	1,13 (0,72; 1,55)

Abbreviations: iPRF – Injectable Platelet-Rich Fibrin; PRP – Platelet-Rich Plasma; RDC/TMD – Research Diagnostic Criteria for Temporomandibular Disorders; DC/TMD – Diagnostic Criteria for Temporomandibular Disorders; MESNA – Pharmacological agent (Active ingredient: synthetic sulfhydryl compound).

1.

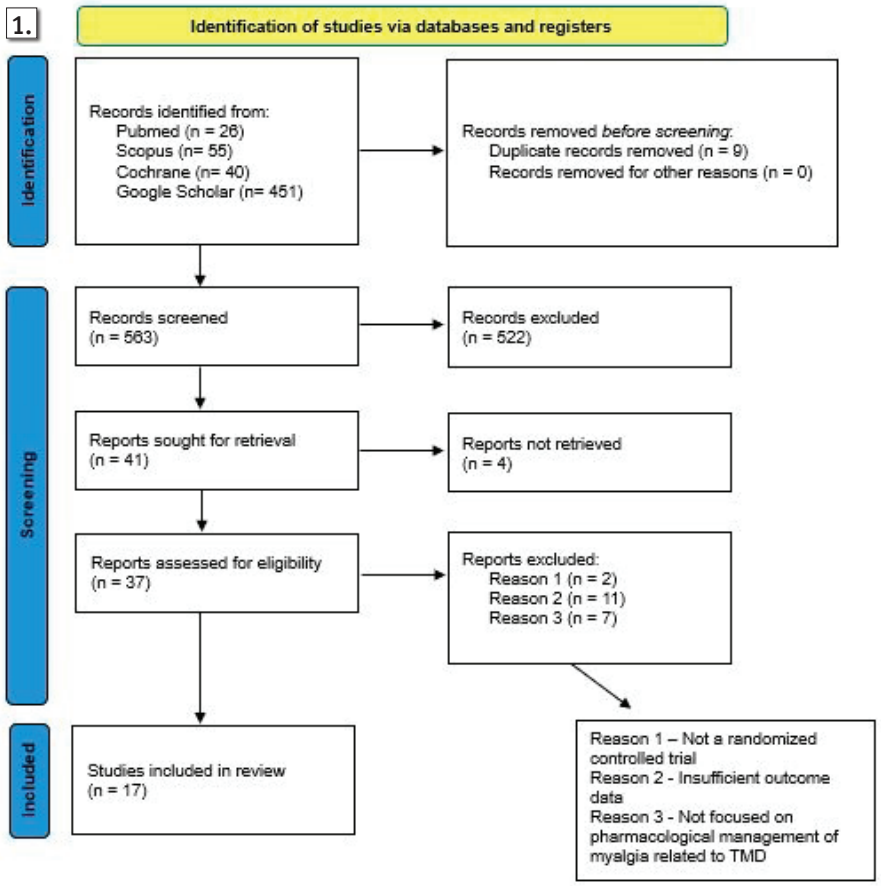
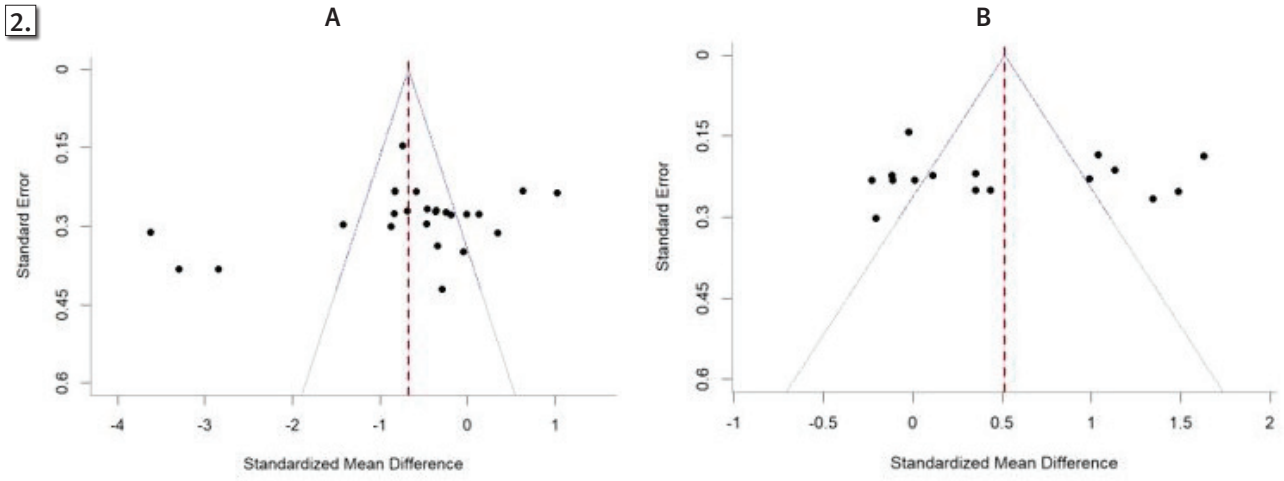


Figure 1 PRISMA flow diagram
Slika 1. PRISMA – dijagram toka

Figure 2 Funnel plot of included studies evaluating the effect on: (A) pain and (B) maximum interincisal opening in temporomandibular disorders. Each point represents an individual study's effect size plotted against its standard error. The vertical dashed line indicates the pooled mean difference. The blue lines represent pseudo 95% confidence limits. Trim and fill method: (A) no missing studies and (B) no missing studies.
Slika 2. Ljevkasti dijagram uključenih studija u kojima se procjenjuju učinak na: (A) bol i (B) maksimalno interincizalno otvaranje kod temporomandibularnih poremećaja; svaka točka predstavlja veličinu učinka pojedinačne studije u odnosu na njezinu standardnu pogrešku; isprekidana okomita crta označava združenu razliku srednjih vrijednosti; plave crte pokazuju pseudogranicu od 95 % pouzdanosti; metoda obrezivanja i popunjavanja: (A) nema nedostajućih studija i (B) nema nedostajućih studija

Figure 3 Rob2 Analysis
Slika 3. Analiza Rob2

2.



3.

4.

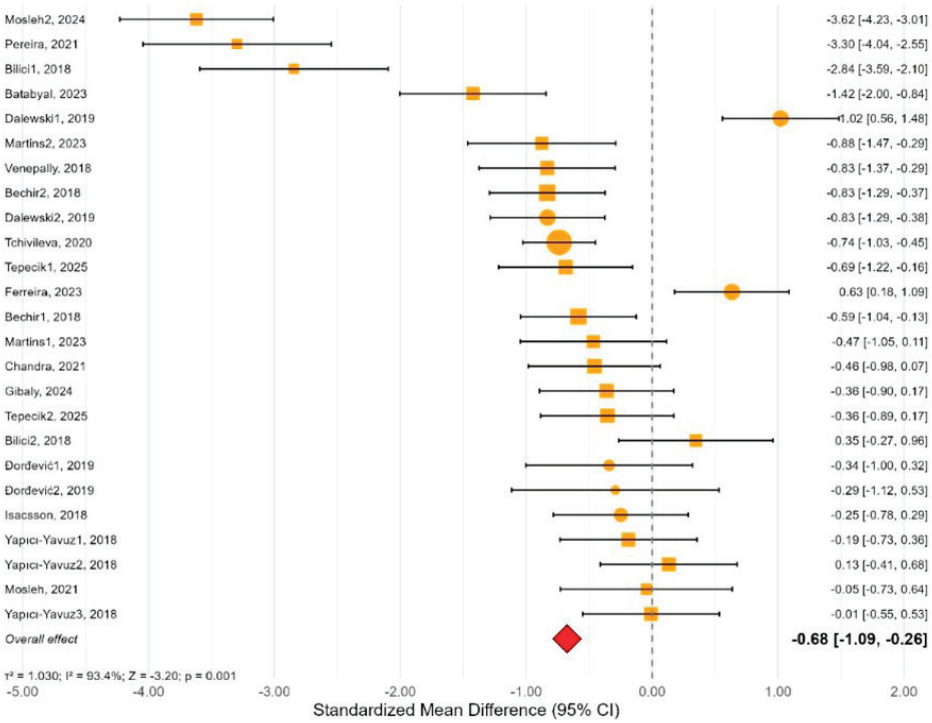


Figure 4 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the effect of pharmacological interventions on myalgia related to temporomandibular disorders. Each point represents an individual study estimate, with the size of the marker proportional to the study's weight. Circles indicate studies with a single follow-up time point, while squares represent studies with more than one follow-up assessment (BLUP estimates). The red diamond represents the overall pooled effect. Negative values indicate a reduction in pain favoring the intervention group. Vertical dashed line indicates no effect (SMD = 0).

Slika 4. Dijagram standardiziranih razlika srednjih vrijednosti (SMD) i 95 % intervala pouzdanosti za učinak farmakoloških intervencija na mijalgiju povezanu s temporomandibularnim poremećajima; svaka točka predstavlja procjenu pojedinačne studije, s veličinom markera proporcionalnom težini studije; krugovi označavaju studije s jednom vremenskom točkom praćenja, a kvadrati studije s više od jedne procjene praćenja (BLUP procjene); crveni romb predstavlja ukupni združeni učinak; negativne vrijednosti označavaju smanjenje bola u korist intervencijske skupine; isprekidana okomita crta označava da nema učinka (SMD = 0)

For the meta-analysis, the following variables were assessed: sex, age, country group, type of pain, presence of dysfunction, the TMD scale used for diagnosis, type of treatment strategy, specific treatment strategy, and active pharmacological agent. For each group, pain (VAS) and maximum mouth opening (MIO measurement) were evaluated.

In the VAS pain assessment, regarding the type of intervention, no significant differences were observed. However, conservative interventions produced the greatest pain reduction, followed by less invasive interventions and combined surgery/injection modalities. Studies including participants with a mean age of 40 years or older tended to report greater pain reduction (SMD = -1.21; 95% CI: -2.36 to -0.07), although the difference between age subgroups was not statistically significant (p = 0.073). No statistically significant effect modifiers were identified in subgroup comparisons.

Pharmacological interventions proved to be more effective in reducing pain associated with myalgia in patients with TMD. Across the 25 studies, the pooled effect size (SMD) for pain showed a favorable effect for the intervention group, with most individual studies reporting negative effect sizes (Figure 4). The overall pooled effect demonstrated a statistically significant reduction in pain (SMD = -0.68; 95% CI: -1.09 to -0.26; p < 0.001), thus suggesting a moderate to high beneficial effect of interventions on myalgia pain. Most of the included studies (n = 18) reported estimates based on

Za metaanalizu procijenjene su sljedeće varijable: spol, dob, zemlja podrijetla, vrsta bolova, prisutnost disfunkcije, TMD ljestvica korištena za dijagnozu, vrsta strategije liječenja, specifična strategija liječenja i aktivni farmakološki agens. Za svaku skupinu procijenjeni su bolovi (VAS) i maksimalno otvaranje usta (MIO mjerenje).

U procjeni bolova VAS-om, s obzirom na vrstu intervencije, nisu uočene značajne razlike. Međutim, konzervativne intervencije rezultirale su najvećim smanjenjem bolova, a slijede ih manje invazivne intervencije i kombinirane kirurške/injekcijske metode. U studijama u koje su bili uključeni sudionici prosječne dobi od 40 godina ili više pokazale su tendenciju izvještavanja o većem smanjenju bolova (SMD = -1,21; 95 % CI: -2,36 do -0,07), iako razlika između dobnih podskupina nije bila statistički značajna (p = 0,073). U usporedbama podskupina nisu ustanovljeni statistički značajni modifikatori učinka.

Farmakološke intervencije pokazale su se učinkovitijima u smanjenju bolova povezanih s mijalgijom kod pacijenata s temporomandibularnim poremećajem (TMD). U 25 studija pokazala je združena veličina učinka (SMD) za bolove povoljan učinak za intervencijsku skupinu, pri čemu je u većini pojedinačnih studija istaknuta negativna veličina učinka (slika 4.). Ukupni združeni učinak pokazao je statistički značajno smanjenje bolova (SMD = -0,68; 95 % CI: -1,09 do -0,26; p < 0,001), što sugerira umjeren do visok blagotvorni učinak

Table 3 Subgroup analysis of pain by VAS scale
Tablica 3. Podskupinska analiza bolova prema ljestvici VAS

	Number of studies	I^2(%)	Cohen's d (95% CI)	p-value
Type of pain				
Arthralgia	11	44.7	-0.38 (-0.61,-0.15)	0.57
Arthralgia + Myalgia	4	94.8	-0.46 (-1.80,0.89)	
Myalgia	7	95.8	-0.85 (-1.68,-0.01)	
Presence of dysfunction				
Yes	20	91.1	-0.62 (-1.04,-0.20)	0.59
No	5	97.0	-0.91 (-2.09,0.27)	
Intervention				
Conservative	10	93.9	-0.89 (-1.30,-0.09)	0.90
Less Invasive	4	93.2	-0.72 (-1.11,-0.32)	
Surgery + Less Invasive	9	52.4	-0.51 (-1.27,0.24)	
Type of intervention				
Mechanic	3	74.1	-0.61 (-0.95,-0.27)	0.92
Pharmacology	3	97.8	-1.11 (-2.93,0.71)	
Intra-articular injection of drugs	4	52.4	-0.72 (-1.11,-0.32)	
Surgery + Intra-articular injection of drugs	7	94.7	-0.72 (-1.62,0.18)	
Active Principle				
Corticosteroids	4	37.2	-0.35 (-0.70,0.00)	0.81
Others	13	96.6	-0.80 (-1.57,-0.03)	
Factor Rich Plasma	3	64.9	-0.73 (-1.26,-0.20)	
TMD Scale				
DC/TMD	6	95.6	-0.76 (-1.69,0.18)	0.75
RDC/TMD	5	93.1	-0.49 (-1.50,0.51)	
Wilkes classification	5	94.5	-1.07 (-2.21,0.06)	
Age				
<40 years	15	80.9	-0.40 (-0.71,-0.09)	0.073
>=40 years	4	94.6	-1.21 (-2.36,-0.07)	
Sex				
<80% Female	8	14.2	-0.69 (-0.87,-0.51)	0.90
>=80% Female	15	94.4	-0.62 (-1.22,-0.01)	
Group of countries				
India	3	48.7	-0.89 (-1.33,-0.45)	0.75
Brazil	4	95.7	-0.98 (-2.37,0.41)	
Europe + USA	8	83.1	-0.37 (-0.78,0.05)	
Muslims	10	94.5	-0.75 (-1.53,0.03)	

multiple follow-up time points. Heterogeneity between studies was very high (I^2 = 93.4%), which was explored through subgroup analysis (Figure 4, Figure 5.(A) – 5.(I), Table 3).

Regarding pain type, in cases of arthralgia there was a significant pain reduction (SMD = -0.38; 95% CI: -0.61 to -0.15, I^2 = 44.7). In the remaining pain types, heterogeneity was high.

In terms of intervention, surgical procedures combined with less invasive treatments did not show a significant effect in reducing pain (SMD = -0.511; 95% CI: -1.27 to 0.24, I^2 = 52.4). Regarding intervention type, mechanical interventions (SMD = -0.61; 95% CI: -0.95 to -0.27, I^2 = 74.1) and intra-articular drug injections (SMD = -0.72; 95% CI: -1.11 to -0.32, I^2 = 52.4) showed significant pain reduction, whereas other subgroups showed high heterogeneity.

For the active agents administered in different studies, corticosteroids (SMD = -0.35; 95% CI: -0.35 to 0.00, I^2 =

intervencija na bol mijalgije. U većini uključenih studija (n = 18) autori su izvijestili o procjenama temeljenima na višestrukim vremenskim točkama praćenja. Heterogenost između studija bila je vrlo visoka (I^2 = 93,4 %), što je istraženo analizom podskupina (slika 4., slika 5.(A) – 5.(I), tablica 3.).

Kad je riječ o vrsti bolova, u slučajevima artralgije zabilježeno je značajno smanjenje (SMD = -0,38; 95 % CI: -0,61 do -0,15, I^2 = 44,7). Kod preostalih vrsta bolova heterogenost je bila visoka.

Što se tiče intervencije, kirurški postupci u kombinaciji s manje invazivnim terapijama nisu pokazali značajan učinak u smanjenju bolova (SMD = -0,511; 95 % CI: -1,27 do 0,24, I^2 = 52,4). Kad je riječ o vrstama intervencije, mehaničke intervencije (SMD = -0,61; 95 % CI: -0,95 do -0,27, I^2 = 74,1) i intraartikularne injekcije lijekova (SMD = - 0,72; 95 % CI: -1,11 do -0,32, I^2 = 52,4) pokazale su značajno smanjenje bolova. Druge podskupine pokazale su visoku heterogenost.

5.

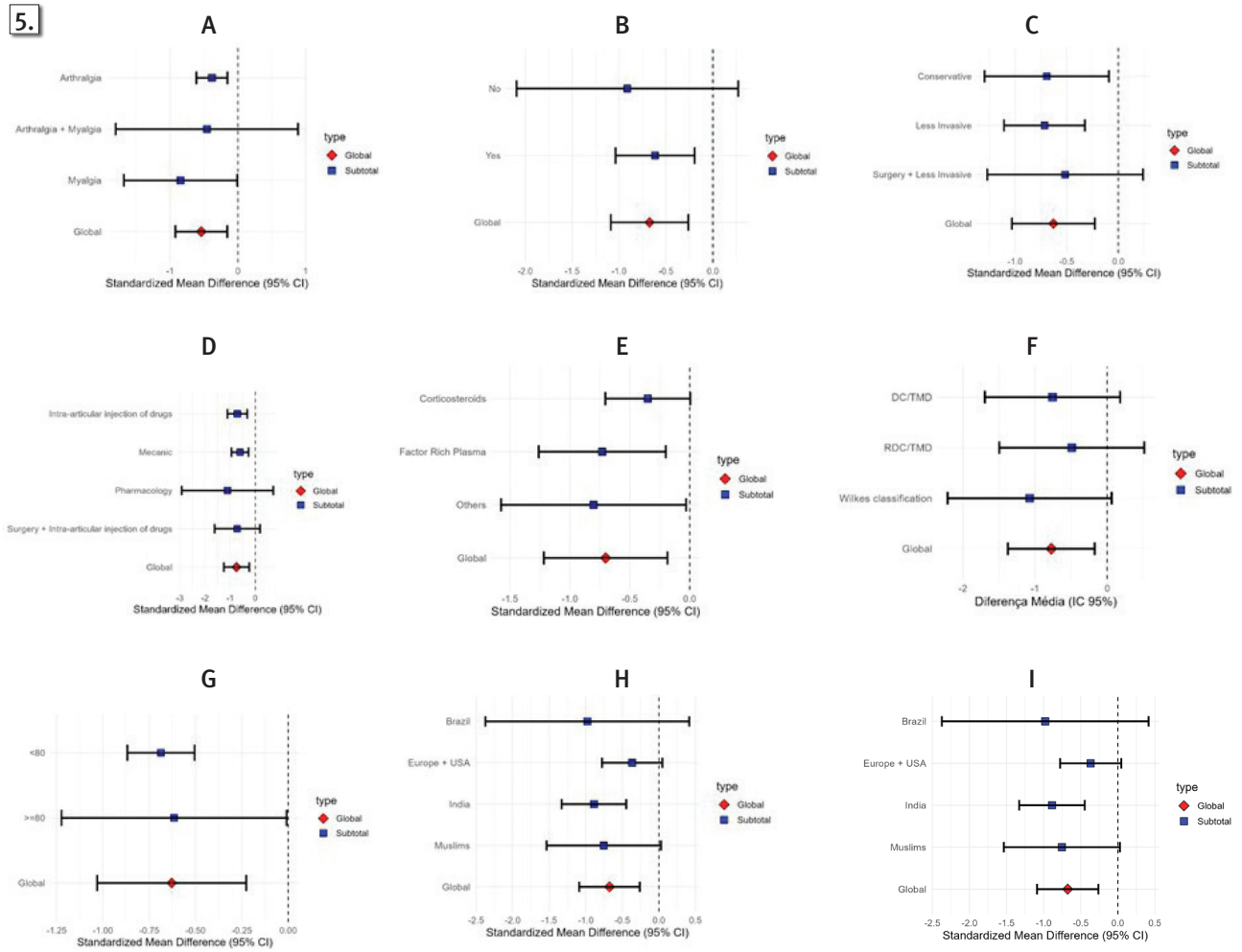


Figure 5 A) Subgroup analysis of the type of pain by VAS scale
Slika 5. A) Analiza podskupina prema vrsti bolova prema ljestvici VAS
Figure 5 B) Subgroup analysis of the presence of dysfunction by VAS scale
Slika 5. B) Analiza podskupina prisutnosti disfunkcije prema ljestvici VAS
Figure 5 C) Subgroup analysis of the intervention by VAS scale
Slika 5. C) Analiza podskupina intervencije prema ljestvici VAS
Figure 5 D) Subgroup analysis of the type of intervention by VAS scale
Slika 5. D) Analiza podskupina prema vrsti intervencije prema ljestvici VAS
Figure 5 E) Subgroup analysis of the active principle by VAS scale
Slika 5. E) Analiza podskupina aktivnoga principa prema ljestvici VAS
Figure 5 F) Subgroup analysis of the TMD scale used by VAS scale
Slika 5. F) Analiza podskupina korištene TMD ljestvice prema ljestvici VAS
Figure 5 G) Subgroup analysis of age by VAS scale (<40 years, >=40 years)
Slika 5. G) Analiza podskupina prema dobi prema ljestvici VAS (< 40 godina, > = 40 godina)
Figure 5 H) Subgroup analysis of sex by VAS scale (<80% Female, >=80% Female)
Slika 5. H) Analiza podskupina prema spolu prema ljestvici VAS (< 80 % žena, > = 80 % žena)
Figure 5 I) Subgroup analysis of the country of origin by VAS scale
Slika 5. I) Analiza podskupina prema zemlji podrijetla prema ljestvici VAS

37.2) and platelet-rich factors (SMD = -0.73; 95% CI: -1.26 to -0.20, I^2 = 64.9) also demonstrated significant pain reduction.

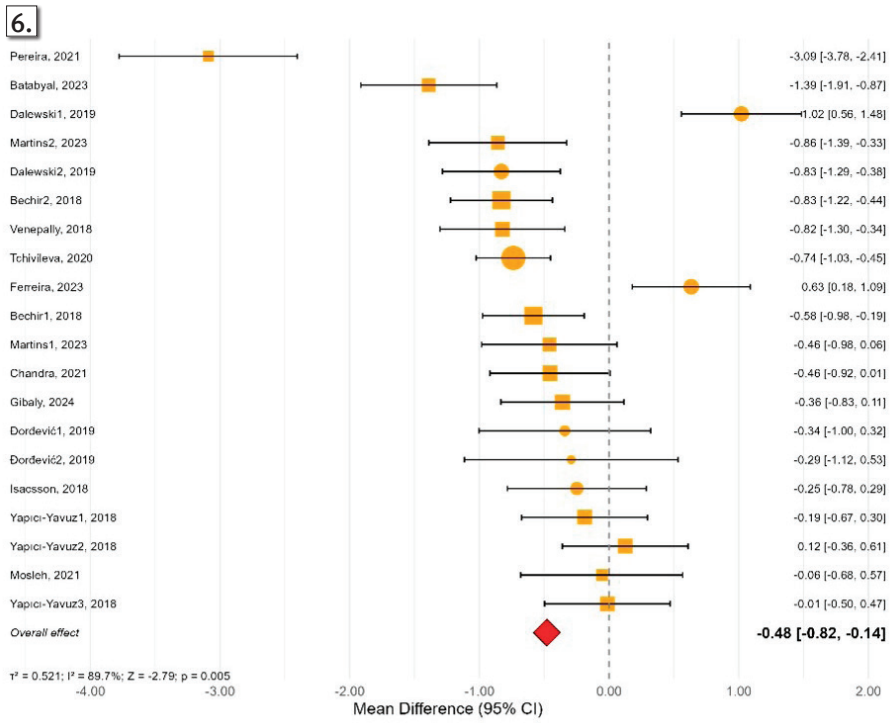
Regarding participant sex, studies with less than 80% female participants showed a significant pain reduction (SMD = -0.69; 95% CI: -0.87 to -0.51, I^2 = 14.2).

For the country group division, studies conducted in India (SMD = -0.89; 95% CI: -1.33 to -0.45, I^2 = 48.7) also reported significant pain reduction, while the other groups showed high heterogeneity.

Za aktivne tvari primijenjene u različitim studijama, kortikosteroidi (SMD = -0,35; 95 % CI: -0,35 do 0,00, I^2 = 37,2) i faktori bogati trombocitima (SMD = -0,73; 95 % CI: -1,26 do -0,20, I^2 = 64,9) također su pokazali značajno smanjenje bolova.

Kad je riječ o spolu sudionika, studije u kojima je sudjelovalo manje od 80 % žena pokazale su značajno smanjenje bolova (SMD = -0,69; 95 % CI: -0,87 do -0,51, I^2 = 14,2).

Što se tiče podjele po skupinama zemalja, u studijama provedenim u Indiji (SMD = -0,89; 95 % CI: -1,33 do -0,45,



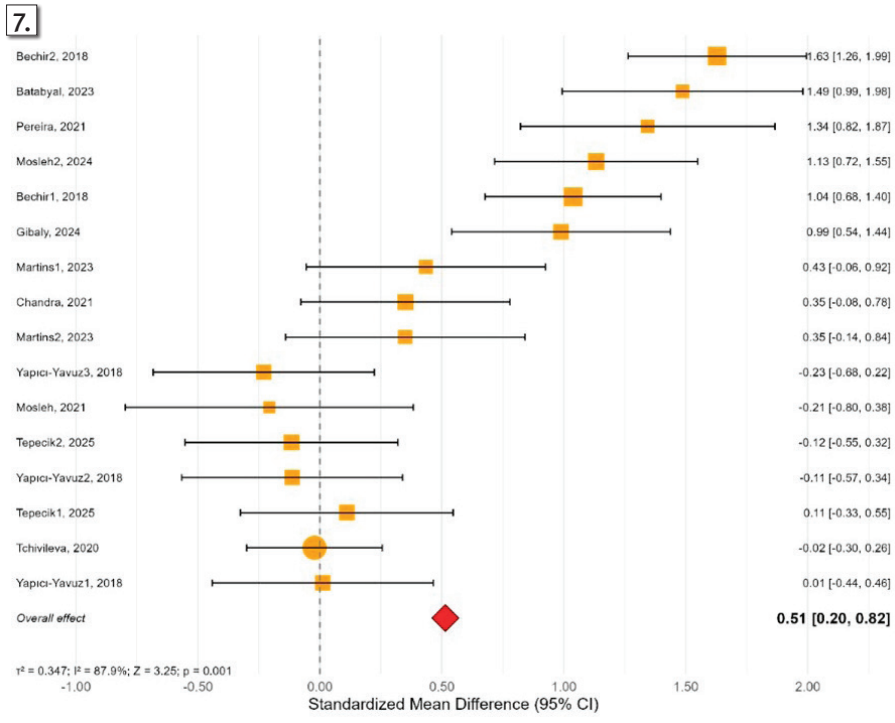


Figure 6 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the effect of pharmacological interventions on myalgia related to temporomandibular disorders without the high-risk studies, after Rob2 analysis

Slika 6. Dijagram standardiziranih srednjih razlika (SMD) i 95 % intervala pouzdanosti za učinak farmakoloških intervencija na mijalgiju povezanu s temporomandibularnim poremećajima bez studija visokoga rizika, nakon analiza Rob2

Figure 7 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the maximum interincisal opening outcome. Each point represents an individual study estimate, with the size of the marker proportional to the study's weight. Circles indicate studies with a single follow-up time point, while squares represent studies with more than one follow-up assessment (BLUP estimates). The red diamond represents the overall pooled effect. Negative values indicate a reduction in pain favoring the intervention group. Vertical dashed line indicates no effect (SMD = 0).

Slika 7. Dijagram standardiziranih srednjih razlika (SMD) i 95 % intervala pouzdanosti za ishod maksimalnoga interincizalnog otvaranja; svaka točka pokazuje pojedinačnu procjenu studije s veličinom markera proporcionalnom težini studije; krugovi označavaju studije s jednom vremenskom točkom praćenja, a kvadrati studije s više od jedne procjene praćenja (BLUP procjene); crveni romb prikazuje ukupni združeni učinak; negativne vrijednosti označavaju smanjenje bola u korist intervencijske skupine; isprekidana okomita crta označava da nema učinka (SMD = 0)

The forest plot of standardized mean differences (SMD) and 95% confidence intervals for the effect of pharmacological interventions on myalgia related to temporomandibular disorders without the high-risk studies, after Rob2 analysis can be found in Figure 6. The global effect decreases to -0.48 (95% CI: -0.82 to -0.14), however, this reduction is not statistically significant.

I^2 = 48,7) također je istaknuto značajno smanjenje bolova, a ostale skupine pokazale su visoku heterogenost.

Dijagram standardiziranih srednjih razlika (SMD) i 95 % intervala pouzdanosti za učinak farmakoloških intervencija na mijalgiju povezanu s temporomandibularnim poremećajima bez studija visokog rizika, nakon analize Rob2, može se pronaći na slici 6. Globalni učinak smanjuje se na -0,48 (95 % CI: -0,82 do – 0,14), no to smanjenje nije statistički značajno.

8.

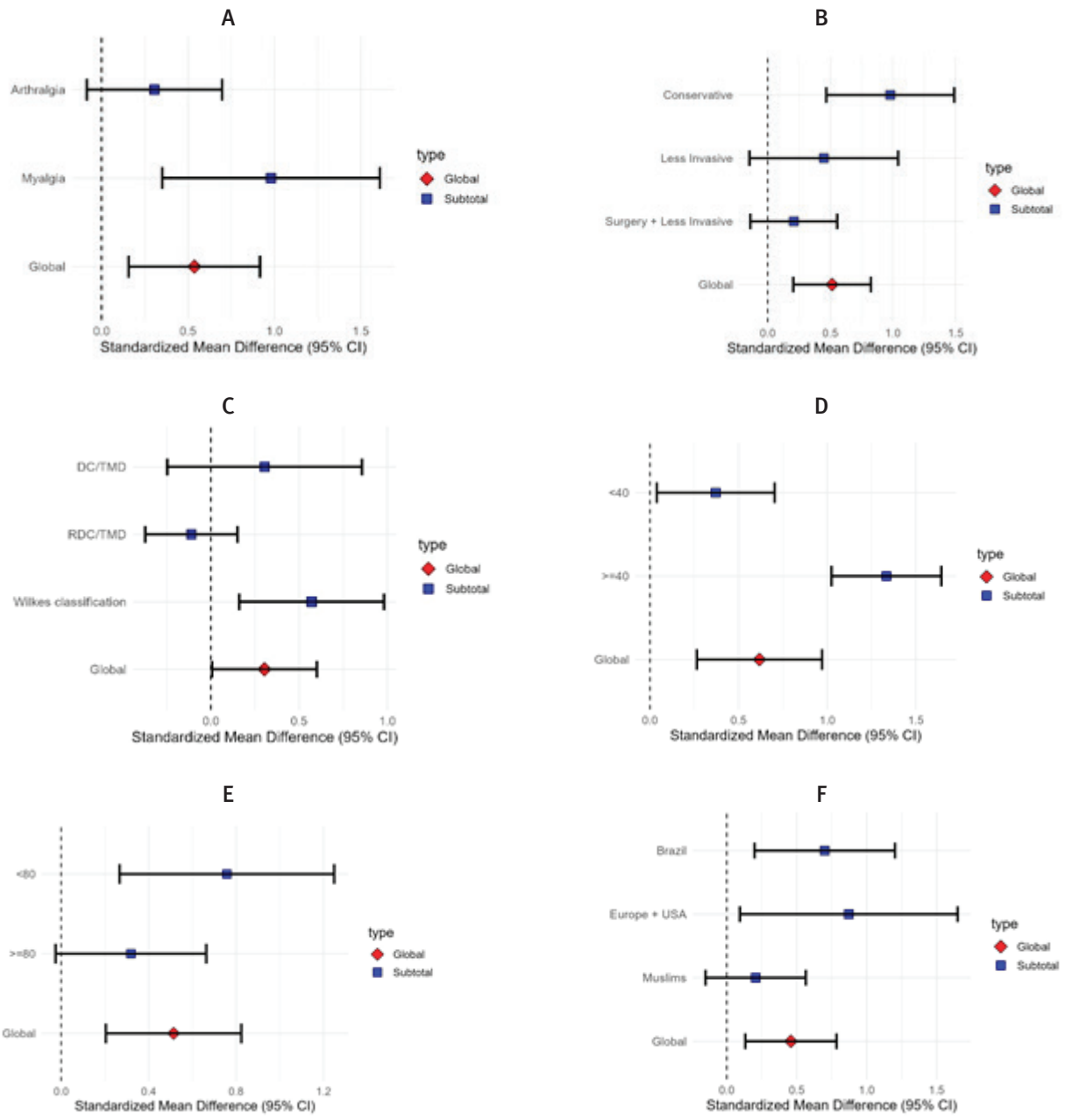


Figure 8 A) Subgroup analysis of the type of pain by MIO scale
Slika 8. A) Analiza podskupina prema vrsti bolova prema ljestvici MIO
Figure 8 B) Subgroup analysis of the intervention by MIO scale
Slika 8. B) Analiza podskupina intervencije prema ljestvici MIO
Figure 8 C) Subgroup analysis of the TMD scale used by MIO scale
Slika 8. C) Analiza podskupina korištene TMD ljestvice prema ljestvici MIO
Figure 8 D) Subgroup analysis of age by MIO scale (<40 years, >=40 years)
Slika 8. D) Analiza podskupina prema dobi prema ljestvici MIO (< 40 godina, > = 40 godina)
Figure 8 E) Subgroup analysis of sex by MIO scale (<80% Female, >=80% Female)
Slika 8. E) Analiza podskupina prema spolu prema ljestvici MIO (< 80 % žena, > = 80 % žena)
Figure 8 F) Subgroup analysis of the country of origin by MIO scale
Slika 8. F) Analiza podskupina prema zemlji podrijetla prema ljestvici MIO

Maximum interincisal opening (MIO, primary outcome)

In terms of MIO evaluation, interventions were associated with an overall improvement in maximum interincisal opening. The overall pooled effect demonstrated a statistically significant increase in MIO (SMD = 0.51; 95% CI: 0.20 to 0.82; p < 0.001), suggesting a beneficial effect of inter-

Maksimalno interincizalno otvaranje (MIO, primarni ishod)

Kad je riječ o evaluaciji MIO-a, intervencije su bile povezane s ukupnim poboljšanjem maksimalnoga interincizalnog otvaranja. Ukupni združeni učinak pokazao je statistički značajan porast MIO-a (SMD = 0,51; 95 % CI: 0,20 do 0,82; p < 0,001), što upućuje na blagotvorni učinak interven-

Table 4 Subgroup analysis of MIO
Tablica 4. Podskupinska analiza MIO-a

	Number of studies	I^2 (%)	Cohen's *d* (95% CI)	p-value
Type of pain				
Arthralgia	8	83.5	0.31 (-0.08,0.70)	0.08
Myalgia	4	91.5	0.98 (0.35,1.61)	
Intervention				
Conservative	5	88.9	0.98 (0.47,1.49)	0.075
Less Invasive	7	85.8	0.45 (-0.14,1.04)	
Surgery + Less Invasive	4	85.8	0.44 (-0.14,0.56)	
TMD Scale				
DC/TMD	4	86.5	0.30 (-0.25,0.80)	0.56
RDC/TMD	3	0.00	-0.11 (-0.37,0.15)	
Wilkes classification	6	72.4	0.57 (0.16,0.98)	
Age				
<40 years	9	80.6	0.37 (0.04,0.70)	<0.001
>=40 years	3	42.4	1.33 (1.02,1.64)	
Sex				
<80% Female	7	90.4	0.76 (0.27,1.25)	0.155
>=80% Female	9	80.3	0.32 (-0.03,0.66)	
Group of countries				
Brazil	3	66.8	0.70 (0.20,1.20)	0.170
Europe + USA	3	93.9	0.87 (0.09,1.65)	
Muslims	8	79.7	0.21 (-0.15,0.56)	

Table 5 Summary of Findings Table with GRADE certainty ratings
Tablica 5. Sažetci nalaza s ocjenama sigurnosti GRADE

Outcome	Nº of participants (studies)	Effect (SMD, 95% CI)	Absolute effect (interpretation)	Certainty of the evidence (GRADE)	What happens	Comments
Pain intensity (VAS)	1,128 (25 comparisons, 17 RCTs)	SMD = –0.68 (–1.09 to –0.26)	Moderate reduction in pain favoring pharmacological interventions	★★◯◯ Low to moderate	Patients receiving pharmacological interventions are likely to experience a moderate reduction in pain compared to placebo or control.	High heterogeneity (I^2 = 93.4%); subgroup analysis showed consistent benefit in arthralgia and with some injectable agents.
Maximum interincisal opening (MIO)	786 (12 RCTs)	SMD = 0.51 (0.20 to 0.82)	Moderate improvement in mandibular function (≈ +2–4 mm)	★★◯◯ Low to moderate	Patients treated pharmacologically are likely to achieve moderate improvement in mouth opening.	Effect more pronounced in patients ≥40 years and in trials using Wilkes classification.
Adverse events	568 (8 RCTs)	Not pooled (heterogeneous reporting)	Mostly mild events (e.g., transient local pain, swelling, gastrointestinal upset); no serious adverse events reported	★◯◯◯ Very low	Adverse events were mild and self-limiting; no serious harms identified.	Evidence limited by poor reporting and inconsistent definitions.
Subgroup: Arthralgia vs. Myalgia	442 (9 RCTs)	Arthralgia: SMD = –0.38 (–0.61 to –0.15); Myalgia: SMD = –0.85 (–1.68 to –0.01)	Pain reduction greater in arthralgia; myalgia results highly heterogeneous	★★◯◯ Low	Patients with arthralgia may benefit more consistently from pharmacological therapy than those with myalgia.	Arthralgia may respond better due to clearer inflammatory mechanisms; myalgia remains multifactorial.

ventions (Figure 7, Figure 8.(A) – 8.(F), Table 4). The effect was more pronounced in studies with participants aged 40 years or older (SMD = 1.33; 95% CI: 1.02 to 1.64; p < 0.001) as well as in those investigating conservative interventions (SMD = 0.98; 95% CI: 0.47 to 1.49; p = 0.075).

cija [slika 7., slika 8.(A) – 8.(F), tablica 4]. Učinak je bio izraženiji u studijama sa sudionicima u dobi od 40 godina ili starijima (SMD = 1,33; 95% CI: 1,02 do 1,64; p < 0,001), te u onima u kojima su se istraživale konzervativne intervencije (SMD = 0,98; 95 % CI: 0,47 do 1,49; p = 0,075).

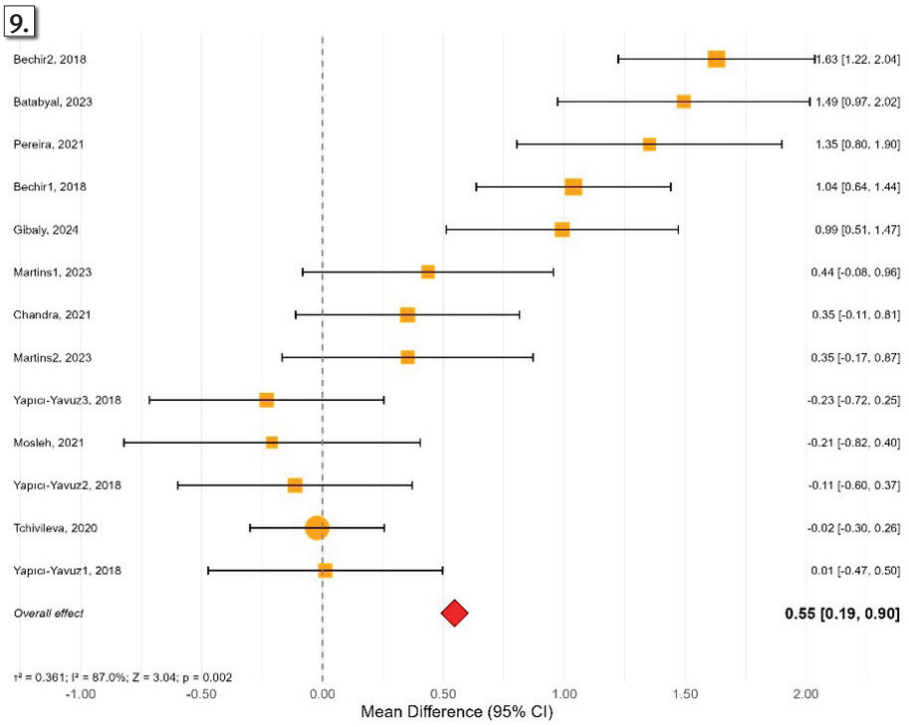


Figure 9 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the maximum interincisal opening outcome without the high-risk studies, after Rob2 analysis.

Slika 9. Dijagram standardiziranih srednjih razlika (SMD) i 95 % intervala pouzdanosti za ishod maksimalnoga interincizalnog otvaranja bez studija visokog rizika, nakon analize Rob2

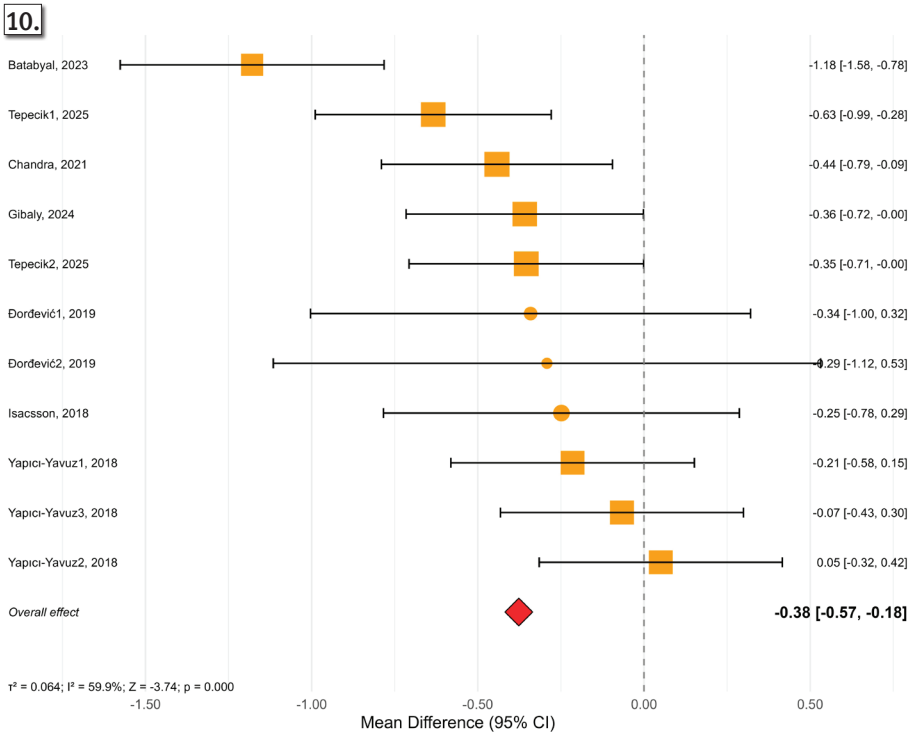


Figure 10 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the VAS scale (arthralgia only-studies)

Slika 10. Dijagram standardiziranih srednjih razlika (SMD) i 95% intervala pouzdanosti za VAS ljestvicu (studije samo o artralgiji)

In other subgroup categories, such as TMD scale, sex, pain type, and geographic region, no significant differences were observed. Study heterogeneity was again extremely high (I^2 = 87, 9%), but subgroup analysis explained some of it. The treatment effect was statistically significant for the TMD scale, age, and country groups regarding MIO evaluation.

U drugim kategorijama podskupina, kao što su TMD ljestvica, spol, vrsta bolova i geografska regija, nisu uočene značajne razlike. Heterogenost studije ponovno je bila iznimno visoka (I^2 = 87,9 %), ali analiza podskupina djelomično je objasnila tu različitost. Učinak liječenja bio je statistički značajan za TMD ljestvicu, dob i skupine zemalja, kad je riječ o procjeni MIO-a.

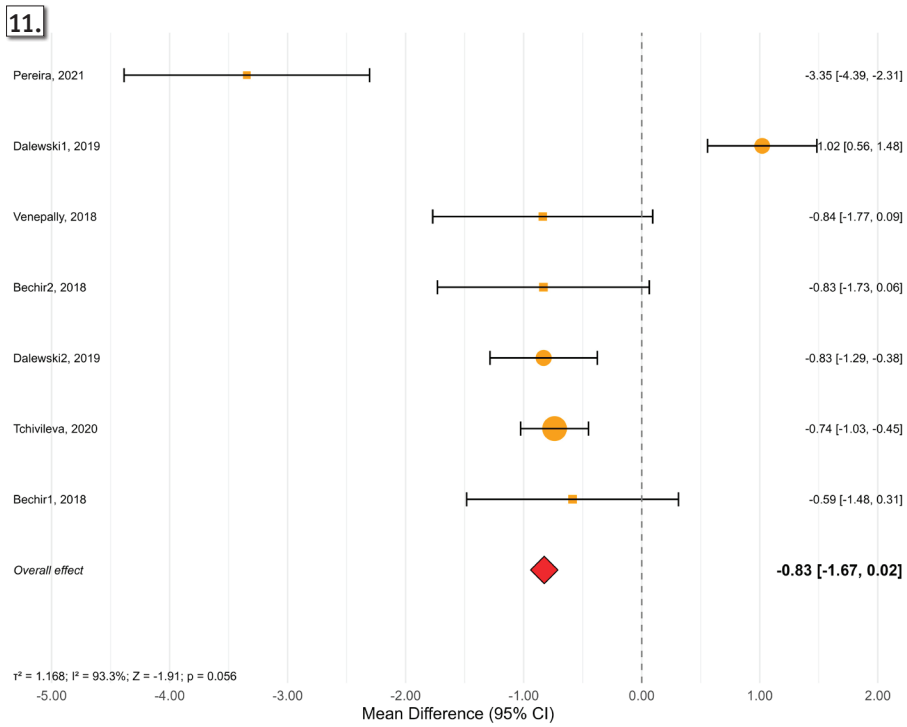


Figure 11 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the VAS scale (myalgia only-studies)

Slika 11. Dijagram standardiziranih srednjih razlika (SMD) i 95% intervala pouzdanosti za VAS ljestvicu (studije samo o mialgiji)

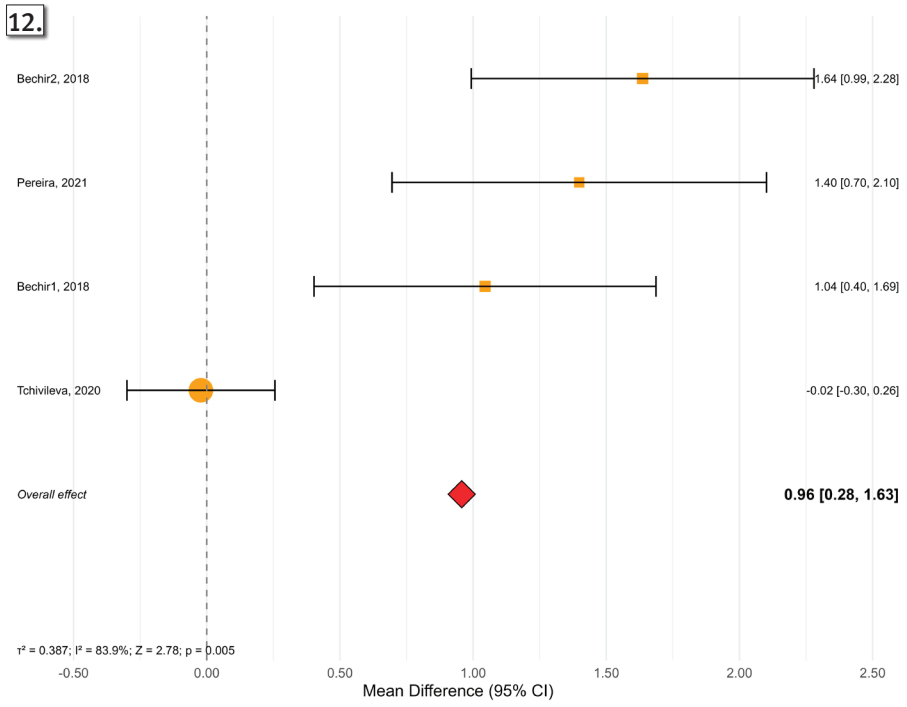


Figure 12 Forest plot of standardized mean differences (SMD) and 95% confidence intervals for the maximum interincisal opening outcome (myalgia only-studies)

Slika 12. Dijagram standardiziranih srednjih razlika (SMD) i 95% intervala pouzdanosti za ishod maksimalnog interincizalnog otvaranja (studije samo o mialgiji)

Regarding the TMD diagnostic scale, the use of the Wilkes Classification was associated with a significant increase in maximum interincisal opening (SMD = 0.57; 95% CI: 0.16 to 0.98, I^2 = 72.4).

In terms of age, there was a significant increase in maximum interincisal opening in participants aged 40 years or older (SMD = 1.33; 95% CI: 1.02 to 1.64, I^2 = 42.4). For the country group division, studies conducted in Brazil (SMD = 0.70; 95% CI: 0.20 to 1.20, I^2 = 66.8) also reported a signif-

Što se tiče dijagnostičke ljestvice TMD-a, korištenje Wilkesove klasifikacije bilo je povezano sa značajnim povećanjem maksimalnoga interincizalnog otvaranja (SMD = 0,57; 95 % CI: 0,16 do 0,98, I^2 = 72,4).

U vezi s dobi dogodilo se značajno povećanje maksimalnoga interincizalnog otvaranja kod sudionika u dobi od 40 godina ili više (SMD = 1,33; 95 % CI: 1,02 do 1,64, I^2 = 42,4). Što se tiče podjele po skupinama zemalja, autori studija provedenih u Brazilu (SMD = 0,70; 95 % CI: 0,20 do

icant increase in maximum interincisal opening, while the other groups showed high heterogeneity.

The global effect for the MIO outcome, excluding high-risk studies, yields similar values (Figure 9).

Additional subgroup meta-analyses were performed separately for studies enrolling exclusively patients with arthralgia and those limited to myalgia.

Pain and MIO (Arthralgia-only studies)

Starting by the pain intensity, when compared with the overall pooled estimate (SMD = –0.68; 95% CI: –1.09 to –0.26, I^2 = 93.4), the magnitude of improvement in arthralgia-only studies was comparable although slightly lower (SMD = –0.38; 95% CI: –0.57 to –0.18, I^2 = 59.9), but the heterogeneity was markedly reduced, suggesting a more stable therapeutic response (Figure 10).

Among the trials restricted to arthralgia, pharmacological interventions showed a consistent and more homogeneous benefit compared with the global estimates (Table 6). Conservative treatments achieved a significant though modest reduction (SMD = –0.34; 95% CI: –0.64 to –0.05; I^2 = 0.00), while less invasive, such as intra-articular injection of drugs approaches, produced larger and clinically relevant effects (SMD = –0.64; 95% CI: –0.94 to –0.34; I^2 = 6.40). In contrast, surgical or combined procedures yielded negligible benefit (SMD = –0.10; 95% CI: –0.30 to 0.10, I^2 = 0.00), thus pointing to a limited additional value of invasive strategies.

Trials applying DC/TMD diagnostic criteria demonstrated significant pain improvement (SMD = –0.39; 95% CI: –0.57 to –0.21; I^2 = 0.00), whereas those using RDC/TMD did not show significant changes (SMD = –0.11; 95% CI: –0.27 to 0.05; I^2 = 0.00).

Regarding MIO, the global effect is non-significant (SMD = 0.19; 95% CI: –0.20 to 0.57, I^2 = 74.9). Less invasive interventions showed a better performance than combined with surgery however the difference was non-significant (p = 0.138). On the other hand, a sex-related difference was observed. Studies including <80% female participants exhibited a large, significant increase in MIO (SMD = 0.90; 95% CI: 0.39 to 1.41, I^2 = 66.5), compared with no measurable effect in studies including at least 80% of female participants (SMD = –0.07; 95% CI: –0.30 to 0.15, I^2 = 0.00) (Table 7).

Overall, the arthralgia-specific findings point to the fact that pharmacological treatments and minimally invasive treatments are particularly effective in reducing pain, which is consistent with the main meta-analysis but showing reduced heterogeneity.

Pain and MIO (Myalgia-only studies)

Myalgia only studies showed a significant improve of MIO (SMD = 0.96; 95% CI: 0.28 to 1.63, I^2 = 83.9) although studies were only 4 and very heterogenous (Figure 11). Because of this low number of available studies, a subgroup analysis for the MIO outcome in myalgia-only trials could not be performed. Consequently, the analysis focused exclusively on the pain outcome.

In contrast to arthralgia studies, studies restricted to my-

1,20, I^2 = 66,8) također su izvijestili o značajnom povećanju maksimalnoga interincizalnog otvaranja, a ostale skupine pokazale su visoku heterogenost.

Globalni učinak na ishod MIO-a, isključujući studije visokog rizika, daje slične vrijednosti (slika 9.).

Dodatne metaanalize podskupina provedene su odvojeno za studije koje su obuhvaćale isključivo pacijente s artralgijom i one ograničene na mijalgiju.

Bolovi i MIO (studije samo za artralgiju)

Počevši od intenziteta bolova, u usporedbi s ukupnom združenom procjenom (SMD = -0,68; 95 % CI: -1,09 do -0,26, I^2 = 93,4), veličina poboljšanja u studijama samo s artralgijom bila je usporediva, iako nešto niža (SMD = -0,38; 95 % CI: -0,57 do -0,18, I^2 = 59,9), ali heterogenost je bila znatno smanjena, što sugerira stabilniji terapijski odgovor (slika 10.).

Među tim ispitivanjima ograničenima na artralgiju, farmakološke intervencije pokazale su dosljednu i homogeniju korist u usporedbi s globalnim procjenama (tablica 6.). Konzervativne terapije postigle su značajno, iako umjereno smanjenje (SMD = -0,34; 95 % CI: -0,64 do -0,05; I^2 = 0,00), a manje invazivni pristupi, poput intraartikularne injekcije lijekova, proizveli su veće i klinički relevantne učinke (SMD = -0,64; 95 % CI: -0,94 do -0,34; I^2 = 6,40). Suprotno tomu, kirurškim ili kombiniranim postupcima postignuta je zanemariva korist (SMD = -0,10; 95 % CI: -0,30 do 0,10, I^2 = 0,00), što upućuje na ograničenu dodatnu vrijednost invazivnih strategija. Ispitivanja u kojima su se primjenjivali dijagnostički kriteriji DC/TMD pokazala su značajno poboljšanje bolova (SMD = -0,39; 95 % CI: -0,57 do -0,21; I^2 = 0,00), a ona u kojima je korišten RDC/TMD nisu pokazala značajne promjene (SMD = -0,11; 95 % CI: -0,27 do 0,05; I^2 = 0,00).

Kad je riječ o MIO-u, globalni učinak nije značajan (SMD = 0,19; 95 % CI: -0,20 do 0,57, I^2 = 74,9). Manje invazivne intervencije pokazale su bolju učinkovitost nego u kombinaciji s kirurškim zahvatom, ali razlika nije bila značajna (p = 0,138). S druge strane, uočena je razlika povezana sa spolom. U studijama u kojima je sudjelovalo < 80 % žena zabilježeno je veliko, značajno povećanje MIO-a (SMD = 0,90; 95 % CI: 0,39 do 1,41, I^2 = 66,5), u usporedbi s time da u studijama u kojima ih je bilo uključeno najmanje 80 % nije bilo mjerljivog učinka (SMD = 0,07; 95m% CI: -0,30 do 0,15, I^2 = 0,00) (tablica 7.).

Općenito, ti nalazi specifični za artralgiju potvrđuju da su farmakološka i minimalno invazivna terapija posebno učinkovite u smanjenju bolova, što je u skladu s glavnom metaanalizom, ali pokazuju smanjenu heterogenost.

Bol i MIO (studije samo za mijalgiju)

U studijama u kojima su se autori bavili samo mijalgijom uočeno je značajno poboljšanje MIO-a (SMD = 0,96; 95 % CI: 0,28 do 1,63, I^2 = 83,9), iako su bile samo četiri i bile su vrlo heterogene (slika 11). Zbog malog broja dostupnih studija, analiza podskupina za ishod MIO-a u ispitivanjima samo s mijalgijom nije se mogla provesti. Posljedično, analiza se usredotočila isključivo na ishod bolova.

Za razliku od studija o artralgiji, studije ograničene na

Table 6 Subgroup analysis of pain by VAS_Arthralgia_only
Tablica 6. Podskupinska analiza boli prema VAS_samo_artralgija

	Number of studies	I^2(%)	Cohen's *d* (95% CI)	p-value
Intervention				
Conservative	3	0.00	-0.34 (-0.64,-0.05)	**0.019**
Less Invasive	4	6.40	-0.64 (-0.94,-0.34)	
Surgery + Less Invasive	4	0.00	-0.10 (-0.30,0.10)	
Type of intervention				
Intra-articular injection of drugs	4	6.40	-0.64 (-0.94,-0.34)	**0.015**
Surgery + Intra-articular injection of drugs	3	0.00	-0.08 (-0.29,0.13)	
Active Principle				
Factor Rich Plasma	3	73.3	-0.65 (-1.06,-0.24)	0.068
Others	6	32.1	-0.25 (-0.44,-0.06)	
TMD Scale				
DC/TMD	3	0.00	-0.39 (-0.57,-0.21)	**0.029**
RDC/TMD	3	0.00	-0.11 (-0.27,0.05)	
Sex				
<80% Female (1)	3	7.30	-0.65 (-1.06,-0.24)	0.055
>=80% Female (2)	8	2.15	-0.26 (-0.43,-0.08)	
Group of countries				
Europe + USA	3	0.00	-0.29 (-0.66,0.09)	0.84
Muslims	6	17.5	-0.24 (-0.36,-0.13)	

Table 7 Subgroup analysis of MIO_Arthralgia_only
Tablica 7. Podskupinska analiza samo_mialgije

	Number of studies	I^2(%)	Cohen's *d* (95% CI)	p-value
Intervention				
Less Invasive	4	80.4	0.42 (-0.15,0.99)	0.138
Surgery + Less Invasive	3	00.0	-0.12 (-0.42,0.17)	
Sex				
<80% Female	3	66.5	0.90 (0.39,1.41)	**0.001**
>=80% Female	5	0.00	-0.07 (-0.30,0.15)	

Table 8 Subgroup analysis of pain by VAS_Myalgia_only
Tablica 8. Podskupinska analiza boli prema VAS_samo_mialgija

	Number of studies	I^2(%)	Cohen's *d* (95% CI)	p-value
Age				
<40 years	4	91.3	-0.33 (-1.12,0.47)	0.135
>=40 years	3	84.6	-1.56 (-2.95,-0.17)	
Sex				
<80% Female	4	0.00	-0.74 (-0.99,-0.49)	0.90
>=80% Female	3	97.2	-1.00 (-2.99,0.99)	

algia displayed more variable and heterogeneous pain results (Figure 12), mirroring the high heterogeneity observed in the overall pooled analysis. The overall effect for the myalgia trials was non- significant (SMD = -0.83; 95% CI: –1.67 to 0.02, I^2 = 87.9). Subgroup analysis did not reveal any significant differences related to age (p = 0.135) and sex (p = 0.90) (Table 8).

mijalgiju pokazale su varijabilnije i heterogenije rezultate kad je riječ o bolovima (slika 12.), što odražava visoku heterogenost uočenu u ukupnoj združenoj analizi. Ukupni učinak za ispitivanja mijalgije bio je beznačajan (SMD = -0,83; 95 % CI: -1,67 do 0,02, I^2 = 87,9). Analiza podskupina nije otkrila nikakve značajne razlike povezane s dobi (p = 0,135) i spolom (p = 0,90) (tablica 8.).

Discussion

This systematic review with meta-analysis synthesized evidence from 17 randomized controlled trials (25 treatment arms) assessing pharmacological interventions for myalgia related to temporomandibular disorders (TMD). The review included all pharmacological interventions reported in the literature, irrespective of the route of administration, focusing on the active substance rather than the delivery method.

Pharmacological therapy was associated with a statistically significant reduction in pain (SMD = –0.68; 95% CI: –1.09 to –0.26) and improvement in maximum interincisal opening (MIO) (SMD = 0.51; 95% CI: 0.20 to 0.82). Subgroup analyses suggested greater efficacy in patients with arthralgia, in participants ≥40 years, and for specific drug classes (platelet-rich factors and corticosteroids). Conservative interventions consistently demonstrated beneficial effects, whereas surgical interventions did not provide significant additional benefit and should be reserved for refractory cases (10).

The included studies evaluated a broad range of pharmacological agents, including NSAIDs, corticosteroids, muscle relaxants, antidepressants, platelet-rich factors, and intra-articular injectables. However, heterogeneity across studies was very high, mainly due to differences in diagnostic criteria (DC/TMD vs. Wilkes vs. RDC/TMD), outcome measures, treatment protocols, and follow-up periods. The high heterogeneity limited the interpretation of the overall estimate, however, subgroup analysis allowed us to control for this factor. The evidence is therefore most applicable to adult populations with clinically diagnosed myalgia or arthralgia, but less generalizable to pediatric or elderly populations where data remain sparse.

Only few placebo-controlled trials were available, but using active comparators is not a weaker design, it is often a more rigorous benchmark, as therapies must show benefit beyond accepted treatments rather than placebo (60-61). Although heterogeneity was high, this was expected from differences in diagnoses, populations and interventions; subgroup analyses showed clearer pain reduction with moderate heterogeneity in arthralgia (I^2 = 44.7%), while myalgia studies were more variable.

Risk of bias assessment showed that only 4 studies were at low risk, with most judged as having "some concerns," and 3 at high risk. Common methodological limitations included small sample sizes, lack of blinding, inadequate allocation concealment, and heterogeneity in diagnostic classification. The certainty of the evidence, therefore, ranges from low to moderate according to GRADE criteria, limiting confidence in the observed effect sizes (Table 5) (62).

A comprehensive search was performed across multiple databases, and grey literature was partially explored via Google Scholar. Funnel plots did not reveal any evidence of publication bias. Nonetheless, the possibility of missing unpublished negative trials cannot be excluded. Furthermore, the inclusion of multi-arm studies may have introduced some unit-of-analysis issues, although these were handled using multilevel models where possible.

Rasprava

U ovom sistematiziranom pregledu s metaanalizom sintetizirani su dokazi iz 17 randomiziranih kontroliranih istraživanja (25 skupina liječenja) u kojima su se procjenjivale farmakološke intervencije za mijalgiju povezanu s temporomandibularnim poremećajima (TMD). Pregled je uključivao sve farmakološke intervencije prijavljene u literaturi, bez obzira na put primjene, s naglaskom na djelatnu tvar, a ne na način aplikacije.

Farmakološka terapija bila je povezana sa statistički značajnim smanjenjem bolova (SMD = -0,68; 95 % CI: -1,09 do -0,26) i poboljšanjem maksimalnoga interincizalnog otvaranja (MIO) (SMD = 0,51; 95 % CI: 0,20 do 0,82). Analize podskupina sugerirale su veću učinkovitost kod pacijenata s artralgijom, kod sudionika ≥ 40 godina i za specifične vrste lijekova (faktori bogati trombocitima i kortikosteroidi). Konzervativne intervencije dosljedno su bile blagotvorne, a kirurške nisu pružile značajnu dodatnu korist i trebale bi se koristiti samo za refraktorne slučajeve (10).

U uključenim studijama procijenjen je širok raspon farmakoloških sredstava, uključujući NSAID-e, kortikosteroide, mišićne relaksante, antidepresive, faktore bogate trombocitima i intraartikularne injekcije. No heterogenost među studijama bila je vrlo visoka, uglavnom zbog razlika u dijagnostičkim kriterijima (DC/TMD vs. Wilkes vs. RDC/TMD), ishodima, protokolima liječenja i razdobljima praćenja. Visoka heterogenost ograničila je interpretaciju ukupne procjene, no analiza podskupina omogućila nam je kontrolu toga faktora. Dokazi su stoga najprimjenjiviji na odraslu populaciju s klinički dijagnosticiranom mijalgijom ili artralgijom, ali manje generalizirani na pedijatrijske ili starije populacije gdje su podatci i dalje rijetki.

Bilo je dostupno samo nekoliko istraživanja kontroliranih placebom, ali korištenje aktivnih kontrolnih skupina nije lošiji dizajn, nego je često rigoroznija referentna vrijednost jer terapije moraju pokazati korist izvan prihvaćenih terapija, a ne placebo (60 – 61). Iako je heterogenost bila visoka, to se očekivalo zbog razlika u dijagnozama, populacijama i intervencijama; analize podskupina pokazale su jasnije smanjenje bolova s umjerenom heterogenošću u artralgiji (I^2 = 44,7 %), a studije o mijalgiji bile su varijabilnije.

Procjena rizika od pristranosti pokazala je da je samo u četiri studije rizik bio nizak, pri čemu je većina ocijenjena kao da ima *neke nedoumice*, a tri su smatrane visokorizičnima. Uobičajena metodološka ograničenja uključivala su male uzorke, nedostatak zaslijepljivanja, neadekvatno prikrivanje alokacije i heterogenost u dijagnostičkoj klasifikaciji. Sigurnost dokaza zato se kreće od niske do umjerene prema kriterijima GRADE, što ograničava pouzdanost u uočene veličine učinka (tablica 5.) (62).

Provedeno je sveobuhvatno pretraživanje više baza podataka, a siva literatura djelomično je istražena putem Googleova Scholara. Ljevkasti dijagrami nisu otkrili dokaze o pristranosti publikacija. Ipak, ne može se isključiti mogućnost da se propuste neobjavljena negativna ispitivanja. Nadalje, uključivanje studija s više krakova moglo je prouzročiti

Our findings align with previous reviews. The Cochrane Review on pharmacological interventions for persistent TMD pain (2021) (8), highlighted insufficient evidence, while more recent reviews (e.g., Christidis et al., 2024) (17) suggested potential benefit for botulinum toxin and muscle relaxants in myogenous TMD. The present synthesis corroborates the role of corticosteroids, particularly in arthralgia, while reinforcing the limited efficacy of surgical approaches (10). Regarding platelet-rich factors, there were heterogeneous outcomes across trials, with both positive and null effects reported. Therefore, the evidence should not be interpreted as uniformly favorable, but rather as preliminary and requiring further high-quality investigation (63). These findings are consistent with the 2024 INfORM/IADR consensus, which emphasized conservative management as first-line and pharmacological interventions as adjunctive strategies (7, 64-66).

Further subgroup analyses restricted to studies enrolling exclusively patients with arthralgia or myalgia provided additional insights into the differential therapeutic response across TMD phenotypes.

In arthralgia-only studies, pain reduction was significant and more consistent (SMD = –0.38) compared with the overall pooled estimate, accompanied by markedly reduced heterogeneity. This suggests that when patient populations are clinically homogeneous and joint-related mechanisms predominate, pharmacological and minimally invasive interventions yield a more stable and predictable therapeutic response. These findings are in agreement with previous evidence indicating a stronger and more reproducible benefit of pharmacological therapies in TMD-A (17, 67). Conservative and intra-articular pharmacological approaches achieved significant pain reduction, while surgical or combined procedures offered negligible benefit, reinforcing that invasive strategies provide little additional value beyond conservative or minimally invasive management (68).

In contrast, myalgia-only studies revealed more variable and heterogeneous pain outcomes (SMD = –0.83; 95% CI: –1.67 to 0.02; I^2 = 87.9), mirroring the high heterogeneity observed in the global analysis. The limited number of available trials and methodological variability, particularly regarding diagnostic criteria, follow-up duration, and intervention type, likely contributed to this inconsistency. Unlike arthralgia, where nociceptive mechanisms are predominantly peripheral, myalgia may involve central sensitization and psychosocial factors, which can attenuate pharmacological responsiveness and explain the wide dispersion of results (69-70).

Regarding mandibular function, the overall MIO improvement was not significant in arthralgia studies, though a marked increase was observed in studies including less than 80% female participants, suggesting potential sex-related modulation of therapeutic response. Conversely, myalgia-only studies demonstrated a significant increase in MIO, although based on only four highly heterogeneous trials. This may indicate that functional recovery is more perceptible in muscular conditions, even when pain relief is inconsistent (10, 47, 49).

probleme s jedinicama analize, iako su oni obrađeni korištenjem višerazinskih modela gdje je to bilo moguće.

Naši nalazi u skladu su s dosadašnjim pregledima. U Cochraneovu pregledu farmakoloških intervencija za perzistentnu bol TMD-a (2021.) (8) istaknuto je da nema dovoljno dokaza, a u novijima se (npr., Christidis i sur., 2024.) (17) sugerira potencijalna korist toksina botulinuma i mišićnih relaksanata u slučaju miogenoga TMD-a. Ova sinteza potvrđuje ulogu kortikosteroida, posebno u slučaju artralgije, a istodobno pojačava ograničenu učinkovitost kirurških pristupa (10). Kad je riječ o faktorima bogatima trombocitima, u ispitivanjima su rezultati bilu heterogeni, sa zabilježenim pozitivnim i nultim učincima. Stoga se dokazi ne bi trebali tumačiti kao jednoobrazno povoljni, nego kao preliminarni te zahtijevaju daljnja visokokvalitetna istraživanja (63). Ti nalazi u skladu su s konsenzusom INfORM/IADR iz 2024. u kojemu je istaknuto konzervativno liječenje kao prva linija i farmakološke intervencije kao dodatne strategije (7, 64 – 66).

Daljnje analize podskupina ograničene na studije u kojima su sudjelovali isključivo pacijenti s artralgijom ili mijalgijom te su pružile dodatni uvid u diferencijalni terapijski odgovor kod različitih fenotipova TMD-a.

U studijama u kojima su se autori bavili samo artralgijom, smanjenje bolova bilo je značajno i konzistentnije (SMD = -0,38) u usporedbi s ukupnom združenom procjenom, uz značajno smanjenu heterogenost. To sugerira da, kada su populacije pacijenata klinički homogene i prevladavaju mehanizmi povezani sa zglobovima, farmakološke i minimalno invazivne intervencije daju stabilniji i predvidljiviji terapijski odgovor. Ti nalazi u skladu su s dosadašnjim dokazima koji upućuju na jaču i obnovljivu korist od farmakoloških terapija u slučaju TMD-a (17, 67). Konzervativnim i intraartikularnim farmakološkim pristupima postignuto je značajno smanjenje bolova, a kirurški ili kombinirani postupci ponudili su zanemarivu korist, što potvrđuje da invazivne strategije pružaju malo dodatne vrijednosti, osim konzervativnoga ili minimalno invazivnoga liječenja (68).

Suprotno tomu, autori studija samo o mijalgiji otkrili su varijabilnije i heterogenije ishode bolova (SMD = -0,83; 95% CI: -1,67 do 0,02; I^2 = 87,9), što odražava visoku heterogenost uočenu u globalnoj analizi. Ograničeni broj dostupnih istraživanja i metodološka varijabilnost, posebno kad je riječ o dijagnostičkim kriterijima, trajanju praćenja i vrstama intervencija, vjerojatno su pridonijeli toj nedosljednosti. Za razliku od artralgije u kojoj su nociceptivni mehanizmi pretežno periferni, mijalgija može uključivati centralnu senzibilizaciju i psihosocijalne čimbenike, što može oslabiti farmakološki odgovor i objasniti široku disperziju rezultata (69 – 70).

Što se tiče funkcije mandibule, ukupno poboljšanje MIO-a nije bilo značajno u studijama o artralgiji, iako je uočen značajan porast u studijama u kojima je sudjelovalo manje od 80 % žena, što sugerira potencijalnu modulaciju terapijskog odgovora povezanu sa spolom. Suprotno tomu, u studijama samo o mijalgiji pokazan je značajan porast MIO-a, iako se temeljio samo na četiri vrlo heterogena ispitivanja. To može upućivati na to da je funkcionalni oporavak uočlji-

Taken together, these findings highlight that the underlying pathology, arthralgia or myalgia, strongly influences treatment response. Pharmacological and minimally invasive therapies are more consistently effective in arthralgia, whereas the variability seen in myalgia underscores the need for individualized and multimodal approaches. This supports the importance of accurate diagnostic stratification and standardized criteria to improve comparability across studies (10, 17).

Current evidence supports the use of pharmacological interventions, particularly corticosteroids, as effective adjuncts to conservative therapy in managing TMD-related myalgia and arthralgia (67). However, pharmacological treatment should not replace assisted self-management and conservative approaches, which remain the cornerstone of care (10, 71-72). Surgical procedures should be reserved for rare, refractory cases with clearly defined indications (10, 73).

Implications for research

Future randomized controlled trials should: adopt standardized diagnostic criteria (DC/TMD) and outcome measures (VAS for pain, MIO in mm); include larger, more representative populations, including older adults and under-represented regions; compare different pharmacological agents head-to-head to identify optimal regimens; incorporate longer follow-up to evaluate sustained efficacy and safety; integrate patient-centered outcomes such as quality of life and functional impact.

Clinical implications for practice and quality of the evidence

The present evidence supports the use of pharmacological therapy as an effective adjunct to conservative management for temporomandibular disorders, particularly in cases of arthralgia, where the pooled analysis showed a significant and consistent reduction in pain (SMD = –0.38; 95% CI: –0.57 to –0.18) and moderate improvement in mandibular function, with lower heterogeneity. In contrast, studies limited to myalgia demonstrated highly variable results and wide confidence intervals, yielding no statistically significant reduction in pain, although a functional improvement in maximum interincisal opening was observed. Overall, pharmacological interventions—including corticosteroids and platelet-rich factors—showed moderate to high benefit when combined with conservative therapy, whereas surgical or combined invasive approaches provided limited additional value. The quality of the evidence ranges from low to moderate, mainly due to small sample sizes, methodological heterogeneity, and limited blinding across trials. Consequently, pharmacological treatment should be individualized, short-term, and reserved as an adjunct to evidence-based conservative management, which remains the cornerstone of care in both myalgia and arthralgia.

Conclusion

The meta-analysis demonstrates that pharmacological interventions, when used as adjuncts to conservative management, produce a moderate overall benefit in pain reduction and

viji kod mišićnih stanja, čak i kada je ublažavanje bolova nedosljedno (10, 47, 49).

Uzevši sve u obzir, ovi nalazi pokazuju da temeljna patologija – artralgija ili mijalgija – snažno utječe na odgovor na liječenje. Farmakološke i minimalno invazivne terapije dosljednije su učinkovite u slučaju artralgije, a varijabilnost uočena kod mijalgije pokazuje da su potrebni individualizirani i multimodalni pristupi. To podupire važnost točne dijagnostičke stratifikacije i standardiziranih kriterija za poboljšanje usporedivosti među studijama (10, 17).

Trenutačni dokazi podupiru farmakološke intervencije, posebno kortikosteroida kao učinkovitih dodataka konzervativnoj terapiji u liječenju mijalgije i artralgije kada su povezane s temporomandibularnim poremećajem (TMD) (67). No farmakološko liječenje ne bi trebalo zamijeniti potpomognuto samoupravljanje i konzervativne pristupe koji ostaju temelj skrbi (10, 71 – 72). Kirurški postupci trebali bi biti rezervirani za rijetke, refraktorne slučajeve s jasno definiranim indikacijama (10, 73).

Implikacije za istraživanja

Buduća randomizirana kontrolirana istraživanja trebala bi usvojiti standardizirane dijagnostičke kriterije (DC/TMD) i mjere ishoda (VAS za bol, MIO u mm), obuhvatiti veće, reprezentativnije populacije, uključujući starije odrasle osobe i nedovoljno zastupljene regije, zatim usporediti različite farmakološke agense da bi se identificirali optimalni režimi, uključiti dulje praćenje da bi se procijenila održiva učinkovitost i sigurnost te integrirati ishode usmjerene na pacijenta kao što su kvaliteta života i funkcionalnost.

Kliničke implikacije za praksu i kvaliteta dokaza

Sadašnji dokazi podupiru upotrebu farmakološke terapije kao učinkovitoga dodatka konzervativnom liječenju temporomandibularnih poremećaja, posebno u slučaju artralgije u kojoj je združena analiza pokazala značajno i dosljedno smanjenje bolova (SMD = -0,38; 95 % CI: -0,57 do -0,18) i umjereno poboljšanje mandibularne funkcije, s manjom heterogenošću. Suprotno tomu, u studijama ograničenima na mijalgiju dobiveni su vrlo varijabilni rezultati i široki intervali pouzdanosti, bez statistički značajno smanjenih bolova, iako je uočeno funkcionalno poboljšanje maksimalnoga interincizalnog otvaranja. Sveukupno, farmakološke intervencije, uključujući kortikosteroide i faktore bogate trombocitima, pokazale su umjerenu do visoku korist u kombinaciji s konzervativnom terapijom, a kirurški ili kombinirani invazivni pristupi pružili su ograničenu dodatnu vrijednost. Kvaliteta dokaza kreće se od niske do umjerene, uglavnom zbog malog uzorka, metodološke heterogenosti i ograničenog zasljepljivanja u ispitivanjima. Slijedom toga, farmakološko liječenje treba biti individualizirano, kratkoročno i rezervirano kao dodatak konzervativnom liječenju temeljenom na dokazima koje ostaje temelj skrbi i za mijalgiju i za artralgiju.

Zaključak

Metaanaliza pokazuje da farmakološke intervencije, kada se koriste kao dodatak konzervativnom liječenju, umjereno su korisne u smanjenju bolova i u funkcionalnom poboljš-

functional improvement in temporomandibular disorders. Evidence is stronger and more consistent for arthralgia, indicating a predictable therapeutic response and lower heterogeneity, whereas myalgia shows greater variability and limited pain reduction, likely reflecting multifactorial and centrally mediated mechanisms. Intra-articular and minimally invasive pharmacological strategies yield the most reproducible outcomes, while surgical interventions provide little additional benefit. The overall certainty of the evidence is low to moderate due to heterogeneity, small sample sizes, and methodological limitations. Further standardized, high-quality randomized controlled trials are required to confirm these findings and to refine phenotype-specific therapeutic recommendations. Factors such as age and geographical context had an impact on therapeutic outcomes, thus highlighting the importance of the clinical and sociocultural context in treatment response.

Conflicts of interest: The authors declare no conflict of interest.

Acknowledgements: This research is supported by the Research Unit of the Center for Statistics and Applications of the University of Lisbon (CEAUL) under the project FCT – Foundation for Science and Technology UIDB/00006/2025 (https://doi.org/10.54499/UIDB/00006/2020). This research is supported by the Dental Forensic Sciences Research Group (FORENSEMED) integrated part of the Oral and Biomedical Sciences Research Unit (UICOB) at Faculty of Dental Medicine of the University of Lisbon. The authors would like to thank Ana Rodrigues, Rui Santos, Francisco Salvado and Francisco Coutinho for their valuable contributions and support during the development of the PROSPERO-registered protocol "Pharmacological Recommendations for management myalgia related to Temporomandibular Disorders: a systematic review with meta-analysis" (PROSPERO 2024, CRD42024554300, available at: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024554300

Author's Contribution: **C.P.P.** - Study Conception and Design; **B.S.**- Data Collection; **J.P.M., C.P.P.** - Analysis and Interpretation of results; **J.P.M., C.P.P., B.S.** -Draft Manuscript preparation. All authors reviewed the results and approved the final version of the manuscript.

šanju temporomandibularnih poremećaja. Dokazi su jači i dosljedniji za artralgiju, što upućuje na predvidljiv terapijski odgovor i manju heterogenost, a mijalgija pokazuje veću varijabilnost i ograničeno smanjenje bolova, vjerojatno odražavajući multifaktorijalne i centralno posredovane mehanizme. Intraartikularne i minimalno invazivne farmakološke strategije daju najponovljivije ishode, a kirurške intervencije daju malo dodatne koristi. Ukupna sigurnost dokaza niska je do umjerena zbog heterogenosti, malog uzorka i metodoloških ograničenja. Potrebna su daljnja standardizirana, visokokvalitetna randomizirana kontrolirana istraživanja kako bi se potvrdili ovi nalazi i poboljšale terapijske preporuke specifične za fenotip. Čimbenici poput dobi i geografskog konteksta utjecali su na terapijske ishode, ističući važnost kliničkoga i sociokulturnoga konteksta u odgovoru na liječenje.

Sukob interesa: Autori nisu bili u sukobu interesa.

Zahvala: Ovo istraživanje podržala je Istraživačka jedinica Centra za statistiku i primjenu Sveučilišta u Lisabonu (CEAUL) u sklopu projekta FCT – Zaklada za znanost i tehnologiju UIDB/00006/2025 (https://doi.org/10.54499/UIDB/00006/2020). Također ga je poduprla Istraživačka skupina za dentalne forenzičke znanosti (FORENSEMED), integrirani dio Istraživačke jedinice za oralne i biomedicinske znanosti (UICOB) na Stomatološkom fakultetu Sveučilišta u Lisabonu. Autori zahvaljuju Ani Rodrigues, Ruiju Santosu, Franciscu Salvadu i Franciscu Coutinhu na njihovu vrijednom doprinosu i potpori tijekom razrade protokola registriranog kod PROSPERO-a – *Farmakološke preporuke za liječenje mijalgije povezane s temporomandibularnim poremećajima: sustavni pregled s metaanalizom* (PROSPERO 2024, CRD42024554300, dostupno na: https://www.crd.york.ac.uk/PROSPERO/view/CRD42024554300.

Doprinos autora: **C. P. P.** – koncept i studijski dizajn; **B. S.** – prikupljanje podataka; **J. P. M., C. P. P.** – analiza i interpretacija rezultata; **J. P. M., C. P. P., B. S.** – priprema nacrta teksta. Svi su autori pregledali rezultate i odobrili konačnu verziju teksta.

Sažetak

Uvod: Temporomandibularni poremećaji (TMD) obuhvaćaju skup stanja koja utječu na žvačne mišiće i temporomandibularni zglob (TMZ) te na funkcionalnost i kvalitetu života pojedinaca. Mijalgija je dijagnoza TMD-a s multifaktorijalnom etiologijom, a strategije liječenja ponajprije su usmjerene na ublažavanje bolova i vraćanje funkcije. Farmakološka terapija dopunjuje konzervativne mjere i obično se smatra drugom linijom liječenja. **Svrha rada:** Istražujući različite učinke među podtipovima TMD-a na temelju podskupinskih analiza, te koristeći se sistematiziranim pregledom i metaanalizom randomiziranih kontroliranih istraživanja (RCT), željela se kod adolescenata i odraslih procijeniti učinkovitost farmakoloških intervencija u liječenju mijalgije povezane s temporomandibularnim poremećajima. **Materijali i metode:** Sistematizirani pregled s metaanalizom proveden je u skladu s Cochraneovim priručnikom za sistematizirane preglede intervencija i objavljen je nakon izjave PRISMA 2020. Uključeno je sedamnaest randomiziranih kontroliranih istraživanja (RCT) objavljenih između 2018. i 2024. godine. Farmakološke intervencije, poput nesteroidnih protuupalnih lijekova, kortikosteroida, mišićnih relaksanata, antidepresiva i intraartikularnih injekcija, uspoređene su s placebom ili drugim aktivnim terapijama. Primarni ishodi bili su intenzitet bolova (vizualna analogna ljestvica — VAS) i maksimalno interincizalno otvaranje (MIO) bez pomoći. **Rezultati :** Ukupno je analizirano 1128 sudionika u 25 skupina liječenja. Farmakološke intervencije bile su povezane sa značajnim smanjenjem bolova (SMD = -0,68; 95 % CI: -1,09 do -0,26; p < 0,001) i poboljšanjem MIO-a (SMD = 0,51; 95 % CI: 0,20 do 0,82; p < 0,001). Analize podskupina pokazale su da su intervencije bile dosljednije i učinkovitije u populacijama samo s artralgijom jer su pokazivale manju heterogenost i predvidljiviji terapijski odgovor, a u populacijama samo s mijalgijom postignute su manje dosljedne koristi. Konzervativne terapije pokazale su dosljednu prednost, što je u skladu s međunarodnim preporukama koje daju prioritet takvim pristupima. **Zaključak:** Farmakološka terapija ukupno umjereno i blagotvorno smanjuje bolove i poboljšava funkciju mandibule u slučaju temporomandibularnog poremećaja (TMD), s jačim i dosljednijim dokazima u populacijama s dominantnom artralgijom, a ishodi povezani s mijalgijom ostaju varijabilniji, što pokazuje da su potrebne prilagođene strategije liječenja.

Zaprimljen: 28. listopada 2025.
Prihvaćen: 9. siječnja 2026.

Adresa za dopisivanje
Cristiana Palmela Pereira
Faculdade de Medicina Dentária da Universidade de Lisboa
Cidade Universitária, Rua Professora Teresa Ambrósio
1600-277 Lisboa, Portugal
cpereira@edu.ulisboa.pt

MeSH pojmovi: poremećaji čeljusnog zgloba; žvačni mišići; mijalgija; artralgija, davanje lijeka unutar zgloba; antidepresivi; hormoni nadbubrežne žlijezde
Autorske ključne riječi: temporomandibularni poremećaji, mijalgija, artralgija, farmakološka terapija, protuupalni lijekovi, mišićni relaksanti

References

1. Mujakperuo HR, Watson M, Morrison R, Macfarlane TV. Pharmacological interventions for pain in patients with temporomandibular disorders. Cochrane Database Syst Rev. 2010 Oct;(10):CD004715.
2. Minervini G, Franco R, Crimi S, Di Blasio M, D'Amico C, Ronsivalle V, et al. Pharmacological therapy in the management of temporomandibular disorders and orofacial pain: a systematic review and meta-analysis. BMC Oral Health. 2024 Dec;24(1):78.
3. Garstka AA, Kozowska L, Kijak K, Brzózka M, Gronwald H, Skomro P, et al. Accurate Diagnosis and Treatment of Painful Temporomandibular Disorders: A Literature Review Supplemented by Own Clinical Experience. Pain Res Manag. 2023 Jan; 2023:1002235.
4. Almeida LHM, Farias BL, Soares MSM, Cruz JSA, Cruz RES, Lima MG. Disfunção temporomandibular em idosos. RFO. 2008 Jan;13(1):35-8.
5. Wieckiewicz M, Shiau YY, Boening K. Pain of Temporomandibular Disorders: From Etiology to Management. Pain Res Manag. 2018 Jun; 2018:4517042.
6. Matheson EM, Fermo JD, Blackwelder RS. Temporomandibular Disorders: Rapid Evidence Review. Am Fam Physician. 2023 Jan;107(1):52-8.
7. Schiffman E, Ohrbach R, Truelove E, Look J, Anderson G, Goulet JP, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for Clinical and Research Applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group†. J Oral Facial Pain Headache. 2014 Jan;28(1):6-27.
8. Beecroft EV, Penlington C, Allison JR, Palmer J, Durham J. Pharmacological interventions for painful persistent temporomandibular disorders (TMD). Cochrane Database Syst Rev. 2021 Dec;(12):CD014919.
9. González-Sánchez B, García Monterey P, Ramírez-Durán MV, Garrido-Ardila EM, Rodríguez-Mansilla J, Jiménez-Palomares M. Temporomandibular Joint Dysfunctions: A Systematic Review of Treatment Approaches. J Clin Med. 2023 Jun;12(12):4156.
10. Manfredini D, Häggman-Henrikson B, Al Jaghsi A, Baad-Hansen L, Beecroft E, Bijelic T, et al. Temporomandibular disorders: INfORM/IADR key points for good clinical practice based on standard of care. Cranio. 2025 Jan;43(1):1-5.
11. Kulkarni S, Thambar S, Arora H. Evaluating the effectiveness of nonsteroidal anti-inflammatory drug(s) for relief of pain associated with temporomandibular joint disorders: A systematic review. Clin Exp Dent Res. 2020 Feb;6(1):134-46.
12. Nandhini J, Ramasamy S, Ramya K, Kaul R, Felix A, Austin R. Is nonsurgical management effective in temporomandibular joint disorders? A systematic review and meta-analysis. Dent Res J (Isfahan). 2018 Jul-Aug;15(4):231-41.
13. Butts R, Dunning J, Pavkovich R, Mettille J, Mourad F. Conservative management of temporomandibular dysfunction: A literature review with implications for clinical practice guidelines (Narrative review part 2). J Bodyw Mov Ther. 2017 Jul;21(3):541-8.
14. Hargreaves K, Abbott PV. Drugs for pain management in dentistry. Aust Dent J. 2005 Dec;50(4 Suppl 2): S14-23.
15. Liu F, Steinkeler A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. Dent Clin North Am. 2013 Jul;57(3):465-79.
16. Ferrillo M, Giudice A, Marotta N, Fortunato F, Di Venere D, Ammendolia A, et al. Pain Management and Rehabilitation for Central Sensitization in Temporomandibular Disorders: A Comprehensive Review. Int J Mol Sci. 2022 Oct;23(20):12164.
17. Christidis N, Al-Moraissi EA, Barjandi G, Svedenlöf J, Jasim H, Christidis M, et al. Pharmacological Treatments of Temporomandibular Disorders: A Systematic Review Including a Network Meta-Analysis. Drugs. 2024 Jan;84(1):59-81.
18. Title TT. PRISMA 2020 expanded checklist. 2021 May.
19. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane. 2024 Aug.
20. Cohen J. A coefficient of agreement for nominal scales. Educ Psychol Meas. 1960 Apr;20(1):37-46.
21. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010 Aug;36(3):1-48.
22. Gwet KL. Computing inter-rater reliability and its variance in the presence of high agreement. Br J Math Stat Psychol. 2008 May;61(1):29-48.
23. Goker F. Evaluation of arthrocentesis with hyaluronic acid injections for management of temporomandibular disorders. 2021 Jun.
24. Suresh R, Ramadoss R, Bargavi P, Sundaram M, Krishnasamy N. Formulation & Characterization of Phytochemical Based Topical Analgesic gel in Management of Myogenous Temporomandibular Joint Pain. Research Square. 2024 Aug.
25. Marrara JR, Helena M, Fernandes R, Bataglion C. Análise da medicação e possibilidade de interações medicamentosas numa amostra de doentes com dor crónica devido a disfunção temporomandibular. 2019 Aug.
26. Ritto FG, Cueto AP, dos Santos Canellas JV, Zuniga JR, Tiwana PS, Pimentel T, et al. Arthrocentesis versus nonsurgical methods in the management of temporomandibular joint closed lock and pain: a double-blind randomized controlled trial. Oral Surg Oral Med Oral Pathol Oral Radiol. 2022 Apr;133(4):369-76.
27. Jain A, Mansuri S, Perti S, Gupta B. Assessment of Temporomandibular Joint Disorders: Retrospective Study of Clinical Presentations. J Pharm Bioallied Sci. 2024 Jul.
28. Rehman F, Rehman IU, Tayyab TF, Tariq U, Amin S, Qaisarani AM. Comparison of Nonsteroidal Anti-Inflammatory Drugs and Muscle Relaxant in Patients with Temporomandibular Dysfunction. Pakistan J Med Health Sci. 2021 Sep;15(9):2745-7.
29. Farhat NB. Descriptive retrospective epidemiological study for 10 years on patients with temporo-mandibular disorders. Al-Manhal. 2019 Aug.
30. Ferreira DMAO, Raimundini AA, Bonjardim LR, Costa YM, Conti PCR, et al. Duloxetine in addition to self-management for painful temporomandibular disorders: a post hoc responder analysis of a randomized, placebo-controlled clinical trial. J Appl Oral Sci. 2024 Oct.
31. Hussain A, Ahmad R. Efficacy of transdermal diclofenac patches in the treatment of pain associated with various temporomandibular joint disorders: A comparative study. J Oral Med Oral Surg Oral Pathol Oral Radiol. 2023 Aug.
32. Akkaya G, Dağıstan S, Çağlayan F. Evaluation of the efficacy of pharmacological treatment in patients with temporomandibular joint dysfunctions using ultrasonography. J Prosthet Dent. 2024 Apr.
33. Clavero MAG, Sanz MVS, Donisa EM, Sobrino RG, Lasaga LE. Influence of the type of anesthesia on 111 arthrocentesis in temporomandibular joint disorders: Results of a prospective study. J Oral Med Oral Surg. 2022 Feb;28(1).
34. Di Giacomo P, Forte G, Capogna I, Casagrande M, Di Paolo C. The role of nutraceuticals in the management of temporomandibular disorders. J Complement Integr Med. 2024 Jul.
35. Therapeutic effect of sodium hyaluronate and corticosteroid injections on pain and temporomandibular joint dysfunction: a quasi-experimental study. Cochrane Library. 2021 Jan.
36. Tang YH, Vos LM, Tuin AJ, Slater J. Arthrocentesis versus nonsurgical intervention as initial treatment for temporomandibular joint arthralgia: a randomized controlled trial with long-term follow. Int J Oral Maxillofac Surg. 2023 Aug.
37. Tartaglia GM, Gizdulich A, Farronato M, Gupta RJ, Connelly ST. Electroporation technique for joint pain - Pilot feasibility study on TMD patients. Clin Exp Dent Res. 2020 Dec;6(6):642-9.
38. Schabrun SM, Si E, Millard SK, Chiang AKI, Chen S, Chowdhury NS, et al. Intramuscular injection of nerve growth factor as a model of temporomandibular disorder: nature, time-course, and sex differences characterising the pain experience. Neurobiol Pain. 2023 Aug;13:100117.
39. Velly AM, Anderson GC, Look JO, Riley JL, Rindal DB, Johnson K, et al. Management of painful temporomandibular disorders: Methods and overview of The National Dental Practice-Based Research Network prospective cohort study. J Am Dent Assoc. 2022 Feb;153(2):144-57.
40. Rodrigues ALP, Cardoso HJ, Ângelo DF. Patient experience and satisfaction with different temporomandibular joint treatments: A retrospective study. J Cranio-Maxillofac Surg. 2023 Jan;51(1):44-51.
41. Mori H. The Efficacy of Prolotherapy in Temporomandibular Joint Dysfunction: A Prospective Study. 2018. PMID: 33584052.
42. Haeffs TH, D'Amato LN, Khawaja SN, Keith DA, Scrivani SJ. What Variables Are Associated With the Outcome of Arthroscopic Lysis and Lavage Surgery for Internal Derangement of the Temporomandibular Joint? J Oral Maxillofac Surg. 2018 Oct;76(10):2081-8.

43. Tchivileva IE, Hadgraft H, Lim PF, Diatchenko L. Efficacy and safety of propranolol for treatment of temporomandibular disorder pain: a randomized, placebo-controlled clinical trial. Pain. 2020 Aug;161(8):1755-67.
44. Bilici IŞ, Emes Y, Aybar B, Yalçın S. Evaluation of the effects of occlusal splint, trigger point injection and arthrocentesis in the treatment of internal derangement patients with myofascial pain disorders. J Cranio-Maxillofac Surg. 2018 Jun;46(6):916-22.
45. Batabyal M. A Comparative Study between the Effects of Intra-Articular Injections of Platelet-Rich Plasma versus Corticosteroid with Local Anaesthetic in Refractory Cases of Temporomandibular Joint Disorders. Bengal J Otolaryngol Head Neck Surg. 2023 Dec;31(3):7.
46. Gibaly A, Abdelmoiz M, Alghandour AN. Evaluation of the effect of dextrose prolotherapy versus deep dry needling therapy for the treatment of temporomandibular joint anterior disc displacement with reduction: (a randomized controlled trial). Clin Oral Investig. 2024 Sep;28(9):513.
47. Isacsson G, Schumann M, Nohlert E, Mejersjö C, Tegelberg Å. Pain relief following a single-dose intra-articular injection of methylprednisolone in the temporomandibular joint arthralgia—A multicentre randomised controlled trial. J Oral Rehabil. 2019 Jan;46(1):5-13.
48. Đorđević I, Todorović A, Lazić V, Obradović-Đuričić K, Milekić B, Stamenković D. Occlusal appliances – An alternative in pain treatment of temporomandibular disorders. Srp Arh Celok Lek. 2019 Sep-Oct;147(9-10):541-6.
49. Ferreira DMAO, Soares FFC, Raimundini AA, Bonjardim LR, Costa YM, Conti PCR. Prediction of duloxetine efficacy in addition to self-management in painful temporomandibular disorders: A randomised, placebo-controlled clinical trial. J Oral Rehabil. 2024 Sep;51(3):476-86.
50. Yapici-Yavuz G, Şimşek-Kaya G, Oğul H. A comparison of the effects of Methylprednisolone Acetate, Sodium Hyaluronate and Tenoxicam in the treatment of non-reducing disc displacement of the temporomandibular joint. Med Oral Patol Oral Cir Bucal. 2018 May;23(3):e351-8.
51. Pereira IF. Efeito da ozonioterapia em distúrbios temporomandibulares. Braz J Case Rep. 2022 Oct-Dec;2(Suppl 3):939-44.
52. Chandra L, Goyal M. Minimally invasive intraarticular platelet rich plasma injection for refractory temporomandibular joint dysfunction syndrome in comparison to arthrocentesis. J Family Med Prim Care. 2021 Jul;10(7):2552-8.
53. Martins IS, Radaic P, Marchi L, Barreto G, Pastore GP. Assessment of postoperative pain in patients undergoing temporomandibular joint arthroscopy with infiltration of dexamethasone disodium phosphate in different concentrations. A randomized controlled trial. J Cranio-Maxillofac Surg. 2023 Feb;51(2):89-97.
54. Tepecik T, Baş MZ. Does the use of injectable platelet-rich fibrin following arthrocentesis for disc displacement without reduction alleviate pain? J Oral Maxillofac Surg. 2024 Sep.
55. Bechir ES, Curt-Mola F, Suciu M, Horga C, Biriș C, Bechir A, et al. Efficacy of associated therapy in the treatment of temporomandibular disorders. Acta Stomatol Marisiensis. 2018;1(1):39-47.
56. Dalewski B, Kamińska A, Szydłowski M, Kozak M, Sobolewska E. Comparison of Early Effectiveness of Three Different Intervention Methods in Patients with Chronic Orofacial Pain: A Randomized, Controlled Clinical Trial. Pain Res Manag. 2019 Aug; 2019:7954291.
57. Mosleh M. Evaluation of the effect of intra-articular injection of macrolide antibiotics versus corticosteroids on internal derangement of temporomandibular joint. Egypt Dent J. 2021 Jul; 67:2333-40.
58. Mosleh AA. Treatment of temporomandibular joint internal derangement using MESNA injection. BMC Oral Health. 2024 Aug;24(1):894.
59. Venepally S, Balmuri PK. Efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) and Pharmacotherapies in Myofacial Pain: A Randomised Study. Indian J Public Health Res Dev. 2018 Jan;9(1):62-6.
60. Ford VJ, Klein HG, Danner RL, Applefeld WN, Wang J, Cortes-Puch I, et al. Controls, comparator arms, and designs for critical care comparative effectiveness research: It's complicated. Clin Trials. 2024 Feb;21(1):124-35.
61. D Arcy M, Stürmer T, Lund JL. The importance and implications of comparator selection in pharmacoepidemiologic research. Curr Epidemiol Rep. 2018 Sep;5(3):272-83.
62. Schünemann HJ, Higgins JPT, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing Summary of findings tables and grading the certainty of the evidence. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions version 6.5. Cochrane; 2024 Aug.
63. Jacob SM, Bandyopadhyay TK, Chattopadhyay PK, Parihar VS. Efficacy of Platelet-Rich Plasma Versus Hyaluronic Acid Following Arthrocentesis for Temporomandibular Joint Disc Disorders: A Randomized Controlled Trial. J Maxillofac Oral Surg. 2022 Dec;21(4):1199-204.
64. Shivakumar S, Abdul NS, Jyoti B, Kalburgi V, Cicciù M, Minervini G. Comparative evaluation of cognitive behavioural therapy versus standard treatment in temporomandibular disorders: A systematic review. J Oral Rehabil. 2025 Apr;52(4):521-30.
65. Zhang SH, He KX, Lin CJ, Liu XD, Wu L, Chen J, et al. Efficacy of occlusal splints in the treatment of temporomandibular disorders: a systematic review of randomized controlled trials. Acta Odontol Scand. 2020 Nov;78(8):580-9.
66. Sá M, Faria C, Pozza DH. Conservative versus Invasive Approaches in Temporomandibular Disc Displacement: A Systematic Review of Randomized Controlled Clinical Trials. Dent J (Basel). 2024 Aug;12(8):244.
67. Torres D, Zaror C, Iturriaga V, Tobias A, Brignardello-Petersen R. Corticosteroids for the Treatment of Internal Temporomandibular Joint Disorders: A Systematic Review and Network Meta-Analysis. J Clin Med. 2024 Aug;13(15):4557.
68. Yao L, Sadeghirad B, Li M, Li J, Wang Q, Crandon HN, et al. Management of chronic pain secondary to temporomandibular disorders: a systematic review and network meta-analysis of randomised trials. BMJ. 2023 Nov;383:e076226.
69. Meng H, Dai J, Li Y. Quantitative sensory testing in patients with the muscle pain subtype of temporomandibular disorder: a systemic review and meta-analysis. Clin Oral Investig. 2021 Dec;25(12):6547-59.
70. Winocur-Arias O, Friedman-Rubin P, Abu Ras K, Lockerman L, Emodi-Perlman A, Greenbaum T, et al. Local myalgia compared to myofascial pain with referral according to the DC/TMD: Axis I and II results. BMC Oral Health. 2022 Feb;22(1):34.
71. Kapos FP, Exposto FG, Oyarzo JF, Durham J. Temporomandibular disorders: a review of current concepts in aetiology, diagnosis and management. Oral Surg. 2020 Nov;13(4):321-34.
72. Vrbanovic E, Deškovic K, Zlendic M, Alajbeg IZ. Profiling of patients with temporomandibular disorders: Experience of one tertiary care center. Acta Stomatol Croat. 2021 Jun;55(2):147-58.
73. Ulmner M, Bjørnland T, Rosén A, Berge TI, Olsen-Bergem H, Lund B. Evidence for minimally invasive treatment A systematic review on surgical management of disc displacement. J Oral Rehabil. 2024 Jun;51(6):1061-80.